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Revision:

Status:

Effective Date:

1 OBJECTIVE

The objective of this document is to describe the management of corrective actions and preventive actions (CAPA) as essential process for continuous improvement.

2 SCOPE

This document applies to everyone involved in CAPA management at Grünenthal group (GRT).

This process is mandatory for all CAPAs derived from QMS processes (e.g., deviations, complaints, audit findings), GxP-related opportunities for improvement (stand-alone CAPAs) and is optional for all other CAPAs, whenever deemed appropriate and beneficial.

CAPAs owned by Drug Safety, EHS or external parties are not in scope.

3 RESPONSIBILITIES

The responsibilities of users assigned to the following roles are described in more detail in section 5. It can be possible that one person has more than one role. In any case it must be ensured that at least two different persons are involved.

In case an external party must be involved, a person within/ acting on behalf of GRT having the relevant role is responsible to follow-up and document the outcome.

Function/ Role	Responsibility
CAPA Approvers	<p>CAPA Approvers are: Head of the affected department(s)/ designee and the respective responsible QA function.</p> <p>The approvers confirm by their signature the following points:</p> <p>Head of affected department(s) or Designee - business approver:</p> <p>Ensure the CAPA plan is adequate as well as appropriately timed to eliminate the root cause or mitigate risk. Ensure appropriate resources are available to execute the plan. Has ultimate accountability for root cause identification and appropriateness defined actions, timely implementation and CAPA effectiveness.</p> <p>QA function (see under “CAPA QA”)</p>
CAPA Owner	<p>Person of the affected department or Business Process Owner of the affected process (in which root cause was happening).</p> <p>The CAPA Owner, in alignment with approver(s), is responsible to define/ document an appropriate CAPA plan and executing/ implementing the plan and, where relevant, effectiveness check, on behalf of the Head of the affected department.</p> <p>Assigns CAPA action(s) to responsible individual(s) (i.e., CAPA Task Assignee=action owner) and establishes/ manages timeline.</p>

Function/ Role	Responsibility
CAPA QA	<p>Person fulfilling a quality assurance function within the organization or a representative of the specific department or unit responsible for ensuring compliance with regulations and company procedures. Responsibilities include:</p> <p>Plan Approval: Assessing the performed RCA from a QA perspective and the adequacy of the CAPA plan in relation to its associated source (e.g., deviation). Ensure the actions proposed aim to prevent/minimize recurrence and/or occurrence, and adequate explanation is given on required effectiveness check. If required, confirm that the effectiveness check is adequately planned and the plan well described. Approving CAPA plan and due date based on risk of the related issue.</p> <p>Final Closure: Assessing and approving the outcome of all CAPA activities including if applicable the effectiveness check. Close the CAPA.</p>
CAPA Task Assignee	Person responsible for implementing CAPA action(s) and reporting results within defined timelines as well as pro-active communication to CAPA Owner, if activities will not be completed as planned.
CAPA Initiator	Any person trained on this procedure, who is responsible to provide/confirm the initial details for the CAPA (e.g., necessary data to plan, execute/coordinate and/or document RCA activities as well as their outcome) and define the appropriate CAPA Owner. The CAPA initiator completes the CAPA initiation.
Extension Request Approver (for CAPA due date)	The persons who approved the CAPA plan (incl. initial CAPA due date) or designees, are responsible to evaluate and approve requested extension of the CAPA due date.

4 TERMS AND DEFINITIONS

Term	Definition
Action Item	<p>Form to request a specified task from a CAPA Task Assignee to be completed until a specified due date in the future.</p> <p>During CAPA management, Action Items can be used to perform activities concerning RCI, CAPA plan or effectiveness checks.</p>
CAPA	Corrective Action, Preventive Action.
CAPA Due Date	CAPAs must be planned with a due date that covers all steps until completed final approval. Appropriate time must be planned for implementation and if required effectiveness check.

