**Document approval**

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**Table of Contents**

[1 Purpose 3](#_Toc120201326)

[2 Scope 3](#_Toc120201327)

[3 Responsibilities 3](#_Toc120201328)

[4 Definitions, terms and abbreviations 4](#_Toc120201329)

[5 Workflow 4](#_Toc120201330)

[5.1 General 4](#_Toc120201331)

[5.1.1 Auditing resources 5](#_Toc120201332)

[5.2 Planning 5](#_Toc120201333)

[5.2.1 Internal Audits 5](#_Toc120201334)

[5.2.2 External Audits 6](#_Toc120201335)

[5.3 Initiation 7](#_Toc120201336)

[5.3.1 Internal Audits 7](#_Toc120201337)

[5.3.2 External Audits 7](#_Toc120201338)

[5.3.3 Deviations from the annual Audits plans 7](#_Toc120201339)

[5.4 Preparation 7](#_Toc120201340)

[5.5 Execution 8](#_Toc120201341)

[5.5.1 Nonconformance notification 8](#_Toc120201342)

[5.6 Reporting 9](#_Toc120201343)

[5.7 Documentation 9](#_Toc120201344)

[6 Applicable documents 10](#_Toc120201345)

[7 Appendices 10](#_Toc120201346)

[8 Document revision history 10](#_Toc120201347)

# Purpose

The purpose of this Standard Operating Procedure (SOP) is to define the procedure for carrying out Internal Audits in various Departments at NBE-Therapeutics and external Audits of suppliers.

# 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 CODETrainingTitle>.

# Responsibilities

Responsible for the content of this SOP is Quality Management Director

|  |  |
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| **Role** | **Definition/Task** |
| Auditee | * informs relevant employees about the objective and agenda of the Audit
* appoints responsible person of staff to accompany Audit Team
* provides all resources needed for the Audit Team in order to ensure an effective and efficient Audit process
* provides access to the facilities and evidential material as requested by the Auditors
* cooperates with the Auditors to permit the audit objectives to achieve
* determines and initiates core action based on the audit findings
* ensures compliance in proper way
* reviews DevNotificationTitle>s
* investigates detected Nonconformances
* initiates, prepares, submits CAPA Requests related to Nonconformances. Acts as CAPA Owner.
 |
| Auditor | * plans and carries out Audit
* collects evidence and gathers information
* prepares, approves Audit Plans, Audit Reports, <
* prepares DevNotificationTitle>s
 |
| Quality Organization | * prepares Internal Audits Plans, External Audits Plans
* maintains Auditors List
* assigns Auditors for particular Audits
 |
| Quality Management Director | * approves initial Internal Audits Plans, External Audits Plans and any further changes and amendments.
* appoints and approves permanent NBE-Therapeuticss Auditors
* keeps Audits related records
 |

# Definitions, terms and abbreviations

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| --- | --- |
| **Term/abbreviation** | **Definition at NBE-Therapeutics** |
| Audit | Systematic, independent and documented process for obtaining Audit evidence and evaluating it objectively to determine the extent to which Audit criteria are fulfilled (e.g., regulation requirements, internal standards, etc.). |
| Audit Conclusion | Outcome of an Audit, after consideration of the Audit objectives and all Audit Findings |
| Audit Criteria | Set of policies, procedures or requirements used as a reference against which objective evidence is compared. |
| Audit Findings | Results of the evaluation of the collected audit evidence against audit criteria.Audit Findings indicate Conformity or Nonconformity. |
| Audit Evidence | Records, statements of facts or other information, which are relevant to the audit criteria and verifiable. |
| Audit Team | One or more persons conducting an Audit, supported if needed by technical experts. |
| Audit Scope | Extent and boundaries of an Audit. |
| Auditee | Organization / Department being audited. |
| Auditor | A person who has the technical qualification, the experience, and trained to perform Audits. |
| Critical Observation | System Deviations that have a confirmed impact on the Product Integrity and may cause product Recalls and patient health risk. |
| External Audit | An audit in which the audited party is a supplier of services or materials. |
| Internal Audit (Self- Inspection) | An onsite verification of activity used to determine effective implementation of documented QMS. |
| Minor Observation | Deviation without impact on Product Integrity. |
| Major Observation | General established system deviations that have potential impact on Product Integrity. |
| Product Integrity | Any negative impact on either/and Safety, Identity, Strength, Purity and Quality of the product or process. |

# Workflow

## General

An Audit is a tool for:

* current processes/products/services risk level measuring,
* compliance verification with external and internal industry standards, applicable regulatory cGMP requirements,
* level of compliance measuring of material and services suppliers according to NBE-Therapeutics’s standards, requirements and bilateral agreements,
* making decisions on cooperation with suppliers of materials and services,
* investigations of Deviations, other nonconformities related to Products, Materials, Services,
* a systemic examination of QMS and related processes,
* for compliance verification with applicable regulatory cGMP requirements,
* for determination the effectiveness in meeting specified objectives.

