**Document approval**

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# Purpose

The purpose of this Standard Operating Procedure (SOP) is to provide guidance on how to handle Deviations at NBE-Therapeutics.

# Scope

This SOP is valid at NBE-Therapeutics for all Organization. The respective training shall be given in accordance with **Training Management CODE Training Management***.*

# Responsibilities

Responsible for the content of this SOP is Quality Management Director.

|  |  |
| --- | --- |
| **Role** | **Definition/Task** |
| Quality Organization | * Responsible for this SOP and management of the Deviation process
* Overseeing the investigation, as appropriate
* Ensuring appropriate actions are taken (e.g., putting product under quarantine)
* Ensuring an appropriate Root Cause analysis, as appropriate
* Determines investigators who will take part in particular investigation
* Approval of the **Deviation Investigation Report**.
 |
| Department Heads / Team Leads | * Oversee their working areas and to work with QM to resolve Deviations through timely and evidence-based investigation, evaluation, and disposition of all affected product.
* Department Heads may delegate authority and/or responsibility to specifically authorized personnel, such as managers, leads, and/or manufacturing lead investigators; however, Department Heads assume all accountability for the decisions and actions of such personnel who have been authorized to act on their behalf and perform activities up to and including disposition approval of Nonconforming Product

/ material.* Initiate the Deviation Notification (Originator role).
* Review Deviation Reports.
 |
| Investigators | * Perform Deviation investigation, analyze probable Root Cause, review investigation related data, propose CAPA measurements, escalate Deviation(s), prepare Deviation Report.
 |
| Regulatory Affairs | * Reviews Deviations classified as major or critical to determine impact on regulatory filings.
 |
| Observer | * Notifies their Line Manager regarding occurred Deviation.
 |
| Originator | * Initiates the **Deviation Notification** (Department Heads / Team Leads)
 |

# Definitions, terms and abbreviations

|  |  |
| --- | --- |
| **Term/abbreviation** | **Definition at NBE-Therapeutics** |
| Critical Deviations | Serious Deviations with potential implications on the product or process integrity that cannot be contained within **NBE-Therapeutics.** |
| Deviation | Departure from an approved instruction or established standard. Any unexpected event or occurrence where an established process was not followed or expected results were not met. |
| Discovery Date | The date NBE-Therapeutics becomes aware of a potential Deviation (for external Deviations, the notification date is considered the Discovery Date). |
| DNRN | Assigned Deviation Notification Reference Number |
| Immediate Action | Any actions immediately taken to minimize product, process and/or patient impact upon observation. |
| Major Deviations | Process or product impact may occur, but the Deviation can be controlled, and issues can be resolved within NBE-Therapeutics. |
| Minor Deviations | Deviations from existing procedures or expectations, without serious impact on product, process, integrity, health, or safety (e.g., documentation errors like ink color or insufficient usage of ALCOA principles of data integrity. |
| Nonconformance | Non-fulfilment of a predefined requirement. |
| Quality Defect (Product’s / Material’s Nonconformance) | Non-fulfillment of a specified Product/Material requirement. Deviation from Specification. |
| Observer | Person observing any unexpected Deviation from an existing process. The Observer serves as originator of the Deviation. |

# Workflow

# General

The Deviation reporting process establishes a mechanism for Departments and individuals to report, correct, track/trend, and escalate Deviations that occur within NBE-Therapeutics.

Each Department is responsible for ensuring appropriate handling of Deviation process flow.
Deviation Management process flow is described on ***Figure 1.***

***Figure 1:*** ***Deviation Management Process***

Examples of Deviations are given in [***Table 1***](#_bookmark7).