Term	Definition
Continuous Improvement	<p><i>“Recurring activity to enhance performance.</i></p> <p><i>Note 1 to entry: The process of establishing objectives and finding opportunities for improvement is a continual process through the use of audit findings and audit conclusions, analysis of data, management reviews or other means and generally leads to corrective action or preventive action.”</i></p> <p>(ISO 9000, 2015)</p> <p>Synonym: Continual Improvement</p>
Corrective Action	<p><i>“Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)” *</i></p>
Effectiveness Check (EC)	<p>Process used to verify if a CAPA has the expected outcome (e.g., elimination of a deviation or complaint root cause, observation/ finding or other undesirable situation)</p>
Integrated QMS process	<p>An integrated Quality Management System (QMS) process is any process that is managed via MasterControl, e.g. training, deviations, complaints, etc.</p>
Investigation	<p>Structured approach, with the objective to determine the cause and associated risk of a problem.</p>
MasterControl (MC)	<p>An integrated software solution supporting the Quality Management System.</p>
Preventive Action	<p><i>“Action to eliminate the cause of a potential non-conformity or other undesirable potential situation. NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)” *</i></p>
Risk-based approach	<p>The level of effort, formality, and documentation of the investigation shall be commensurate with the level of risk.</p>
Root Cause	<p>The most fundamental factor based on objective evidence, which has been determined to be responsible for the deviation, complaint, audit observation/ inspection finding, trend, or unexpected result.</p>
Root Cause Analysis (RCA)	<p>Root Cause Analysis (synonym: Root Cause Investigation) is a systematic approach that covers different in-depth techniques and methodologies, e.g., Ishikawa and 5 Whys, used to identify the root cause(s).</p>

*Definition is copied from ICH Q10 which references to ISO9000:2005. Although there is a more recent version (ISO9000:2015), the definitions are not affected.

5 PROCESS

5.1 General

CAPAs are initiated risk based. **CAPA timelines must take into consideration the risk associated** to the issue from which they are originated.

CAPAs are mandatory for

- critical and major deviations (PROC-004019)
- justified critical and major (e.g., RAS class I - II) complaints (PROC-004270)
- confirmed audit observations and findings
- identified critical trends in GxP processes

CAPAs should be originated for (recommendation)

- other identified trends
- reviews (e.g., opportunities for improvement e.g., Stand Alone CAPA's)
- other situations that require tracking and trending of actions and issues requiring short, mid and long-term monitoring and resolution

CAPAs can be originated for

- minor deviations, only if sufficiently reasonable and explained.

Within MasterControl (MC) one CAPA form is generated per issue, e.g., for a deviation. Only for minor audit observations/ findings it is allowed to issue only one CAPA for several minor observations/ findings.

The process starts with CAPA initiation and ends with final QA approval of the CAPA record (details see section 5.3.).

If a CAPA requires a technical or product design change, this must be managed and approved as a Change Control according to PROC-007059. The CAPA can only be closed when the related Change Control is at least in step implementation.

5.2 SMART Principles

“SMART” concept is a valuable tool to facilitate effective CAPA management:

SMART Attributes	Definition
Specific	Each CAPA must have its own record and workflow. It must be specifically defined to allow an effective improvement.
Measurable	The CAPA plan must include appropriate action items resulting in measurable output.
Achievable	All action items must be clearly assigned to a responsible person, considering, but not limited to, availability, qualification, and access to necessary resources.
Relevant	The CAPA plan must be defined in relation to the real needs of/ situation at GRT.
Timely	For each CAPA a reasonable timeframe must be defined.

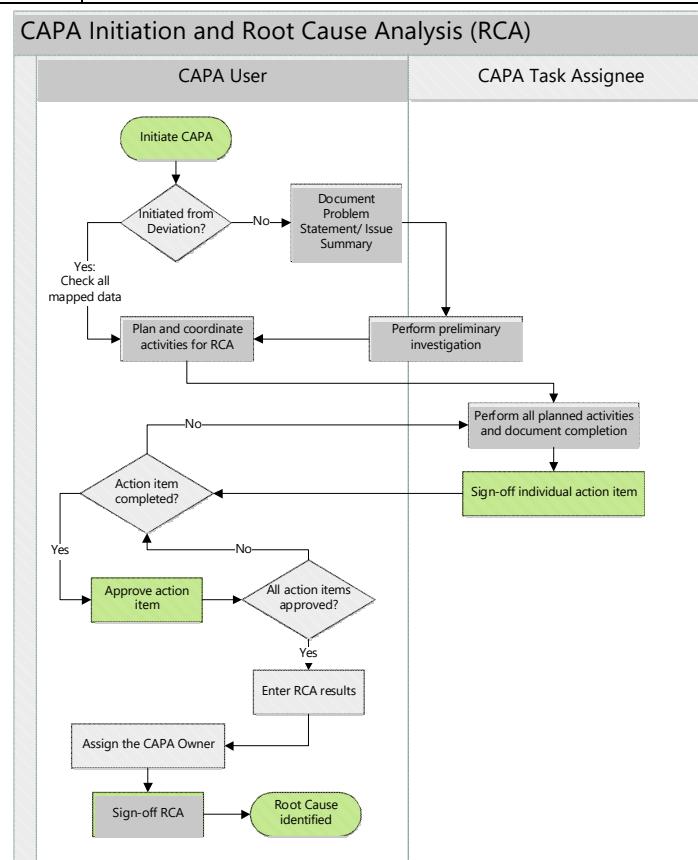
5.3 CAPA Workflow

Detailed step-by-step information and guidance on how to document CAPAs in MasterControl is provided in [TMAT-000654](#).

