**Document approval**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Name** | **Date** | **Signature** |
| **Author’s designation**  **e.g., Quality Specialist** |  |  |  |
| **Reviewer’s designation**  **e.g., Quality Management Director Deputy** |  |  |  |
| **Approver’s designation**  **e.g., Quality Management Director** |  |  |  |

|  |  |
| --- | --- |
| **Effective Date** |  |

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# Purpose

The purpose of this Standard Operating Procedure (SOP) is to define the procedure for the creation, revision, obsolescence, and control of GxP Main Documents as Master Documents (MD), Policies (POL), Standard Operating Procedure (SOP), Working Instructions (WI) as well as their associated Appendices (forms, reports, records, plans).

# 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 applies to all NBE-Therapeutics personnel and Departments, who may create, revise, approve, or obsolete Main Documents including Appendices within a GxP environment.

# Responsibilities

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

| **Role** | **Definition/Task** |
| --- | --- |
| Approver | Employee who approves documents and/or records. |
| Author | The person who is responsible for the creation, content and regular maintenance of a specific document. The term is also used when the person has taken over the responsibility for the document from a predecessor. |
| e.g., Quality Management Director | approves all GxP-documents except Master Documents,  approves related DCRs for Main Documents,  Defines Main Document’s Effective Date. |
| e.g., CEO | approves Master Documents, strategy outcome of the executive committee and Annual Product Quality Review summary. |
| Line Manager | determines the scope of validity and training as well as the Effective Date,  ensures that employees completing **Document Change Request** **Forms** are trained on this procedure,  reviews all documents authored/owned by their functions and roles. |
| e.g., Quality Specialist | processes all document related requests,  assigns the document codes,  ensures that the creation or revision of documents is completed on schedule,  checks for consistency, comprehension, plausibility, compliance with regulatory and internal requirements, redundancy,  maintains the NBE-Therapeutics document lists and statuses,  ensures adequate storage and archiving of QMS-related documents. |
| Reviewer | is an employee who reviews:  the technical content of documents (accuracy, completeness, comprehension, plausibility)  the document compliance with this SOP. |

# Definitions, terms and abbreviations

| **Term/abbreviation** | **Definition at NBE-Therapeutics** |
| --- | --- |
| Appendix | Appendices (Appendix, Form, List, etc.) constitute integral parts of main documents (e.g., SOP, WI, MD) and shall mean the documents, which are attached to this main document. |
| Approval Date | Approval Date is the date on which a document is approved by the authorized person. Main Documents are not automatically valid from this date but from the specified Effective Date. |
| e.g., CEO | is the highest-ranking executive in the company, whose primary responsibilities include establishing the vision, making major corporate decisions, managing the overall operations and resources of the company, acting as the main point of communication between the board of directors (the board) and corporate operations, and being the public face of the company. |
| Change Management | is a systematic approach to proposing, evaluating, approving, implementing, and reviewing all changes across the entire product lifecycle. |
| DCR | DCR is the abbreviation for Document Change Request. Initial step for change or creation of any GxP Main Documents. |
| Effective Date | The Effective Date is the date of implementation of the Main Documents after approval and training. |
| Job Description | Job Description is a document summarizing the duties of an employee with regard to the tasks and responsibilities assigned to the employee in particular role(s). |
| Main Document | A Main Document is either a Master Document (MD), a Policy (POL), a Standard Operating Procedure (SOP), or a Working Instruction (WI) including its Appendices and forms. Main Documents must be trained before they are put into effect. |
| Master Document (MD) | A Master Document contains a basic description of the quality concept at NBE-Therapeutics. |
| n/a | n/a refers to not applicable and explains the status when something does not apply. |
| SOP | SOP refers to Standard Operating Procedure and contains the mandatory, approved description of a company-specific work process, the materials and equipment required to carry it out and the responsibilities involved. |
| WI | WI refers to Working Instruction which is a written instruction describing the individual/specific steps of recurring operations, including the materials and methods to be used. |

# Workflow

## General Principles

GxP-related documents and records relate to actions or operations that may directly or indirectly affect product quality, patient safety or data integrity.

There are four (4) main types of documentation used to manage and record GxP compliance as described in the **MD-01 Quality Manual**:

* + MDs,
  + POLs,
  + Instructions (e.g., SOP, WI),
  + Records, reports, plans, forms, checklists (documentation of resulting activity, e.g., qualification efforts).