***Table 1: Examples of Deviations***

|  |  |
| --- | --- |
| **Functional Area / Department** | **Examples of Deviations** |
| Manufacturing | * in-process controls are out of specification
* Yield out of range
* Hold or process times out of range
* Wrong material or wrong amount (quantity or volume)
* Incompliance in the manufacturing line or equipment clearance
 |
| Laboratory / QC | * Equipment malfunction
* Calibration missing or failed
* Test record error
 |
| Labelling / Packaging | * Wrong material label or missing labels
* Unapproved packages
* No original or damaged tamper seals
 |
| Transportation | * Temperature ranges not within specification
* No dataloggers
 |
| Documentation | * Missing records (e.g., training, batch, test records)
* Failure to follow Good Documentation Practice
 |
| Facility | * Heating ventilation and conditioning system error
* Temperature excursion
* Pest control abnormalities
 |

# Deviation Discovery and Notification

Observer informs the Line Manager of any potential Deviation discovered. Any discovered Deviation shall be reported to the Line Manager immediately on the day of discovery.

Line Manager verifies all available data and records related to the event. If there are sufficient grounds Line Manager (Originator) notifies Quality Organization about the event and submits appropriate records **not later than end of next working day** according to **Deviation Notification Form**. Observer records all witnesses of the incident for the purpose of further investigation.

All appropriate Immediate Actions shall be taken immediately.

At a minimum, the following events result in generation of a **Deviation Notification** record:

* + Failure of a critical control point
	+ Nonconforming product made available for distribution

Quality Organization representative shall verify completeness of **Deviation Notification** record, register and assign DNRN.

# Deviation Investigation

Quality Organization registers submitted **Deviation Notification**, assigns DNRN and initiates Deviation investigation. Quality Organization determines and assigns Investigators who will take part in the particular investigation. Investigators may represent different Departments depending on the area of investigation and their SME’s expertise areas.

If product conformance is in question, Quality Organization ensures that all involved products or materials are placed in quarantine until the following steps occur:

* Investigation is completed to determine conformance/Nonconformance of product/material.
* Final decision is made regarding product/material disposition and the decision is approved.
* Quarantine and release status are documented on the **Deviation Investigation Report**.

# Major and Critical Deviations

The following investigation shall be done if the Deviation is classified as Major or Critical:

* + - * Perform comprehensive document review and conduct interviews with Deviation Observers.
			* Assess other potential impacted processes or products.
			* Perform a Risk Assessment according to **Quality Risk Management CODE Quality Risk Management**.
			* Perform Trends assessment and historical record verification for reoccurring issues.

Establish Root Cause by using **Quality Investigation and Assessment Tools Appendix**. Usual Root Causes are poor procedures, training, other systemic errors, etc. "Human Error /Personnel failure" as potential Root Cause may be suspected only in exceptions.

In case of closure timelines exceeding on critical Deviations, escalate to Leadership Team.

# Minor Deviations

For Minor Deviations a minimal investigation and appropriate Immediate Actions are required.

# Reporting and Closure

Investigators record the progress of the Investigation and its results in the **Deviation Investigation Report**. Investigators propose and initiate appropriate suitable CAPA measurements for at least Major and Critical Deviations according to **CAPA Management CODE CAPA Management**.

Departments/Heads or Team/Leads review the **Deviation Investigation Report** than Quality Management Director approves the **Deviation Investigation Report**.

Deviation Closure is expected within thirty (30) days.

# Escalation

If necessary, Investigators can escalate any Deviations by informing Department Heads /Team Leads, for example:

* + - * unfavorable trends (e.g., multiple Minor Deviations / Quality Defects on the same issue),
			* Minor Deviation / Quality Defects or group of Minor Deviations / Quality Defects to a Major or Critical Deviation.

# Deviation Metrics

Quality Organization reports Deviation Management metrics and trends to NBE-Therapeutics Leadership Team as part of the Management Review process in accordance with
**Management Review CODE Management Review.**

# Applicable documents

Quality Manual CODE Quality Manual

Documentation Management CODE Documentation Management

Training Management CODE Training Management

CAPA Management CODE CAPA Management

Management Review CODE Management Review

Quality Risk Management CODE Quality Risk Management

# Appendices

The following appendix(ces) is/are integral part of this SOP: Appendix Deviation Notification Form

Appendix Deviation Investigation Report Form

Appendix Quality Investigation and Assessment Tools Appendix

# Document revision history

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Valid from** | **Description of the revision** | **Reason for the revision** |
| 1 | See header | Document created | QMS implementation |