**Document approval**

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# Purpose

The purpose of this Standard Operating Procedure (SOP) is to provide a guideline for handling and management of Complaints of Products and for handling of products Recall.

# Scope

This SOP is valid at NBE-Therapeutics for all Organization. The respective training shall be given in accordance with **SOP-10 Training Management**.

This SOP is applicable for all oral and written Complaints received, and for the prompt and effective Recall of products known or suspected to be defective.

This SOP is not applicable for the processing of cases, related to adverse events and pharmacovigilance processes.

# Responsibilities

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

| **Role** | **Definition/Task** |
| --- | --- |
| All employees | * Acceptance and conveying of any product quality Complaints to Quality Organization within twenty-four (24) hours.
 |
| Quality Organization | * conducts Complaint Preliminary Assessment
* initiates Complaint investigation
* maintains Complaints Log
* organizes, facilitates, and supports the investigation of Complaints
* prepares, distributes, agrees, Complaint Invevtigation Plan
* coordinates, takes an active part in Complaint investigating
* collects, reviews, provides investigation supportive data and documents
* maintains List of Recall Committee Members
* stores records and other documents related to Complaints investigations, Recalls, Mock Recalls
 |
| SMEs | * take an active part in Complaints investigating
* collects, reviews, provides investigation supportive data and documents
* investigate potential defect root case
* assess the risk and Qualify Defect classification
* propose CAPA measures to eliminate the product defect associated with the Complaint
* prepare Complaint Investigation Report
 |
| Marketing Department | * sends formal Complaint response to the Customer
 |
| Operation Department, specifically the Warehouse and Supply Team | * takes an active part in Complaints investigating
* collects, reviews, provides investigation supportive data and documents
* determines product distribution chain, provides product Complaint distribution records and other related data for any investigation, Recall and Mock Recall purposes
* sends Recall Statement to all identified clients for particular product distribution chain
* monitors on daily basis Recall steps performance and updates product Recall status
 |
| Quality Management Director | * approves Complaint Preliminary Assessment, Complaint Invevtigation Plan, Complaint Investigation Report
* appoints Recall Committee Members
* acts as Recall Coordinator or appoint employee at this role
* shares investigation and other related data as required by any authority/Contract Giver/Qualified Person etc.
 |
| Recall Coordinator (RC) | * Organizes, coordinates, supports, facilitates, all Recall activities and Mock Recalls
* monitors product Recall status and Mock Recall status
* prepares Recall Statement, Recall Report drafts.
* Initiates rapid alert notifications, if required
* Defines Mock Recall design and its legend (class, depth, particular batch numbers, etc.)
 |
| Recall Committee Members | * make decision on the need for a Recall, determines Quality Defect Class, depth and all necessary actions related to the Recall
* review, approve Recall Statement
* reviews, approve Recall Report
* allocate required resources, if needed.
 |

# Definitions, terms and abbreviations

| **Term/abbreviation** | **Definition at NBE-Therapeutics** |
| --- | --- |
| Adverse drug experience (ADE) | Any adverse experience associated with the use of a drug product in humans, whether or not considered drug-related, includes the following:* adverse experience occurring from the use of a drug product in professional practice,
* adverse experience occurring from drug overdose whether accidental or intentional,
* adverse experience occurring from drug abuse,
* adverse experience occurring from drug withdrawal,
* any failure of expected pharmacological action.
 |
| Class 1 Quality Defect | Quality Defect is potentially life-threatening and could pose a serious health risk. |
| Class 2 Quality Defect | Quality Defect may result in illness or inappropriate treatment and does not come under Class 1. |
| Class 3 Quality Defect | Quality Defect does not pose a significant health risk (Recall not essential). |
| CRN | Complaint Reference Number |

# Workflow

## Complaint maintenance

### Acceptance of Complaint

The process is initiated with the receipt of a Complaint. A Complaint may be received from consumers, healthcare professionals, government / regulatory agencies, trade sources or from any other source, in any form (written or verbal, post, fax, email or through the website and social networks). Complaints are taken by all employees and conveyed to Quality Organization within twenty-four (24) hours. Employee must request all relevant information about the product under Complaint from the Customer, i.e.:

* name of the product,
* size/strength of package,
* lot/batch number,
* manufacturing date,
* expiry date,
* description of Complaint,
* product packaging details
* product samples availability for return, and complainant contact details.

The employee who receives the Complaint fills out **Complaint Notification Form** and sends it to Quality Organization.