The purpose and type of content of all categories of GxP documents and records used shall be defined. Records management systems are in place that describe the controls for the issuance, review, replacement, and withdrawal of all documents (both paper and electronic). Change histories are maintained, including the rationale for creating new documents and revising existing documents, so that the current status of all documents is known. Where changes have a significant impact on the GxP process, they are managed through the **SOP-05 Change Management** procedure.

If training is required prior to the use of the document due to the introduction of a new procedure or a change to an established procedure, it shall be provided according to **SOP-10 Training Management** to affected individuals before they use the new/revised procedure.

If the documents contain instructions, e.g., provide rules, guidelines or characteristics for an activity or its results, e.g., processing, packaging and testing instructions, specifications, SOPs, they are subject to periodic review at specified intervals, which are described in the relevant procedures. Following the review, the document is updated as necessary. However, if a document needs to be updated, it is updated at the time the change is required, regardless of the review period specified.

The most recent version of the approved document is available for use by employees and systematic checks are carried out to avoid the use of obsolete documents, either by automatic replacement of electronic documents or by physical management of paper controlled copies.

All principles of Good Documentation Practice shall be applied according to **SOP-02 Good Documentation Practice.**

## Document Change Request

Before creating or revising a document, all information required by Quality Organization is to be provided in a procedure according to **Appendix Document Change Request Form**.

* + Document Reviewers, Approvers either approve or reject the Request.
  + After final review and approval of **Document Change Request Form** Quality Organization initiates the document’s creation, revision or obsolescence.

The Document Change Request numbering scheme is:

* + DCR,
  + Dash,
  + Consecutive numbering in format XXX (consecutive number starting with 001).

All Requests are logged by Quality Organization in Documents request List and contains:

* + DCR Number
  + Document’s Author/Owner
  + Document Number
  + Document Title
  + Revision Number
  + Revision Purpose
  + Target Effective Date,

Note: Appropriate Effective Dates should allow enough time to obtain required approval signatures and training.

### Type of Change

The following type of changes are to be provided in the Request Form:

* + - * **Minor Change** –This type of change is to correct formatting, identified typographical errors or other minor changes that do not impact content. Training is not required.
      * **Major Change** – This type of change is related to content updates e.g., implementation of regulatory requirements, corrective action / preventive action (CAPA) changes, implementation of new forms. Training is required.
      * **New** – A new policy or procedure. Training is required.
      * **Obsolete** – Removing a document from publication because it is no longer relevant to the functions of the company. Training is not required.

One **Document Change Request Form** can be completed for a single document or a bundle of documents that are implemented together.

When completed, the Author submits the filled **Document Change Request Form** to related Departments and Quality Organization for review and approval. The Document creation shall be started by Author upon approval of the **Document Change Request Form**.

## Internal Document Identification

All Documents shall be identified by combination of the Main Document’s code, the document’s title, the document’s category (Appendix, Form, List, Plan) which are assigned by Quality Organization.

The internal document unique identifier includes:

**Main Document Code**

* + - * two (2) to three (3) letters corresponding to the abbreviation for the related Main Document category:

**MD** Master Documents,

**POL** Policies,

**SOP** Standard Operating Procedures,

**WI** for Working Instructions),

* + - * dash,
      * consecutive numbering in format **XX** (consecutive number starting with **01**),
      * space,

**Document Title**,

* + - * Space

**Main Document appendix type** (Appendix, List**,** Form**,** Plan)

**Examples:**

MD-01 Quality Manual

MD-01 Organigram Appendix

SOP-01 Documentation Management

SOP-01 Document Change Request

SOP-01 SOP and WI Form

## Content of Main Document

To ensure that the actual process is described accurately and in detail, the employees at operational level who carry out the process on a regular basis must be involved. The following rules must be observed:

* + - * + The actual process must be described in the correct sequence.
        + All the necessary working steps and responsibilities must be outlined.
        + The text must be brief (concise) and clear language must be used.
        + Terms and abbreviations that are not widely understood must be avoided or explained.
        + “The use of “may, might, should, could” is to be interpreted that the activity or process is optional and are therefore to be avoided when describing processes (rather give clear instructions).
        + The use of “shall or must” is to be interpreted that the activity or process is required.
        + Vague or interpretable expressions (e. g., long enough, as usual, about) must also be avoided when the process is described.

