Frederick National Laboratory for Cancer Research, Frederick, MD

BDP

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Inspections by Regulatory Agencies

SOP Number: 24301

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1.0 Purpose

This procedure describes the management of inspections at the Frederick National Laboratory for Cancer Research (FNLCR), Biopharmaceutical Development Program (BOP) facilities conducted by domestic or international Regulatory Agencies. These facilities are operated by the contractor Leidos Biomedical Research, Inc.

2.0 Scope

This procedure applies to FNLCR personnel who may interface with Regulatory Agency Investigators during inspections of the BOP.

3.0 Authority and Responsibility

3.1 BDP/Biopharmaceutical Quality Assurance (BOA) personnel are responsible for maintaining constant presence with Regulatory Agency Investigators while they are on site.

3.2 The BOP Program and Technical Director is responsible for the acceptance of a Notice of Inspection, such as Form FDA-482, and a Notice of Adverse Findings (such as Form FDA-483).

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

If the BDP Program and Technical Director is unavailable, the BDP BQA & Regulatory Affairs (RA) Directors will be the designated alternates and can accept Notices of Inspections or inspection findings. If the BDP/BQA & RA Directors are unavailable, then the BDP BQA Compliance/Audit Managers can accept the forms.

3.3 BDP BQA and RA are responsible for documenting the transactions and results of inspections. BDP BQA and RA are also responsible for processing documentation requests, making any required copies, and reviewing documents prior to presentation to Regulatory Agency Investigators.

3.4 BDP RA is responsible for providing a written response to any Regulatory Agency observations.

3.5 The BDP Program and Technical Director and the BDP BQA Director are jointly responsible for implementing decisions on actions to be taken if areas of the BDP Facilities, operations, or procedures are found to be out of compliance.

3.6 The BDP BQA Director shall inform the President of Leidos Biomedical Research, Inc., Chief Operating, and Chief Medical Officers of any recommended compliance actions. The President of Leidos Biomedical Research, Inc., Chief Operating, and Chief Medical Officers shall take appropriate actions to obtain NCI approval for any facility or operational changes, as necessary.

3.7 BDP BQA is responsible for quality oversight of this operation.

4.0 Procedure

The following steps are to be followed by BDP personnel upon arrival of Regulatory Agency Investigators.

4.1 Any BDP employee approached by a Regulatory Agency Investigator must immediately notify the BDP BQA Director or the designated alternate (BDP BQA or RA Management). The BDP employee should not answer questions prior to BDP BQA being present. The BDP employee will escort the Investigator to the security office if they have not signed in and wait for BDP QA to arrive and escort them to the ATRF E2618 (or if unavailable to E2824) conference room. The BDP BQA Director or the designated alternate will then identify an appropriate conference room where the inspection contact team will assemble.

4.1.1 If a Regulatory Agency Investigator is found alone in a work area, immediately call the BDP BQA Director or designated alternate (BDP BQA) and escort the investigator to security if not signed in or to the conference room designated by BDP BQA. The employee should remain with the investigator until BDP QA arrives.

4.1.2 If a Regulatory Agency Investigator arrives after normal work hours, BDP BQA may request the individual to return during normal work hours. A Form FDA-482 or other notification of inspection is not accepted at that time but can be accepted upon the return of the investigators. If the objective of an inspection is to review a process being conducted after hours, the FDA has the right to inspect the process. If there is an after-hours inspection, the BDP employee should contact the President of Leidos Biomedical Research, Inc., or designated alternate (Chief Medical Officer, BDP BQA Director, BQA RA Director, BDP Program and Technical Director, or BQA Compliance/Audit Managers, in the order listed). One of these

individuals must be present to accept an FDA-482. BDP BQA will notify any production people involved.

4.1.3 The conference room identified for use during the inspection should be a location where all documents requested can be reviewed. Use of a conference room for regulatory agency inspections has priority over other BDP meetings taking place or scheduled.

4.2 Upon notification of the arrival of Regulatory Agency Investigators, the BDP BQA Director or delegate notifies the BDP Inspection Contact Team to report to the designated conference room. This initial Contact Team will consist of the BDP BQA Director, the BDP Program and Technical Director, the BDP BQA Auditing Manager, and the BQA RA Director or their designated alternate(s) as described in Table 1.

Table 1: BDP Inspection Contact Team

Team Member	Alternate(s)
Director, BDP BQA*	Director, BQA Regulatory Affairs Managers, BDP BQA Compliance/Auditing
Manager, BDP BQA Auditing	BDP BQA Quality Engineering Manager
Director, BQA Regulatory Affairs	BDP BQA Representative
BDP Program and Technical Director	BDP Director, Late Process Sciences

* Main Contact Person for Inspection.

