Table of Contents

1.0 Purpose

This procedure describes how critical quality issues, including product-specific complaints, are documented, investigated, and resolved.

2.0 Scope

This SOP applies to Biopharmaceutical Quality Assurance (BQA) staff who manages the investigation of critical quality issues for presentation to the Material Review Board. It also applies to the members of the Material Review Board (MRB).

This procedure also applies to GLP and CGMP projects produced by the Biopharmaceutical Development Program (BDP) in which the BDP serves as a manufacturer to a third party or sponsor.

Product-specific complaints are considered MRB issues and are managed according to this procedure.

Any event that could possibly compromise the safety, identity, strength, quality, or purity of a BDP manufactured drug product, whether internal or external, e.g., occurring at repositories or clinical trial sites, is documented and managed according to this procedure.

3.0 Authority and Responsibility

3.1 The Director, Regulatory Compliance has the responsibility and authority to:

3.1.1 Determine which quality issues are presented to the MRB in accordance with the direction of this SOP.

3.1.2 Oversee the investigation of the quality events either in preparation for an MRB review or as a result of an MRB review.

3.1.3 Oversee any corrective/preventive action required as a result of an MRB review.

3.1.4 Make the final decision, when required, on the disposition of any product affected by the MRB review.

3.1.5 Arrange for MRB meetings, as applicable, in a timely manner.

3.2 The BDP MRB members or designees, have the responsibility and authority to:

3.2.1 Review the MRB issue and provide input into the investigation/resolution of the quality issue.

3.2.2 Provide resources, appropriate to their areas of responsibility, to correct and resolve quality issues brought before the MRB.

3.2.3 Oversee any corrective/preventive action required as a result of an MRB review.

3.3 The BQA Compliance Manager, or designee, is responsible for:

3.3.1 Scheduling/facilitating meetings of the MRB.

3.3.2 Creating an MRB tracking number.

3.3.3 Facilitating investigations and coordination of actions as they relate to MRB activities.

3.4 It is understood that even though the BDP may release a product for use, that the NCI-BRB, and subsequently, any third party or sponsor may, of its own volition, determine that a product is not suitable for any particular use.

3.5 BDP employees are responsible for documenting complaints or concerns with BDP products or processes and submitting these to BQA

4.0 Overview

4.1 Quality Events are evaluated according to the event's potential for product impact and patient impact. Generally, impact is categorized as Insignificant, Minor, Major, or Critical. This categorization defines the level of review required to adequately evaluate the quality event. Increasing potential impact requires increased review. The formal body that reviews quality issues of increased impact is the Material Review Board (MRB).

4.2 Issues for review come to the MRB through the Director of Regulatory Compliance and may originate from a variety of sources and BDP quality management systems.

NOTE: Any product-specific complaint is considered an MRB issue and will be managed through the MRB.

4.3 The MRB will monitor the management of the event to assure that it has been correctly investigated, evaluated, and documented and that any necessary material disposition, notifications, corrections, or preventive actions are completed.

5.0 Makeup of the Material Review Board

5.1 The MRB is composed of the following BDP members or their designees.

5.1.1 Director, Regulatory Compliance

5.1.2 Director, Process Analytics/Quality Control

5.1.3 Associate Director, Regulatory Affairs

5.1.4 BDP Program and Technical Director

5.1.5 Appropriate Project Scientist(s)

5.1.6 Any other person requested to attend by any of the Board members listed above.

5.2 Biological Resources Branch (BRB) individuals may be requested to attend and provide input as appropriate.

6.0 Potential Issues for MRB Review

6.1 The following are examples of events that would likely lead to an MRB review.

6.1.1 Critical Deviations (Class IV) that have resulted in, or are likely to result in, a product failing established specifications or general product expectations (for example, lack of sterility or particulate level exceeding specifications, etc.).

6.1.2 Confirmed Out-of-Specification events (that indicate that the product has failed established specifications).

6.1.3 Post-release quality issues (for example, label discrepancies or inaccuracies).

6.1.4 Adverse event reports.

6.1.5 Product complaints (from within the BDP, from sponsors, or users of BDP products and services).

6.1.6 Container/closure failure.

6.1.7 Facility, utility, and equipment failures that would likely impact product quality.

7.0 Procedure

7.1 Selection of Items for MRB Consideration

7.1.1 Product-specific complaints are managed through the MRB. Other issues may be added for MRB review at the discretion of the Director Regulatory Compliance. The issue for review may be one of the following.