All involved personal is responsible for ensuring appropriate handling of Audit process flow.
Audits Management process flow is described on ***Figure 1.***

***Figure 1:*** ***Audits Management Process***

### Auditing resources

Quality Management Director appoints and approves permanent NBE-Therapeuticss Auditors consisting of SMEs in their respective areas. The members of the Audit Team may be appointed from inside the company, or get support from an external source (e.g., Freelance Auditor) on behalf of the business.

The assigned Audit Team consists of independent, experienced, trained company employees who can objectively verify the implementation of the developed methodologies and procedures.

Quality Organization maintains **Auditors List** according to **Auditors List Form.**

Auditors shall be selected on the basis of following criteria:

* Candidate shall have relevant experience, knowledge and auditing skills
* Candidate shall have minimum experience of one (1) year in the company
* Candidate is aware of the Audit procedure and has Audits participating experience (as Auditor, Auditee, Observer)

Annual training program for this persons shall be adjusted according to this auditing role in NBE-Therapeutics accordingly.

## Planning

### Internal Audits

Quality Organization prepares **Internal Audits Plan** annually covering all Departments according to **Internal Audits Plan Form**. Each Department shall be audited frequently, at least annually. The vertical and horizontal approach shall be applied for Internal Audits planning.

Quality Management Director approves initial **Internal Audits Plan** and any further changes and amendments.

#### Horizontal audit approach

This approach can be applied in case of any unforeseen circumstances (Investigations, Recalls, Deviations, Nonconformances, Complaints). This type of audit is unplanned, i.e., it is not included in the annual schedule.

Examples:

1.) When the Quality event occurs, an Internal Audit shall be carried out as part of the investigation. This type of audit is called “for-cause-audit".

2.) The company received a comment during the GMP inspection about an unsatisfactory training program. As part of the Investigation and CAPA, such training activities are audited in all departments.

#### Vertical audit approach

A vertical audit approach is chosen for various activities within a particular Department. For example, a scheduled audit is executed at the warehouse following the vertical approach.

During this type of Audit, all particular activity sections related to Department’s responsibility are evaluated. This case may include, but is not limited to

* Auditee Department structure,
* GMP compliance,
* Access management,
* Area controls (e.g., temperature and humidity controls)
* Training and safety
* Data integrity

Regular Internal Audits per schedule follow the vertical approach according to **Internal Audits Plan**. This approach may be used complementarily, or based on an event, Market Complaint, Customer Complaint, Audit Observations, Deviations, Nonconformances and repetitive failures.

### External Audits

Quality Organization prepares **External Audits Plan** annually covering all Departments according to **External Audits Plan Form**.

When planning external audits, the following factors should be considered:

* approved CAPA actions as a result of investigations or risk assessments
* established frequency of re-audits
* planned changes in suppliers of materials or services (new or revision of existing ones)
* Availability and willingness of the supplier to accept the audit
* Available resources (Auditors)

Quality Management Director approves initial **External Audits Plan** and any further changes and amendments.

## Initiation

### Internal Audits

Two weeks before planned Internal Audit period Quality Organization assigns Auditors for Internal Audit. Notifies assigned Auditors, defines the scope, purpose and objects of Internal Audit and auditing criteria.

Auditors confirm their participation, request internal Auditee provide and confirm appropriate Auditing period (exact Internal Audit dates).

### External Audits

One month before the planned External Audit period Quality Organization assigns Auditors for External Audit. Notifies assigned Auditors, defines the scope, purpose and objects of External Audit and auditing criteria.

Auditors confirm their participation, contact, negotiate, request internal Auditee provide and confirm appropriate Auditing period (exact External Audit dates). Provides Auditee with detailed **Audit Plan** upon request.

In case of disagreement or other circumstances, the Auditors escalate the Issue to Quality Organization to resolve it.

### Deviations from the annual Audits plans

An Internal or External Audit can be expedited or postponed in the following situations:

* The Internal Audit area is under shutdown during planned period of Audit.
* For the proposed period a regulatory Audit is scheduled.
* Proposed period is inconvenient to Auditee due to other commitments.

Advancing or postponing Audit dates in such cases shall be done only after authorization of Quality Organization representative. Internal Audit can be postponed by one month. For an External Audit, longer deviations are possible depending on reasons and circumstances that cannot be influenced.

