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1.0 Purpose

This SOP describes the procedure for the removal (field withdrawal) or correction of investigational product that had been distributed by Leidos Biomedical Research, Inc., (LBR)/Biopharmaceutical Development Program (BDP) where the quality or safety may be compromised and the use of, or exposure to, may cause adverse health consequences.

2.0 Scope

This procedure applies to the field withdrawal or correction of BDP products, based on the evaluation of incidents such as, but not limited to, product complaints, adverse events, and confirmed Out-of- Specification (OOS) that occur after an investigational product has been shipped for use. The procedure also outlines how to evaluate the seriousness of the incident, along with the intended use of the product and the potential for patient injury or harm, and to determine the necessity to issue a withdrawal/correction communication.

3.0 Policy

LBR BDP manufactures products at the behest of the National Cancer Institute (NCI) to NCI specifications. LBR is not responsible for control of LBR/BDP manufactured product once it has been released and delivered to a client. The IND sponsor is responsible for control of the product. The IND sponsor or BDP may conduct stability testing on products manufactured for the NCI. BDP shall notify the NCI of any OOS results, complaints, or non-conformances and their associated investigations. As a contractor to the NCI, this procedure was developed to assist the NCI if it is determined that a field withdrawal or correction is required.

4.0 Authority and Responsibility

4.1 The BDP Quality Assurance Department (QA) has the responsibility, if it has been determined that the safety, identify, strength, quality, or purity of a product manufactured and distributed by BDP as directed by the NCI has been potentially compromised, to determine if action(s) listed in this SOP are necessary.

4.2 The BDP Material Review Board (MRB), which includes NCI/BRB, is responsible for determining the need for a field withdrawal or correction.

4.3 BDP BQA is responsible for the following activities:

4.3.1 Initiating an MRB meeting and coordinating the investigation of product complaints, adverse events reported by a client, confirmed OOS results, or similar incidents that could result in an investigational product field withdrawal or correction notice.

4.3.2 Implementing a customer notification strategy.

4.3.3 Managing effectiveness checks during and after the field withdrawal.

4.3.4 Receiving notice of failures or discrepancies and tracking and expediting the progress of failure investigations.

4.3.5 Propose the numerical designation, i.e., I, II, or III, to indicate the degree of health hazard presented by the product being recovered (See Section 6.3.)

4.3.6 Initiating any extended investigation, in addition to Process Analytics failure investigation.

4.3.7 Filling out the Product Correction/Removal Evaluation Form 24101-01 and preparing interim and final reports.

4.3.8 Designing and implementing a strategy for product recovery or correction.

4.3.9 Distribution of reports.

4.4 Any LBR/BDP employee who receives a product complaint or other information concerning possible product quality, safety, or potency problems is responsible for immediately forwarding the complaint to BQA management.

4.5 Process Analytics (PA) is responsible for testing and evaluation of Out-of-Specification Results and will notify BQA immediately of any confirmed OOS failure investigations that occur after an investigational product has been shipped for use. BQA may then notify the NCI and others as necessary, of the product failure and potential product impact.

5.0 Procedure

5.1 Upon communication by the FDA, or any Regulatory agency, that a product recovery is required, BQA management will request a MRB meeting to discuss the field withdrawal strategy and notify the NCI within two business days of receipt of the communication.

5.2 Upon receipt of a complaint, confirmed OOS result, or adverse event, that may result in a field withdrawal or correction, BQA management will coordinate an MRB meeting and/or investigation to evaluate the complaint, OOS, or adverse event.

5.2.1 For BioPharm products (i.e., non-cell therapy products), the MRB should be scheduled to occur within two business days of notification of the issue.

5.2.2 For Cell Therapy products, the MRB should be scheduled to occur within one business day as notification of the issue.

5.3 The Director of Regulatory Compliance will appoint a BQA coordinator to gather the relevant information related to the MRB evaluation (such as product shipping/ inventory forms).

5.4 The BQA coordinator will fill out as much of the Product Correction/Removal Evaluation Form (Form 24101-01) prior to the meeting and distribute the form to the MRB members with any supportive documentation prior to the meeting. After the meeting, the BQA coordinator will document the MRB meeting action items, as well as any product recovery strategy required.

5.5 The MRB meeting participants, including NCI/BRB, will determine whether any correction or field withdrawal is needed, the depth of product recovery, and suggest a recovery or correction strategy to alert the client/consignee and any regulatory agencies (if necessary). The MRB will also evaluate BQA's proposed numerical designation that indicates the degree of health hazard.

5.6 Notification of Planned Field Withdrawal or Correction

5.6.1 The Director of Regulatory Compliance is responsible for contacting the President of LBR, and Chief Medical Officer, to notify them immediately if a field withdrawal is planned, and if any field product recovery communications will be sent.

5.6.2 For BioPharm products, BQA Management (or designee) will notify the NCI/BRB to notify the appropriate client/consignee. LBR may help with the notification of NCI clients/consignees if requested to do so by the NCI/BRB.