Quality Organization representative reviews completeness of **Complaint Notification** record and assigns CRN number.

Further CRN numbering assignment principle is applied as follows:

MC-YY-ZZZ

where MC stands for Market Complaint, YY stands for the last two digit of the year. 22 for 2022 and 23 for 2023 and so on, ZZZ stands for Serial number starting from 001 for each calendar year.

First Complaint for the year 2022 shall be numbered as MC-22-001 and for the year 2023 shall be numbered as MC-23-001, and so on.

Quality Organization logs all received Complaints into **Complaints Log** according to **Complaints Log Form**, whether they are justified or not.

Quality Organization conducts a preliminary assessment according to **Complaint Preliminary Assessment Form** within twenty-four (24) hours. Quality Management Director approves **Complaint Preliminary Assessment** and preliminary proposalsfor furtheraction plan**.**

Purposes of preliminary assessment are:

* Complaint categorization,
* decide whether the Complaint is justified or not,
* define potential reason for associated Quality Defect,
* determine preliminary action plan,
* decision for further Complaint investigation.

The Complaint may be dismissed, and the procedure completed if there are compelling reasons for doing so. Examples of unfounded Complaints (no product Quality Defects):

* particles found on the outside
* subjective organoleptic sensations/feelings
* application history, different presentation (old mock-ups, SKUs, leaflets)
* inflated consumer expectations that do not match the product profile.

### Investigation of Complaint

When **Complaint Preliminary Assessment** is done and Quality Organization confirms founded Complaint, Quality Organization initiates a Complaint investigation. Investigation scope and goals shall be formalized according to **Complaint Invevtigation Plan Form**. For the purposes of the investigation, Subject Matter Experts (SMEs) from different departments may be involved, depending on the areas and scope of the investigation. If necessary, an internal communication should be held with all stakeholders to discuss and agree on **Complaint Invevtigation Plan**.

The most important objectives of the investigation are:

* identification of Root Cause,
* risk assessment, measure risk level,
* determine the real size of the problem (particular batch/lot, tray of batches/lots, whole product),
* taking immediate actions to isolate the problem and mitigate the associated risks.

Quality Organization prepares and distributes proposed **Complaint Invevtigation Plan** to all involved Departments within twenty-four (24) hours.

Department Heads or designated SMEs shall apply and review **Complaint Invevtigation Plan**.

All rational and reasonable proposals shall be discussed and agreed upon. Any additional activities and actions that have arisen since the approval of the **Complaint Invevtigation Plan** must be reflected in the **Complaint Investigation Report**.

All involved Departments and SMEs are responsible for investigating the Complaint according to **Complaint Invevtigation Plan**. All time delays and other problems shall be communicated and approved by Quality Organization prior.

**Appropriate containment measures (quarantine) should be taken if current risks to the product are identified.**

#### Investigation by Quality Organization

The Complaint case is investigated by Quality Organization. This may include the following points:

* examination of the Complaint sample
* if necessary, examination of the return sample and other samples or batches
* comparison with previous, similar Complaints
* resulting Corrective Actions and Preventive Actions (CAPAs), if applicable
* further measures which may help to clarify the respective facts
* evaluation of the defect
* reasoning or investigation of the cause

Depending on the nature of the Market Complaint, QC analytical data shall also be reviewed. If required, stability data and trend data shall also be reviewed.

Note: Reference samples, Retention samples and Complaint samples, if available, shall be inspected and compared.

When necessary, Reference samples, Retention samples and Complaint samples (if available) shall be analyzed for relevant parameters to establish the acceptability of the product. However, if the Complaint samples are received in suspicious conditions (storage, handling, damage), justification for not analyzing the Complaint samples shall be documented.

Based on the Root Cause identified during the investigation, an impact assessment of the Complaint batch shall be evaluated. Other batches of the same product or production line may be evaluated to understand the overall extent of the potential issue.

#### Investigation by Manufacturing Department

Complaint case is processed by the Manufacturing Department in cooperation and support of Quality Organization. This can include the following points, among others:

* checking the batch documentation (production and packaging records) and, if necessary, carrying out further research to clarify the facts of the case,
* if necessary, questioning of the corresponding contract manufacturer,
* evaluation of the source material,
* the reasoning or Root Cause analysis,
* if necessary, resulting CAPAs,
* further measures contribute to the clarification of the respective facts,
* evaluation of the defect.