4.3 The Director, BDP BQA or designated alternate shall determine the purpose of the visit from the Regulatory Investigators. Refer to Attachment 1 for an Attendance log that can be used to document who is present during an inspection.

4.3.1 BQA or RA will verify the identity of the Regulatory Agency Investigator(s) by requesting and checking an official badge, identification photo, or identification packet. The investigator's full name, credential number and expiration date should be recorded on the Inspection Contact Record (Attachment 2). In addition, the names of all personnel present with the Regulatory Agency Investigator(s) will be recorded on the Inspection Contact Record.

4.3.1.1 If the purpose of the visit is an FDA inspection, the Director, BDP BQA or designated alternate accepts Form FDA-482, Notification of Inspection. **No one other than the BDP BQA Director, the BDP Program and Technical Director, the BQA Regulatory Affairs Director, BQA Compliance/Audit Managers, President of Leidos Biomedical Research, Inc., the Chief Operating Officer, or the Chief Medical Officer accepts a Form FDA-482.**

The Notice of Inspection will contain the name of the Program Head, title, the company name, address, date, and the FDA Investigator's signature. If a Notice of Inspection form is not offered, it should be requested. A separate notice must be submitted for each FDA inspection, but a separate notice is not required for each day of an FDA inspection that continues for more than one day.

4.3.2 Regulatory Agency Investigators from foreign countries may or may not present a Notice of Inspection form (or equivalent). If a form is not offered, the Leidos Biomedical Research, Inc., initial contact, see above, should determine the purpose of the inspection. The Chief, Biological Resources Branch, NCI, or designee, is to be notified that a regulatory agency inspection is being initiated.

4.3.3 Once the purpose of the inspection is established, the BDP BQA Director or designated alternate (main contact person) will determine how many Escort Teams will be needed. Multiple inspection teams are necessary if there is more than one investigator and the investigators plan to split up and perform simultaneous and separate focus and/or inspection groups. The number of teams needed will be based on the number of investigators present, the focus of each investigator, and the number of tours that may be needed. Refer to Attachment 3 for who should comprise the Escort Teams.

4.3.4 During the initial meeting with the investigators each day, the main contact person (BDP BQA Director or designee), should try to establish an agenda and schedule for the inspection.

4.4 In the initial discussions with Regulatory Agency Investigator(s), most investigators will try to gather details about the organization of the company and the names of responsible corporate officials. Provide the investigators with a copy of an annual report, and/or organizational chart.

4.5 The main contact person (BDP BQA Director or designee) is responsible for accompanying the investigator(s) during the entire time they are on the premises.

4.5.1 BDP BQA shall contact the manufacturing or support area Director or designee if possible before entering work areas with the Regulatory Agency Investigator(s). Work should proceed as normal.

4.5.2 The BDP BQA Director or designee shall request that the investigators inform the escort personnel as to deficiencies and observations at the time that they are observed.

4.6 Taking Notes During an Inspection

4.6.1 At least one individual from the BDP BQA & RA will be assigned to take notes (the scribe) during the inspection. The notes will be used to compile a comprehensive Regulatory Agency Inspection Report by BDP BQA. This report will be attached to the Inspection Contact Record (Attachment 2). The notes should record as much as possible and include:

4.6.1.1 A time/place log showing what was inspected when.

4.6.1.2 Key questions and answers given, and by whom. Record as much as possible.

4.6.1.3 Comments made as to the adequacy or inadequacy of processes or procedures.

4.6.1.4 A listing of documents, records, data, etc., reviewed, including comments made by the Regulatory Agency Investigator(s) and, to the extent possible, items noted by the investigator(s). Refer to Attachment 4 for a Document Request form that can be used for logging document requests.

4.6.1.5 Key points of discussion with the Regulatory Agency Investigator(s) should be noted.

4.6.1.6 A list, with copies, of all documents requested and provided to the Regulatory Agency Investigator(s) for them to keep should be attached to the Inspection Contact Record. The list of documents should indicate which documents were only reviewed, versus copies actually taken by the investigators.

4.6.1.7 A listing of any commitments made during the inspection.

4.7 Answering the Regulatory Agency Investigator(s) Questions

4.7.1 Answer honestly the questions that are asked. Do not elaborate beyond the scope of the question that was asked. If a question is vague, ask the investigator to clarify its meaning or intent. **Do not volunteer information or give opinions.**

4.7.2 If a member of the Escort Team or employee is unsure of whether an investigator's questions or requests go beyond the scope of his/her authority to answer, he/she should defer the question to the BDP BQA Director (or main contact person).