The CAPA process consists of the following steps: **Initiation** and based on identified root cause allocation of responsible CAPA Owner, **CAPA plan definition**, **CAPA Plan approval**, plan **implementation**, **effectiveness check** (if applicable), **Final QA Review**.

5.3.1 CAPA Initiation and Root Cause Analysis (RCA)

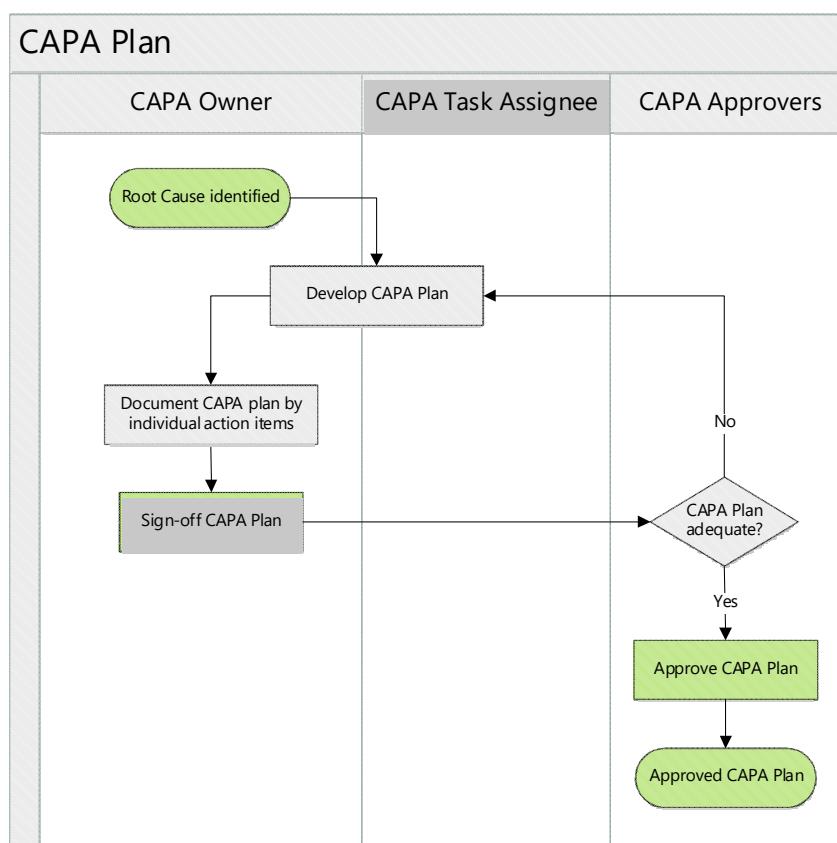
Step	Role	Activity
1	CAPA User (Initiator)	CAPA initiated from an integrated QMS process: <ul style="list-style-type: none"> Review mapped data and correct/complete as needed. Stand-alone CAPAs: <ul style="list-style-type: none"> Enter data for problem statement (e.g., what, where, when).
2		<ul style="list-style-type: none"> Select team members to support the RCA, if needed, and document RCA method (PROC-003381) Initiate RCA activities via action items (step 3),.
3	CAPA Task Assignee	<ul style="list-style-type: none"> Perform assigned action items within agreed timelines, Provide appropriate documentation, confirm completion by signature.
4	CAPA User (Initiator)	<ul style="list-style-type: none"> Coordinate required RCA activities, Approve completion of all action items and document dates, incl. upload of related documentation, if applicable, Provide RCA results summary, select CAPA Owner, Propose a CAPA due date, Confirm by signature: root cause identified according to the current state of knowledge.