SOPs and WIs shall be prepared according to **SOP and WI** **Form** and shall contain:

* + - * + **Document approval** - Approvals by the Author and all involved employees to denote that the procedure is to be carried out as defined and that it is ready to release.
        + **Table of Contents** – the list of all related sections in document.
        + **Purpose** - High level description containing the purpose of the document.
        + **Scope** - Covered activities and business areas, as well as excluded areas as applicable.
        + **Responsibilities** - A description of who is responsible for carrying out the procedure.
        + **Definitions** - Explanation of terminology used in the procedure.
        + **Workflow -** Steps/action/requirements for completion of a task or process. If steps of a procedure are not sequence dependent (can be performed in any order), it is acceptable to use bullets in lieu of numbering.
        + **Applicable Documents** - Internal or external document that provide additional guidance or directly impact the process/procedure.
        + **Appendices -** Documents used to record activity and or processes. Attachments can be additionally used to complete certain processes or activities conducted in the Appendices.
        + **Revision History** - Denotes the revision history of the document with description of past revisions.

Any section not applicable to a specific SOP shall be noted as “n/a”.

This content does not apply to MDs and POLs.

## Appendices

Appendices are created separately and are not included in the page numbering of the Main Document. However, they are integral parts of the Main Document and are accordingly revised and always stored together.

All Appendices must be listed in **Section** [**7**](#_bookmark25) with their exact title and type.

## Review Flow

All documents are electronically created and reviewed at NBE-Therapeutics either in Electronic Documentation Management System or on the network. Whenever technically feasible, reviews shall be made using “track changes” making visible the revisions to the previous version. When this is done, the following principles must be observed:

* + - * + The Author or Reviewer shall be any person who is familiar with the process being described.
        + The Reviewer is at least the responsible Line Manager.
        + The Author and the Reviewer must not be the same person.
        + The Approver is e.g., CEO for all Master Documents (**MD**); and e.g., Quality Management Director or delegate/e.g., CEO for GxP documents (e.g. **POL**, **SOP**, **WI**), or the responsible Line Manager(s) for non-GxP documents.

**Note:** Approval flows and roles (Author, Reviewer, Approver) for any other GxP documents (Plans, Protocols, Reports, Records) shall be explained in related SOPs.

Development, discussion and other types of collaboration in the process of creating or modifying documents can be carried out using local network resources, cloud solutions, e-mail.

For adequate traceability of changes, it is advisable to use such tools for working with documents as "Comments", " Track Changes”.

Reviewer of GxP document reviews the Document to ensure:

* formatting of the document is consistent with this SOP,
* appropriate references are included and correctly referenced within the document text and in the references section.

Although it is not required to send non-GxP document to Quality Organization for review, it is however highly recommended to ensure that internal standards are met.

## Approval Date

Main Documents including their Appendices are approved at NBE-Therapeutics electronically or manually. However, the approved Main Document is not automatically comes in force from this date, but only after successful document training from the explicitly stated valid/Effective Date.

## Effective Date

The Effective Date of a Main Document is determined by e.g., Quality Management Director in consultation with the responsible Line Manager.

* Where no training is required (e.g., plans, reports, records), there is no Effective Date but only an Approval Date.
* e.g., Quality Management Director will apply the Effective Date to the Main Document including the Appendices.
* Previous revisions (if applicable) and obsolete documents Copies shall be returned to Quality Organization, marked “OBSOLETE” and taken out of the active internal SOP publication file.
* Quality Organization will release and distribute the new revision of document.
* NBE-Therapeutics personnel in the scope of validity shall have appropriate access to the valid version of Main Documents including their Appendices.

## Determination of training needs

The Document Scope and required training activities for Main Document is determined by Document’s Authors, Reviewers and Approver during **Document Change Request** phase. The training details are defined and documented in accordance with **SOP-10 Training Management**.

## Document Control and Distribution

All valid Effective documents are stored in [Electronic Document Management System] and are available at any time for employees defined in the scope of validity of the document.