4.7.3 BDP BQA may ask the manufacturing or support area Director or designee to respond to questions on a specific production process in their area. Subordinates should only answer questions directed to them that are related to a specific production process. Production subordinates should refer questions asked of them to their supervisors if they are not completely sure of the answer. Never guess; it is better to be honest and say, "I don't know", if necessary.

4.7.4 Commitments for corrective actions should only be made jointly by the BDP Program and Technical Director and the BDP BQA Director.

4.7.5 Legal counsel prohibits any Leidos Biomedical Research, Inc., employee from signing affidavits.

4.8 Investigator Requests for Records

4.8.1 The Investigator is entitled to review and obtain copies of records required to be maintained under the Good Manufacturing Practice (GMP) regulations. BDP BQA and designees will process requests for documentation, make any needed copies, and review documents prior to presentation to Regulatory Investigators.

4.8.2 Regulatory Agency Investigators are **not** entitled to: financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications and training of technical and professional personnel performing functions subject to the Food, Drug, and Cosmetic Act), and quality assurance audit reports.

4.9 Documents copied for a Regulatory Agency Investigator must be stamped "True and Exact Copy" on the first page of the document only. If the document contains proprietary or confidential information, it must be marked confidential. Do **not** stamp all documents confidential. To do so will invalidate the use of the confidential designation.

4.10 If an investigator requests a sample of any material, (raw material, in process sample, bulk or final product, retain, etc.), double the amount of material to be taken and split the sample in half. Half the sample should go to the investigator, and half should be retained by BDP. A receipt should be obtained from the Regulatory Agency Investigator for any samples taken and a copy put in the associated batch or preparation record. This receipt can be a Form FDA-484 "Receipt for Samples" that describes the samples obtained.

4.11 Photographing by Regulatory Agency Investigators is not allowed. If a photo attempt or request is made, the BDP BQA Director will inform the investigator that the taking of photos during inspections is not permitted. Leidos Biomedical Research Inc., legal counsel may be consulted on the issue if the regulatory agency persists in its demand to take photos.

4.12 Sound recording is not permitted during inspections.

4.13 If at all possible, observed deficiencies or violations should be corrected immediately while the investigators are still on site. Proof of these corrections is to be presented to the investigators prior to their preparation of an FDA-483 or other documented list of deficiencies. Although this may not prevent the inclusion of the item on the investigators' list, it should result in the investigator noting on the list of deficiencies that the item was corrected during the inspection.

4.14 At the end of each day of an inspection, there should be a debriefing meeting with the investigator(s) to highlight or clarify any potential areas of concern and establish the schedule of action items for the next day. Then a second meeting will take place immediately after the investigators leave to discuss each participant's notes, action items, and preparations to meet investigator requests in a timely manner.

4.15 Exit Interview and Form FDA-483

4.15.1 At the conclusion of the inspection, the investigator will normally request an exit interview with the Escort Team, and senior management or responsible head. This should include at minimum the BDP BQA Director; the BDP Program and Technical Director; and the Regulatory Affairs Director. Other individuals may also be present at the request of the Escort Team. The Chief, Biological Resources Branch, NCI, or designee, will also be notified when an exit interview is to take place.

4.15.2 **The purpose of the exit interview is to discuss and clarify any issues of concern and ensure that the Regulatory Agency Investigator(s) and the Leidos representatives understand the results of the inspection. Any comments or commitments made by BDP should only be made after joint agreement by the BDP Program and Technical Director and the BDP BQA Director. Comments and commitments shall be documented by the scribe present.**

4.15.3 The FDA investigators' list of observations is recorded on a Form FDA-483. The observations recorded on the Form FDA-483 are areas where the FDA investigator believes the company is non-compliant or deviates from GMPs and/or a firm's established practices. In those cases where an Investigator has noted no deviations, no Form FDA-483 will be issued. If a Form FDA-483 is issued, the President of Leidos Biomedical Research, Inc., or designated alternate, is responsible for accepting this form.

4.15.4 Foreign investigators should be encouraged to leave a list of their observations although it may not be required. Foreign investigators may send a letter after their inspection listing issues they want addressed and to which they want a response.