## Preparation

Auditors prepare, approve **Audit Plan** according to **Audit Plan Form** and provide Auditee and Quality Organization one week prior to the Audit.

In case of External Audits, this period may be extended according to the requirement of the Auditee or respective approved/reached mutual agreements.

**Audit Plan** contains the following details:

* Auditee,
* Audit Period,
* Purpose,
* Scope,
* Audit Criteria,
* Audit Agenda
* Audit Team approval

## Execution

Auditors shall have an opening meeting with Auditee and explain the purpose of Audit, Audit procedure being followed and follow ups.

During the Audit Auditors shall cover all related areas, processes and systems, and ensure that Audit Agenda and procedure are being followed.

Auditors shall:

* be free from bias and influences, which could affect objectivity
* report critical Nonconformance to the Auditee immediately after Discovery
* remain within the Audit Agenda
* exercise objectivity. As far as possible objective evidence shall be collected
* for traceability of Audit Findings of Nonconformity, mention the details such as product name, batch no., reference document no., page no., line no., date, name of the person

Evidence shall be collected through interviews, examination of documents, and observation of activities and conditions in the areas of concern.

Clues suggesting Nonconformance are recorded, including those not explicitly outlined in any documents, instructions, or SOPs. Such clues can indicate systemic issues and should be investigated further.

In case of uncertainty, information gathered through interviews may be cross-checked by verifying the same information from other sources, such as physical observation, measurements, and records.

At the end of the Audit, in closing meeting, Auditor(s) shall discuss with the Auditee Audit Findings, areas of concern, areas for improvement in presence of all concerned personal.

### Nonconformance notification

If any Nonconformances during the Audit were found Auditor Team shall issue **Deviation and Nonconformance Notification record** in accordance with **Dev NC CODE Deviation and Nonconformance Management,** according to which the Auditor becomes an observer and initiator of the Nonconformity.

In closing meeting, Auditor Team notifies Auditee about discovered Nonconformance.

Auditee reviews, provides comments and explanations, signs the **Deviation and Nonconformance Notification record**.

After Audit Auditors submit **Deviation and Nonconformance Notification** record to Quality Organization for further investigation and appropriate CAPA measurements implementation according to **Dev NC CODE Dev NC CODEDevMng\_Title>.**

Quality Organization assigns the Investigators roles to Auditors, Auditee’s representatives and any other impacted Departments representatives. Auditee’s representative shall be assigned as the CAPA Owner according to **CAPA Management CODE CAPA Management**, if the Nonconformance does not go beyond the responsibility of the Auditee.

In other cases, Quality Organization determines the CAPA Owner based on Nonconformance nature and affected areas.

For External Audits the investigation shall cover at least previously received Materials or services and their potential impact on manufactured Products. Quality Organization becomes a CAPA Owner for CAPA measurements related to external Nonconformances.

In this case, CAPA Owner accepts, monitors execution progress, monitors efficiency for CAPA measurements related to External Audits Nonconformances.

If it is not possible to check the effectiveness of CAPA measures taken after completion of their implementation, such effectiveness monitoring shall be carried out during the next Audit.

## Reporting and Closure

Not later than two weeks after the end of the Audit, Auditor Team prepares **Audit Report** according to **Audit Report Form**.

Audit Report shall include:

* Auditee details
* Audit period
* Purpose
* Scope
* Audit Criteria
* Introduction (description of Auditee, previous Audits results, CAPAs implementation status)
* Audited areas description, evaluation, related findings, evidences
* Audit Findings (description, assigned Nonconformances DNRNs and classification, Audit Criterias)
* Identification of opportunities for improvement
* Audit Conclusion

**Audit Report** shall be signed by all Auditors and approved by Quality Organization representative.

## Documentation

Quality Organization keeps all Audits related records in respective audits files of suppliers and internal departments according to Archiving CODE Archiving. Other records related to Nonconformances investigations and CAPA measures implementation handled according to respective procedures.

# Applicable documents

Quality Manual CODE Quality Manual

Documentation Management CODE Documentation Management

Dev NC CODE Deviation and Nonconformance Management

CAPA Management CODE CAPA Management

Quality Risk Management CODE Quality Risk Management

Training Management CODE Training Management

Complaints and Recalls Management CODE Complaints and Recalls Management

Material Management CODE Material Management

Outsourced activities Management CODE Outsourced activities Management

# Appendices

The following appendix(ces) are integral part of this SOP:

Appendix Internal Audits Plan Form

Appendix External Audits Plan Form

Appendix Auditors List Form

Appendix Audit Plan Form

Appendix Audit Report Form

# Document revision history

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