5.3.2 CAPA Plan

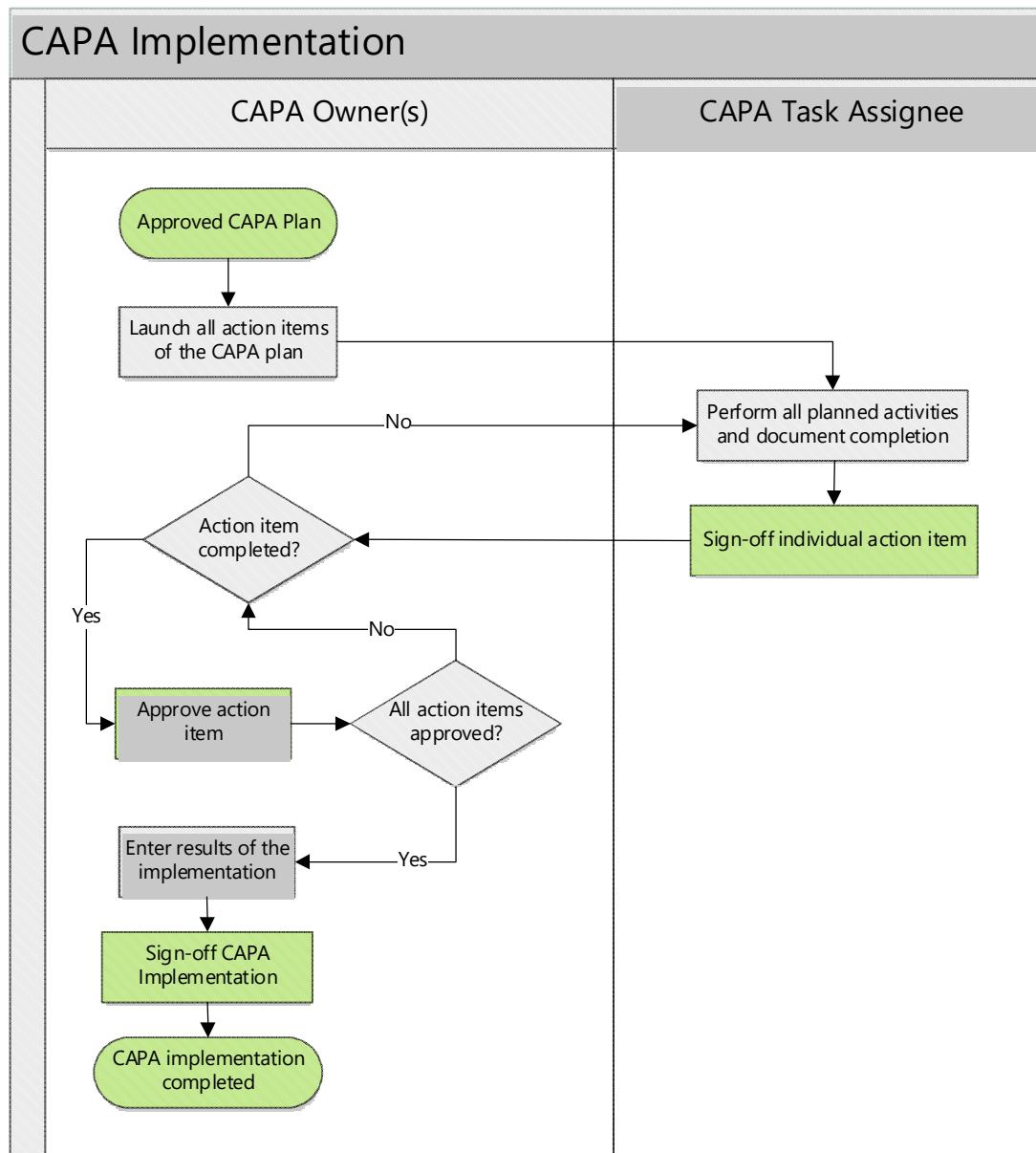
Step	Role	Activity
1	CAPA Owner	<ul style="list-style-type: none"> Review data, Provide meaningful and reasonable CAPA plan*, Provide EC plan or justification if none is required (details, see section 5.3.4.), Select appropriate team to support CAPA activities, Define appropriate action items for individual corrective and preventive actions, as needed, State whether the activities will eliminate or diminish the identified root cause, Verify and if needed adjust the CAPA due date.
2	CAPA Task Assignee	<ul style="list-style-type: none"> If needed, support CAPA Owner in action item definition.
3	CAPA Owner	<ul style="list-style-type: none"> Sign-off CAPA plan.
4	CAPA Approvers	<ul style="list-style-type: none"> Review and approve the CAPA plan (In case of rejection, provide a reason and ensure that respective changes are implemented).