4.16 Follow-Up to Inspection

4.16.1 After the Regulatory Agency provides a written summary of observations at the end of an inspection, a written summary of corrective actions taken and planned by BDP will be prepared by Regulatory Affairs. This response will be submitted to the appropriate Regulatory Agency as soon as possible, preferably within one week of the inspection and no later than two weeks after the inspection. The Regulatory Affairs Director or designee will coordinate the response effort.

4.16.2 Violations cited during the inspection and agreed on by the person responsible for the CGMP facility must be addressed immediately, if possible.

4.16.3 The manufacturing or support area Director or designee shall be notified of the outcome of the inspection by BDP BQA or designated alternate. BDP BQA may convene a meeting to discuss the inspection report and assign responsibilities and target completion dates for corrective actions.

4.16.4 A copy of the inspection report (Form FDA-483), response letter, and plans for corrective actions shall be provided to the Chief, Biological Resources Branch, NCI, through the NCI Contracting Officer as soon as they become available.

4.17 All information relating to an inspection is stored by BDP BQA for at least five (5) years.

5.0 Definitions

5.1 **FDA-482 –** U.S. Food and Drug Administration (FDA) official notice of inspection which needs to be accepted by a responsible individual before an inspection can begin. An FDA-482 form must be provided to initiate an inspection by the FDA.

5.2 **FDA-483 –** U.S. Food and Drug Administration - List of adverse findings presented to the company by a Regulatory Agency Investigator upon completion of inspection. An FDA-483 form will only be provided if observations are noted during the inspection.

5.3 **FDA-484 –** U.S. Food and Drug Administration – Provided by the Regulatory Agency Investigator describing the samples obtained during the inspection.

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

6.0 Attachments

6.1 **Attachment 1** Form 24301-01, Attendance Log

6.2 **Attachment 2** Form 24301-02, Inspection Contact Record

6.3 **Attachment 3** Escort Teams

6.4 **Attachment 4** Form 24301-03, Document Request Log

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

Attachment 1

Form 24301-01, Attendance Log

FNLCR, BDP
Form No.: 24301-01
SOP No.: 24301
Revision 06: MAY 30 2019

Biopharmaceutical Development Program

Inspection Attendance Log

Inspection Date: _____ Meeting Location: _____

Regulatory Agency Performing Inspection: _____

Printed Name	Signature	Affiliation

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

Attachment 2

Form 24301-02, Inspection Contact Record

FNLCR, BDP
Form No.: 24301-02
SOP No.: 24301
Revision 06: MAY 30 2019

INSPECTION CONTACT RECORD

Inspection Date(s): _____ Time: _____

Investigators' Names	Credential Number	Expiration Date

Issuance of an FDA Form FDA-482 or equivalent notice of inspection (for foreign regulatory agencies):
◯ Yes ◯ No ◯ N/A

Accepted By: _____ Date: _____

Reason for Inspection:

BDP Personnel present per day:

Attach Inspection Report to this Contact Record. ☐

Attach a list, with copies, of all documents requested and provided to Regulatory Agency Investigator(s) indicating which were reviewed on-site and which were taken off-site. ☐

Issuance of FDA Form FDA-483 or equivalent notice of inspectional observations (for foreign regulatory agencies):
(If YES, attach a copy) ◯ Yes ◯ No ◯ N/A

Issuance of FDA Form FDA-484 or equivalent notice of sample receipt (for foreign regulatory agencies):
(If YES, attach a copy) ◯ Yes ◯ No ◯ N/A

Form completed by: _____ Date: _____

Inspection closed by: _____ Date: _____

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

Attachment 3

Escort Teams

Escort Teams will be comprised according to the following scheme when possible. If more than one escort team is required, the second escort team will be comprised of the alternates as listed in the specified order.

Escort Teams	
Main Contact	BDP BQA Director BDP BQA Regulatory Affairs Director BDP BQA Compliance/Audit Managers
Scribe	BDP BQA Regulatory Affairs Director ⇩ BDP BQA Personnel Other BDP Personnel
Runner	BDP BQA Personnel Other BDP Personnel
Area Owner	Manufacturing or Support Area Director or Designee

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

Attachment 4

Form 24301-03, Document Request Log

FNLCR, BDP
Form No.: 24301-03
SOP No.: 24301
Revision 06: MAY 30 2019

Biopharmaceutical Development Program

Documentation Request Log

Inspection Date:_____ Location:_____

Regulatory Agency Performing Inspection:_____

Document Title/Description of Request	Document Number	Check: Copy or Original Requested		Date and Time Provided	Comments
		Copy	Original		
		☐	☐		
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