### Complaint investigation results reporting

Any Market Complaint received shall be closed within thirty (30) days from receiving the Complaint. In case a Complaint is critical and determined to be serious, the Manufacturing Department shall take immediate actions with the cooperation and support of Quality Organization.

When **Complaint Invevtigation Plan** was realized, associated Root Cause analysis and CAPA measures, associated risks were defined. SMEs finalize **Complaint Investigation Report** **Complaint Investigation Report Form**. Affected Departments Heads review **Complaint Investigation Report** andQuality Management Director approves final **Complaint Investigation Report.**

All defined CAPA measures are carried out in accordance with **SOP-07 CAPA Management**.

The Marketing Department sends the Customer a formal Complaint response in three (3) days. This response shall contain the company’s decisions regarding:

* decision for Complaint foundation (founded or unfounded),
* completion of investigation,
* declaration on the subsequent elimination of the defect and the reasons that caused it (without description of specific measures to be taken).

## Product Recall

### Quality Defects Classification

Quality Defects classification is based on the risk impact to patients/public. Quality Defects consideration shall base on principles and approaches of **SOP-09 Quality Risk Management.**

***Table 1: Quality Defects Classification Description and Examples***

|  |  |
| --- | --- |
| **Class** | **Description and Examples** |
| Class I | Quality Defects are dangerous/ potentially life-threatening when they predictably or probably could cause a serious health risk/adverse reaction or even death and could cause permanent debilitating health issues.**Examples:*** Wrong product (label and contents are different products).
* Correct product but wrong strength, with serous medical consequences.
* Microbial contamination of sterile injection or ophthalmic product.
* Chemical contamination with serious medical consequences.
* Mix up of some products with more than one container involved.
* Wrong active ingredient in a multi-component product with serious medical consequences.
* Lack of effectiveness for a life-threatening condition.
 |
| Class II | Quality Defects could cause illness, temporary or medically reversible adverse health problem or mistreatment, and the recovery of the patient is likely.**Examples:*** Mislabeling e.g., wrong or missing text or figures.
* Missing or incorrect information leaflets or inserts.
* Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences.
* Chemical/ physical contamination (significant impurities, cross-contamination, particulates).
* Mix-up of products in containers.
* Non-compliance with specification (e.g., assay, stability, fill/weight, or dissolution).
* Insecure closure with serious medical consequences (e.g., cytotoxics, potent products).
* Lack of efficacy/effectiveness for medical condition that is not life threatening.
 |
| Class III | Quality Defects may not pose a significant hazard to health i.e., low risk to health but Recall may be initiated for other reasons, due to quality, safety, or efficacy concerns. |

**Note:**

**Class I or Class II quality defects may require an urgent safety recall.**

**Class III quality defects may require normal non-safety recall.**

### Recall Levels

In determining the Recall type (level or depth), the principal factors to be considered are:

* the significance of the hazard (if any),
* the channels by which products have been distributed, and
* the level to which distribution has taken place.

***Table 2: Recall levels***

|  |  |
| --- | --- |
| **Level** | **Definition** |
| Wholesale level | Product held by a third party for distribution to retailers or other organizations before being supplied to end users. |
| Retail Level | Includes community pharmacies, medical, dental and other healthcare professionals, and general retail outlets. |
| Consumer/Public Level | Patients and other consumers.May include: wholesale and retail levels.This level of Recall is used where there is a significant risk of harm to the consumer or user. |

### Recall process

#### Assembling Recall Management Team

Quality Management Director shall designate Recall Coordinator and Recall Committee Members. Recall Committee Members shall represent organization key functions and stakeholders such as: Quality Organization, Manufacturing, Pharmacovigilance, Regulatory, Supply Chain, Marketing, Legal. All RCC members shall be listed in actual list **Recall Committee Members** according to **Recall Committee Members Form.**

#### Recall initiation

Product Recall might be initiated by:

* NBE-Therapeutics, as a result of Complaints, Deviations, Nonconformances investigation, pharmacovigilance considerations regarding safety or efficacy (voluntary Recall).
* local or overseas health authorities, or from information received directly from such authorities (statutory Recall).

The Recall Coordinator (Quality Management Director or designated person on this role) organizes and coordinates all Recall activities. If there is a need to initiate a Recall, Recall Coordinator arranges a meeting of the RCC immediately.

RCC shall decide

* whether Recall is required or not,
* what is the Quality Defect Class,
* what is the Recall Level,
* which are the Recalled products (lots/batches),
* which are the Recall related actions,
* who shall be notified and how.