*In case it turned out that a CAPA plan is not needed, the CAPA can only be closed by completing all further steps. Therefore, the CAPA Owner must enter a justification in the field "CAPA plan" (other mandatory fields can be filled with "not applicable"). After the CAPA plan approval (by responsible management and CAPA QA), the CAPA Owner completes all further steps in the CAPA workflow with the appropriate justification. After Final CAPA QA approval the CAPA is closed.



5.3.3 CAPA Implementation

Step	Role	Activity
1	CAPA Owner	<ul style="list-style-type: none"> Launch all corrective and if required preventive action items.
2	CAPA Task Assignee	<ul style="list-style-type: none"> Perform assigned action items within defined time, Provide appropriate documentation, Confirm adequate completion by signature.
3	CAPA Owner	<ul style="list-style-type: none"> Approve completion of all action items and document dates, incl. upload of related documentation, if applicable, Provide a summary of results, Sign-off completion of implementation.



5.3.4 Effectiveness Checks

Activities to check effectiveness are mandatory for CAPAs initiated for critical issues. The EC closes the loop between the identified root cause and its correction.

Whether or not to execute an effectiveness check must be described in the CAPA plan (see [section 5.3.2. step 1](#)) including

- Who will check the effectiveness
- What will be checked (e.g., products, processes)
- How data will be collected (e.g., Gemba Walks, audits, assessments, metrics, interviews, process observations, technical measurements, metrics, verification/validation reports)
- The time period for data collection to ensure sufficient time for evaluation based on statistical probability of re-occurrence of the root cause
- Criteria to be fulfilled in order to define if the CAPA was effective

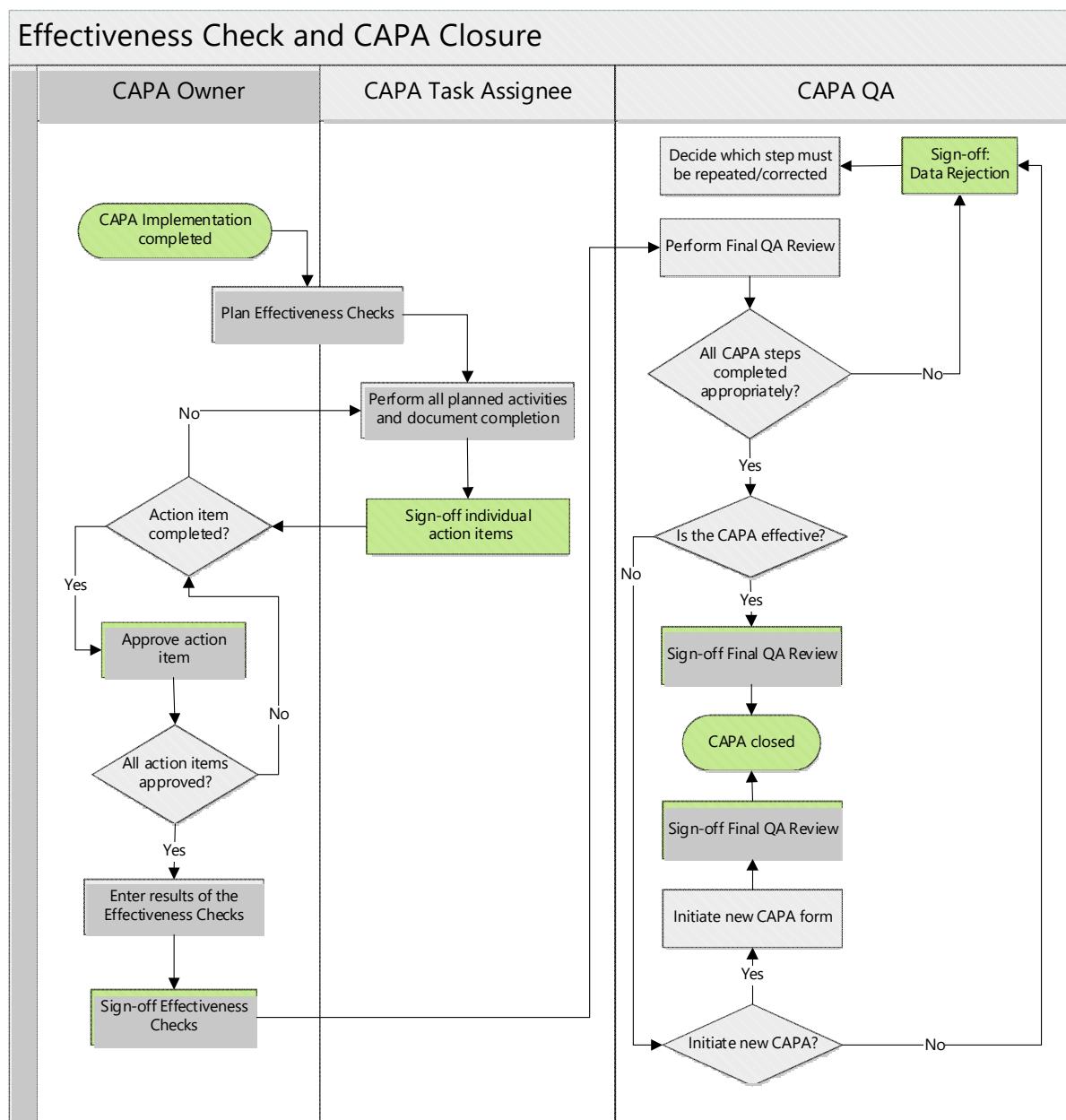
An effectiveness check might not be required when it can be shown that the root cause was sufficiently addressed immediately.