## Controlled printouts and copies

[Electronic Document Management System] allows employees to print documents when needed. The following instructions in the footer of the documents guarantees the adequacy of printouts only at the moment of issuance:

Footer text:

**“[Printed Main Documents are valid only on the date of printing. Printed Appendices for recording are valid only when issued by the assigned responsible employee with date and Initials, either as handwriting on the first page of printouts or as watermarks in protected digital documents. <Printing Date and Time>”.]”**

* The date and time of printing also shall appear in the footer enabling traceability.
* When required, paper-based authorized copies (Main Documents excluded) can be issued by Quality Organizaton or the responsible Line Manager and shall be stamped only as follows:

"***Authorized copy, date, employee's Initials***" on each sheet.

## Main Documents Review

* Main Documents including Appendices shall be reviewed no later than every two years. All planned Main Document revisions shall be initiated by Quality Organization according to documents revision plans and schedules. Quality Organization shall assign and notify the document reviewer (Author) 2 months before the end of latest revision date. For planned revision purpose the Author shall initiate this process according to **Document Change Request Form**.
* The latest revision dates are based upon the most recent Effective Date of the document plus established standard revision period (e.g. for 2 years revision frequency the document revision begins on 23 month and ends at the end of 24 month).
* One **Document Change Request Form** is used for the Main Document including all Appendices. The target Effective Date is 30 days following issuance of **Document Change Request Form**.

If no need for change is identified during the periodic review by the Author, the Author documents the review in the document revision history as follows:

***"Periodic planned review. Workflow and responsibilities are unchanged”.***

**The version number of each updated document is incremented regardless of whether changes were recorded or not to make the periodic review clearly visible to everyone**. The updated approved document must be trained (for Main Documents) or communicated prior to its implementation in accordance with **SOP-10 Training Management**.

## Record Managing and Labelling

Each Main Document in the QMS must define how records resulting from execution of such a document must be managed, i.e., it must specify the following:

* Record code (record number, version number, and record title),
* Hardcopies and softcopies storage places and locations for GxP regulated documents,
* Person responsible for the storage,
* Persons responsible for review, approval,
* Controls for record protection.

While records are in use, the person responsible for maintaining the record guarantees exactness of the entered data, and prevents unauthorized entry, changes and destruction of such records as described in the relevant documents.

## Record availability and retrieval

Employees in the scope of validity of the report may access stored records as defined in the Main Document. If the sensitivity of certain records is such that permission for access must be obtained from a responsible Line Manager, this must be stated in the related Main Document.

Access and retrieval rights for records are determined by the Line Managers. Quality Organization is responsible for destroying all electronic and paper-based records of which the retention time has expired or ensuring that the destruction of sensitive data occurred.

## Main Documents List

All activities related to document creation, revision and control shall be entered in the Main Documents List stored on the NBE-Therapeutics’s local server or on electronic cloud. Main Documents List is a summary table (e.g. excel file format .xlsx) containing all internal and external documents used for purposes of QMS in NBE-Therapeutics. Main Documents List is only used to combine and reflect the data related to actual state and status of each particular Main Document. Main Documents List is maintained exclusively by Quality Organization and all NBE-Therapeutics employees have only reading rights to it. The Quality Organization is responsible for ensuring that all relevant data is entered in a timely manner.

The status of any QMS related document must be verifiable at all times in [Electronic Document Management System] (or using the hard copies) and the Master Documents List.

The following data (including but not limited to) shall be recorded and maintained in connection with this SOP in the Main Documents List:

* Document number,
* Document title,
* Version number of the document,
* Revision status (draft, in review, approved, in training, valid),
* Effective Date (DD.MM.YYYY),
* Responsible for the content,
* Next revision on DD.MM.YYYY,
* Author, Reviewer(s) and Approver,
* Applicable Appendixes documents titles, codes, types,
* Applicable regulations.

## Archiving

Original signed 'master copies' of both paper and electronic GxP documents (including various types of media such as tapes or disks, as well as sample storage) may be kept at the workplace when immediate access to them is required, however, as soon as they become 'inactive', they are transferred from this temporary storage to the designated secure archive. All Archiving procedures shall be executed according to **SOP-16 Archiving**.

# Applicable documents

MD-01 Quality Manual

SOP-02 Good Documentation Practice

SOP-05 Change Management

SOP-10 Training Management

SOP-16 Archiving

# Appendices

The following Appendix is integral part of this SOP:

Appendix Document Change Request Form

Appendix SOP and WI Form

# Document revision history

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Valid from** | **Description of the revision** | **Reason for the revision** |
| 1 | See header | Initial SOP introduction | QMS implementation |