**Recall shall be initiated for: Class I within twenty-four (24) hours; Class II within forty-eight (48) hours; Class III within five (5) days.**

After discussion and assessment, RCC Members approve **Recall Statement** according to **Recall Statement Form**.

#### Recall Notification

The Operation Department, specifically Warehouse and Supply Chain (WSC) Team sends approved **Recall Statement** to all identified Customers for the particular product distribution chain. The product distribution chain is determined based on the product distribution records. The WSC Team shall provide to Recall Coordinator and Recall Committee Members product related distribution records summary for all affected products and Customer contact details.

Distribution records shall contain further sufficient Customer’s information:

* + addresses
	+ phone and/or fax numbers inside and outside working hours
	+ product Lots/Batches numbers
	+ delivered product amounts

#### Rapid alert system

In case of a severe health hazard, the rapid alert shall be initiated by NBE-Therapeutics parallel to public warning in- line with the applicable notification timeline, to make sure that information is conveyed to end-users i.e., patients.

An official communication shall be written with all respective authority’s representatives in a timely manner. The list of QP/ contact persons shall be included in this communication.

All concerned regulatory authorities shall be informed in advance in cases where products are intended to be Recalled. For very serious issues, i.e., those with the potential to seriously impact patient health, rapid risk-reducing actions such as a Product Recall may have to be taken in advance of notifying the regulatory authorities.

For all exported products, all country representatives/agents/importers shall be informed as soon as the decision for the Recall is taken. A list of contact details of Qualified Person, MAH, and importer shall be maintained separately product-wise. In case of export, the Recalled Product shall be destroyed in the exported country in the presence of local regulatory authority, if required, or in the presence of representative/importers, if required.

#### Recall performance

Recall Coordinator monitors Recall performance and status for each particular product distribution chain. Recall Coordinator this status on a daily basis until its completion and reporting. If there are difficulties or delays in providing information or taking any actions by distribution stakeholders, Recall Coordinator escalates this to Recall Committee Members for appropriate decision-making.

#### Recall completion and reporting

After Recall completion, Recall Coordinator prepares a **Recall Report** according to **Recall Report Form**. Recall Committee Members review, discuss and approve final **Recall Report.**

The **Recall Report** shall be supported by appropriate evidence (communication evidence, stock transactions, disposal/destruction records, distribution records, etc.). Full product reconciliation shall be done and explained in report.

In case of Deviations, Nonconformances detected during Recall execution, process participants shall follow **SOP-06 Deviation and Nonconformance Management and SOP-07 CAPA Management**.

### Mock Recall trials

This test shall be carried out once a year and cover both within office-hour situations as well as after- hours office situations.

If any product is actually Recalled as per the above-mentioned procedure in the current year, there is no need to carry out Mock Recalls as the effectiveness of the arrangements of Recall procedure shall be established from the records of the actual Recalled product.

Recall Coordinator plans and organizes annual Mock Recall. Recall Coordinator shall select any batch of any product which should be a fast-moving item having the farthest distribution chain. The Wholesale level of Recall shall be assigned. The batch selected shall have been distributed.

This exercise shall be performed only to verify the effectiveness of Recall, but an actual product Recall will not be performed. All Customers (distributors) and other stakeholders shall be informed that it is not a real Recall, but a mock Recall process intended for evaluation of Recall system.

The Mock Recall is considered successful if all the records are accurate and the tracing back to the stock level is completed.

After completion of Mock Recall, Recall Coordinator shall circulate the **Recall Report** to Recall Committee Members for review and assessment.

In case of Deviations, Nonconformances detected during Recall execution, process participants shall follow **SOP-06 Deviation and Nonconformance Management and SOP-07 CAPA Management**.

Mock Recall outputs shall be taken into consideration during **Management Review.**

# Applicable documents

SOP-01 Documentation Management

SOP-04 Management Review

SOP-06 Deviation and Nonconformance Management

SOP-07 CAPA Management

SOP-09 Quality Risk Management

SOP-10 Training Management

# Appendices

The following appendices are integral part of this SOP:

Appendix Complaint Notification Form

Appendix Complaints Log Form

Appendix Complaint Preliminary Assessment Form

Appendix Complaint Invevtigation Plan Form

Appendix Complaint Investigation Report Form

Appendix Recall Committee Members Form

Appendix Recall Statement Form

Appendix Recall Report Form

# Document revision history

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