Step	Role	Activity
1	CAPA Owner	<ul style="list-style-type: none"> • Select an appropriate team to support the EC, • Initiate and coordinate all necessary activities. <p>If no EC was performed or the initial plan had to be modified, document a justification.</p>
2	Task Assignee	<ul style="list-style-type: none"> • Support the CAPA Owner in defining action items, • Perform assigned action items within defined time, • Provide appropriate documentation, if applicable.
3	CAPA Owner	<ul style="list-style-type: none"> • Approve completion of action items, document dates and upload related documentation, if applicable, • Provide results summary, • Sign-off completion of the EC.

5.3.5 CAPA Closure

Step	Role	Activity
1	CAPA QA	<ul style="list-style-type: none"> • Review complete CAPA documentation, • Evaluate effectiveness of the implemented CAPA (for ineffective CAPA, decide to trigger a new CAPA or to reject CAPA to initiate new activities), • Sign off the Final QA Review (In case of rejection, select the step that should be corrected).

Only QA may reopen a CAPA form, and only if the form contains incorrect or misleading information. A justification and indication of changes must be provided.



5.4 Timelines/Overall Due Date

CAPAs are assigned an overall due date that covers the time required to complete all steps of the workflow. Due Dates of individual Action Items cannot be adjusted and the respective action is counted as overdue once the defined due date is exceeded.

The CAPA overall due date can be adjusted by the CAPA Owner during CAPA plan development and before sign-off, as no action items for corrective and preventive actions are launched at that time.

If during the implementation phase or effectiveness check completion, the CAPA Owner identifies that the CAPA overall due date cannot be met, this must be addressed to the affected management and QA in order to define appropriate measures.

5.5 Trend Analysis

A regular trend analysis of CAPAs related to GxP must be performed by Quality Assurance at least on a quarterly basis. The outcome of that regular trend analysis must be shared with the affected Management, e.g., in the frame of periodical Management Review in order to define suitable actions if required.

5.6 Business Continuity

The MasterControl system can be restored in less than 12 hours (PROC-001798). This temporary unavailability of MasterControl has a low risk concerning product quality, patient safety or other critical business. Therefore, a special process for business continuity for CAPA management is not needed.

Nevertheless, in case MC system is not available for a longer time, Quality Assurance or other similar function (if QA is not available the responsible person of the affected area) must be contacted to discuss a paper-based documentation. As soon as the system has been restored, the information documented on paper must be completely transferred into the system by the user who is in charge of the process step at the time the system is recovered. The transferred information in the CAPA form must be reviewed for completeness and correctness by a second person. Both persons must sign the respective step in MC.

6 REFERENCES

- DIN EN ISO 9000:2005, Quality management systems – Fundamentals and vocabulary (2015)
- DIN EN ISO 9000:2015, Quality management systems – Fundamentals and vocabulary (2015)
- ICH Q10: Pharmaceutical Quality System (2008). Harmonised Tripartite Guideline of the International Conference on Harmonisation (ICH)

7 HISTORICAL INDEX

Revision no.	Description of changes
01	New global process. This document replaces PROC-004629.
02	Updates concerning roles and responsibilities and definitions. Section "General" includes new requirements for timelines and link to related processes. Section "Effectiveness Check" includes now more details on how to plan and execute. Section "Timelines" removed the table how to request due date extension. Flowcharts included in the process description instead of keeping them at the end.