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Title:

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Scope:

Area:

Country:

Previous Number:

Document Information

Revision:

Status:

Effective Date:

1 OBJECTIVE

The objective of this document is to describe the global process of Change Control within the Grünenthal Group to ensure that all GxP-related changes are documented, assessed, approved, implemented, verified and closed.

2 SCOPE

This document applies to everyone involved in the management of GxP-related changes within the Grünenthal Group.

The process applies to the following change types:

- Product Change
- Technical Change

The process can be applied to non-GxP related changes, whenever deemed appropriate, business relevant and beneficial.

Out of scope are:

- All GVP-related Changes
- IT Infrastructure Changes (see [PROC-004973 "IT infrastructure Change Management"](#))
- Label/text changes to Printed Packaging Material ([PROC-004879 "Global Label Management Process"](#))
- SAP adjustments/enhancements with non-GxP impact managed via SAP Service Request or via IT Change in the ITSM system ([SUP-004246 "List of SAP Service Request types"](#))
- "Like for Like" exchanges of removable parts (identical in function and construction) of GMP regulated systems, devices, equipment (e.g., HVAC filter exchange)

3 RESPONSIBILITIES

Role	Function/Profile
Approver	<p>Business representative (Process/System owner or a person at management level) and/or Quality Assurance representative.</p> <p>The Approver from the business is responsible to ensure that all the changes are managed in compliance with this procedure.</p> <p>The Approver from Quality Assurance function is responsible to ensure that all the changes are managed in compliance with regulations and company procedures.</p> <p>Quality Assurance approval is mandatory for all GxP-related changes.</p>
Extension Request Approver	<p>The Extension Request Approver has the responsibility to evaluate and approve requests for the step due date extensions.</p> <p>The Extension Request Approver role can be assigned only to users having also the Approver role.</p>

Role	Function/Profile
MOC Task Assignee	The MOC Task Assignee is responsible to timely complete individual action items and/or change impact assessment through the checklist completion (acting as Subject Matter Expert). If applicable evidence must be included.
Nominated Responsible Person [NRP]	The NRP (the change manager) must be a person with profound knowledge of the affected process and is responsible to coordinate the activities from the assessment to the verification step.
Requester	The requester is anyone within the organization authorized to initiate a change request and to provide all the data necessary for evaluation of change feasibility.
Reviewer	The Change Reviewer is a person with profound process knowledge about the respective change, being able to evaluate the feasibility of the change proposal and ensuring compliance with company procedures.
Subject Matter Expert [SME]	A person with deep knowledge and understanding of a specific subject such as a business process, product, validation, computerized system, equipment, material, regulatory subjects, etc.

It is possible that more than one role is assigned to a single user if allowed by the segregation of duties.

In case an external party must be involved and its feedback documented in the system, the user having the relevant role in the respective workflow must be the responsible person to follow-up and document the outcome.

4 TERMS AND DEFINITIONS

Term	Definition
Action Item [AI]	Form to request a specified task from a MOC Task Assignee to be completed until a specified due date in the future. Along the Change Management process, AI can be used to perform activities concerning the implementation step, verification step (e.g., effectiveness check) or tasks coming from meeting minutes.
Change Type	The GxP-related change can be classified as Product Change or Technical Change. Note: any change impacting a Computerized System is classified as Technical Change.
Change Level	The level of the change can be classified as Major or Minor depending on the impact of the change
Chemistry, Manufacturing and Controls [CMC]	CMC Compliance function is the business responsible for driving and executing the product change.
Computerized System [CS]	A Computerized System includes hardware, software, peripheral devices, personnel, and documentation e.g., manuals, standard operating procedures including work instructions.

Term	Definition
Data Integrity (DI)	<p>Data integrity is the degree to which data are complete, consistent, accurate, trustworthy, reliable and that these characteristics of the data are maintained throughout the data life cycle.</p> <p>The data must be collected and maintained in a secure manner, so that they are attributable, legible, contemporaneously recorded, original (or a true copy) and accurate.</p>
DATA Management	<p>In the frame of this document DATA refers to all process/ product/ system/ equipment affected by the change</p>
Effectiveness Check [EC]	<p>The prove of the effectiveness of changes implemented is part of the Change Management process.</p> <p>The effectiveness check aims to confirm that the change meets its intended objectives and pre-defined acceptance criteria with no unexpected consequences.</p> <p>The Acceptance criteria must define:</p> <ul style="list-style-type: none"> - WHAT to be monitored and measured (e.g., deviations/ incidents after the implementation) - HOW to be measured (e.g., trend analysis, CPV, Periodic Incident reviews, % of deviations) - HOW MANY: maximum limit accepted if measurable (e.g, less than 2% of new deviations) - HOW LONG: the duration of monitoring period (e.g., monitor the number of deviations within 6 months after the implementation, or a specific number of produced batches, or based on a periodic review scheduled etc.) <p>The check of the effectiveness is mandatory for all major changes, but applicable to minor changes as well whenever deemed appropriate and beneficial.</p>
Emergency Change	<p>Any technical GxP-related change (CS Change) that must be implemented in a compressed timeframe in order to ensure the business continuity. This is generally caused by either one or several of the following circumstances:</p> <ul style="list-style-type: none"> ▪ A productive system is completely down. ▪ The imminent go-live or upgrade is jeopardized. ▪ The core business processes are seriously affected. ▪ No approved workaround available.
GxP	<p>GxP is a general abbreviation for “good practice” quality guidelines and regulations. In the frame of this SOP The “x” might stands L = laboratory, C = clinical, M = manufacturing, D = distribution,) and includes all processes impacted by regulations, standards or guidelines, e.g., EMA regulations, ICH guidelines, ISO standards.</p>