7.1.1.1 One that has been investigated and the investigation and conclusions (including corrective and preventive actions) need to be discussed.

~OR~

7.1.1.2 One that has been submitted to MRB for review BEFORE a formal investigation has taken place (in which case, the MRB will help direct the investigation, and identify corrective and preventive action).

7.1.2 BQA will assign a unique MRB tracking number for each event and log the event into the MRB log.

7.1.2.1 The format for the MRB tracking number will be **YYYY-MM-NN** where-

7.1.2.1.1 **YYYY** is the year the MRB event was designated for review.

7.1.2.1.2 **MM** are the two digits designating the month the MRB event was designated for review.

7.1.2.1.3 **NN** is a sequential number beginning each month for MRB events designated for review.

7.1.2.1.4 For example, MRB 2007-04-02 is the second MRB event designated for review in April 2007.

7.1.3 The BQA Compliance Manager will initiate Form 21008-01.

7.2 Product Control

7.2.1 At the direction of the Director Regulatory Compliance, affected product or potentially affected product, or material under MRB review may be placed on QA Hold or Quarantine until the MRB review is completed and the Director Regulatory Compliance dispositions the product(s). Reference ***SOP 21704 - Biopharmaceutical Quality Assurance Hold/Quarantine Policy for Materials and Product***.

7.3 MRB Meeting Organization

7.3.1 BQA will coordinate an MRB meeting in a timely manner.

7.3.2 BQA will distribute information (as available) regarding the MRB action (before the scheduled MRB meeting, when possible).

7.3.3 If the MRB concerns the manufacturing or testing of a third party's or sponsors product, and if they have requested to be notified of deviations and/or MRBs, then they shall be notified of the MRB prior to the meeting to allow them to participate in the MRB process. The notification is documented on Form 21008-01.

NOTE: BDP Quality Assurance reserves the right to declare any material manufactured by the BDP as unfit for use and release. Third parties or sponsors may not overrule such a decision. However, they have the independent right to reject any material independent of the BDP's determination to approve and/or released the product.

7.4 MRB Meeting

7.4.1 During the meeting, the issue is presented and discussed.

7.4.2 BQA defines the problem and results of the investigation, if conducted.

7.4.3 BQA and other MRB members present possible proposal(s) for solution.

7.4.4 The goal of the meeting is to reach consensus when possible, on the following issues:

7.4.4.1 Status of product.

7.4.4.2 Need for any notification of third party or sponsors.

7.4.4.3 Need for notification of FDA.

7.4.4.4 Corrective action (to address defects in existing product and/or processes).

7.4.5 BQA documents the corrective and preventative (CAPA) actions to be taken to ensure that the cited incident has a low probability of reoccurring in the future.

7.4.6 Issues for further follow-up may include a decision to recommend a field withdrawal or correction of the product, or to assist the IND sponsor in a field withdrawal or correction. See also ***SOP 24101 - Field Withdrawal or Correction of Investigational Products***.

7.4.7 Product disposition is the responsibility of the Director Regulatory Compliance who will take the information and recommendations presented at the MRB meeting(s) into consideration.

7.5 MRB Trending

7.5.1 BQA reviews investigations regularly to determine trends requiring further consideration. Any identified trends are reviewed at the Quality Board meeting.

7.6 Notification

7.6.1 The occurrence of an MRB event (Reference Step 6.1) shall be communicated to BDP management, the NCI-BRB, Principal Investigator, and relevant third party or sponsor, if any, who has requested notification through a Quality Agreement (see Step 7.3.3 and the NOTE above).

8.0 Documentation

8.1 Actions of the BDP MRB are documented by BQA using Form 21008-01 and tracked using a unique MRB tracking number.

8.2 BQA maintains records relating to investigations in accordance with the BDP records retention policy, ***SOP 21407 - Records Retention.*** Records are marked **Confidential**.

9.0 References

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

SOP 24101 *Field Withdrawal or Correction of Investigational Products*

SOP 21407 *Records Retention*

Form 21008-01 *Material Review Board Investigation Form*