5.6.3 For Cell Therapy products, BQA Management (or designee) will notify the Sponsor and/or designated Sponsor representatives. NCI/BRB should be copied on the notification.

5.7 The following guidelines will be used for a field withdrawal or correction communication (21 CFR 7.49):

5.7.1 Be brief and to the point.

5.7.2 Clearly identify the product, size, lot number(s) and any other descriptive information.

5.7.3 Explain the hazard involved and reason for the field withdrawal or correction.

5.7.4 Provide specific instructions on what must be done to correct or return the product. BQA will usually recommend quarantine of any recovered product.

5.7.5 Provide a mechanism for the institutions that received the field withdrawal/correction notice to communicate with the BDP. (Postage-paid/self-addressed postcard, phone number, fax, E-mail, etc.)

5.7.6 The withdrawal/correction communication must not contain irrelevant materials or information, or statements that may detract from the message.

5.7.7 Cell Therapy withdrawal/correction communications may require the use of specific forms or require additional information, as noted in the IND documentation (e.g., CMC, MOP, clinical protocol, etc.).

5.8 In the event of a BDP product field withdrawal, the BQA assigned coordinator will be responsible for reconciliation of product shipped from LBR/BDP. The coordinator will be responsible for communications sent, documentation of client/consignee receipt (such as certified/return receipt or Federal Express), and with follow-up phone calls to assure receipt and understanding of any information sent. Wording to be used in any communications must be approved by the Director of Regulatory Compliance.

5.9 Product Returned to the BDP

5.9.1 Upon receipt of the returned product at the BDP, the product must be placed at the correct temperature and BQA and PA/QC notified of the receipt. BQA will place a quarantine notice on the material per ***SOP 21704 - Biopharmaceutical Quality Assurance Hold/Quarantine Policy for Materials and Product***.

5.9.2 If requested by BQA, the PA/QC Department shall sample the product for analysis.

5.9.3 An inventory of returned products shall be made and reconciled against what was requested to be returned.

5.9.4 Those recipients that failed to return product shall be contacted and requested to do so. Documentation of whether each product recipient returned the product that they had received will be recorded on Form 24101-01.

5.10 The BQA coordinator will draft interim and close-out reports for the BQA Director's approval. The reports will indicate the success rate (product recovery efficiency) in getting product recovered and include any communications sent. BQA will distribute investigation and close-out reports to the President of LBR, the Director of Clinical Operations, and the NCI/BRB Chief.

5.11 BQA Documentation will maintain any investigation and close-out reports on file.

6.0 Definitions

6.1 **Consignee –** anyone who received or used the product being recovered.

6.2 **Field Withdrawal –** the removal or recovery of a distributed investigational product.

6.3 **Field Withdrawal Classification –** the numerical designation, i.e., I, II, or III, assigned by the BDP to a product recovery to indicate the relative degree of health hazard presented by the product being recovered.

6.3.1 Class I, Critical, is a situation in which there is a reasonable probability that the use of, or exposure to, a compromised product will cause serious adverse health consequences or death.

6.3.2 Class II, Major, is a situation in which use of, or exposure to, a compromised product may cause temporary or medically-reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

6.3.3 Class III, Minor, is a situation in which the use of, or exposure to, a compromised product is not likely to cause adverse health consequences.

6.4 **Field Withdrawal Strategy –** a planned specific course of action to be taken in conducting a specific field withdrawal, which addresses the depth of recovery, need for investigator warnings, and extent of effectiveness checks for the recovery.

6.5 **Material Review Board (MRB) –** is represented by at least one member from the following departments: Quality Assurance, Process Analytics/Qualify Control, Regulatory Affairs, the BDP Program and Technical Director, or designee, and BDP Project Scientist. The in-house recipient of the complaint, and any other person requested by one of the other members will also attend. The MRB will review those product complaints, adverse events, or Out-of-Specification (OOS) results from stability testing, that BQA has indicated may result in a field withdraw and make recommendations for product disposition. See ***SOP 21008 - BDP Material Review Board***.

6.6 **Product –** an article subject to the jurisdiction of the Food and Drug Administration, including any food, drug, and device intended for human or animal use, any cosmetic and biologic intended for human use.

6.7 **Product Correction –** the repair, modification, adjustment, relabeling, destruction, or inspection of a product without its physical removal to some other location.

6.8 **Recall –** a firm's removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure. Since the BDP does not manufacture marketed products, recall procedures would not apply to products made in the BDP.

7.0 References and Related Documents

SOP 21008 *BDP Material Review Board*

SOP 21704 *Biopharmaceutical Quality Assurance Hold/Quarantine Policy for Materials and Products*

SOP 22004 *Managing Out-of-Specification Test Results or Unexpected Test Results*

Form 24101-01 Product Correction/Removal Evaluation Report

21 CFR Part 7, Subpart C - Recalls (Including Product Corrections) Guidance on Policy, Procedures, and Industry Responsibilities.

Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance

8.0 Change Summary