Term	Definition
GxP-related changes	Any change that might be related to GxP processes and might affect – directly or indirectly – the patient safety and/or rights, quality, efficacy of medicinal products, investigational medicinal products, medical devices, any related pharmaceutical material (including active pharmaceutical ingredients, excipients or any further raw material) or the validity of GxP data.
IT infrastructure	IT infrastructure comprises all IT systems and IT services that are needed to deliver IT applications to end-users.
Major Change	All changes that might affect, but not limited to: <ul style="list-style-type: none"> - Patient safety and/or rights, quality, efficacy of medicinal products, investigational medicinal products, medical devices, any related pharmaceutical material (including active pharmaceutical ingredients, excipients or any further raw material) - Data integrity - Business Continuity
Management of Change [MOC]	Module available in MC to manage the change control process.
MasterControl [MC]	An integrated software solution supporting the Quality Management System provided by MasterControl Inc.
Minor Change	Any change not classified as Major change (e.g. change to batch record template layout, administrative change to regulatory dossier not requiring approval, changes to equipment not requiring process validation activities)
Product Change	A change that can be related to one or more medicinal products, medical devices, investigational products and materials (For examples see SUP-007521 “Guideline for the Sub-Category Selection in MOC process”)
Technical Change	Any change related to Equipment/System Facility/Utility/Process/Service with no direct impact to a specific medicinal product, medical device, investigational product or material. (For examples see SUP-007521 “Guideline for the Sub-Category Selection in MOC process”)

5 PROCESS

5.1 General

All GxP-related changes must be requested, reviewed, assessed, approved, implemented, verified and closed through a defined change control process. This must

be documented in MasterControl. An unique identification change number is assigned automatically to Changes by the system.

Any employee, who has any initiative of a GxP-related change proposal, has to ensure the reporting in MasterControl and follow-up the tasks to get the respective final decision leading to the potential approval for implementation.

The description of the change must be clear and written in a language that can be understood by all involved people and any concerned parties.

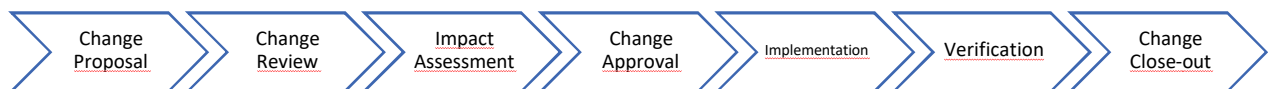
The GxP-related change can be classified as Product Change or Technical Change. The classification determines the change control approach and the responsibility matrix.

Any potential risk for the continuation of any step might require clarifications and/or escalation to the Project Change framework by the step responsible person and the final decision must be documented in the system by means of attachments or meeting minutes (see § 5.4).

More information on how to document the steps in MasterControl [TMAT-001129 "Management of Change \(MOC\)"](#).

5.2 Process Steps

The Change Management Process consists of the following steps:



Each step (except Implementation and Verification) has a pre-defined step duration in order to:

- Ensure the management of the change on timely manner
- Guide the user through the workflow.

If a step cannot be completed according to the set due date, an extension request must be created, justified by the responsible of the respective step and approved by the appropriate function (see section 3).

5.2.1 Change Proposal

Documentation of initial information and details related to the proposed GxP-related change.

Step	Role	Activity
1	Requester	<ul style="list-style-type: none"> ▪ Enter the relevant information in all fields (e.g., title, location/site, source, change description, justification, scope of impact, change type, reason for emergency change, etc) ▪ List all product or process/systems or equipment impacted by the proposed changes ▪ Define if any notification to the client/ Supplier/ Vendor/ Authorities is needed ▪ Select Suppliers or Customers impacted ▪ Link any infocard supporting the change proposal (e.g, Data Management infocard) ▪ Attach any relevant Supporting Materials to justify the change ▪ Select the reviewers (see Table 1) ▪ Sign-off the completion of the change request.

Table 1. “Reviewer Assignment”

Product Change	Technical Change
CMC compliance (mandatory), and other business functions (if needed)	Business Function (e.g., System/Process Owner or Responsible), and/or QA function if needed according to the organization
Note: Multiple reviewers can be selected	

5.2.2 Change Review

The defined Change Reviewer(s) are involved for the change proposal revision in terms of completeness of information and feasibility to continue to the impact assessment.

Step	Role	Activity
1	Reviewer	<ul style="list-style-type: none"> ▪ Review the change proposal content and if all information needed was provided ▪ Select the appropriate option: <ul style="list-style-type: none"> ○ Approve (Confirm) the change proposal <ul style="list-style-type: none"> ⊖ Insert the NRP and Approvers based on the Change Type (see Table 2) ○ Cancel the change to close the change ○ Revise Proposal to request more details in the change proposal ▪ Sign off the completion of the change review. In case of proposal revision or change cancellation, provide the reasons of the respective selection. The change can be cancelled in case the proposal is not feasible (all the reviewers have to sign off with the “Cancelled” option selected) .

Table 2. “NRP and Approver(s) assignment”

Role	Product Change	Technical Change
NRP	CMC Compliance Function or another Function agreed with CMC	Business Function (e.g., System/Process Owner) or QA Function
	Only one NRP name can be selected	
Approver	CMC Compliance Function or Business Function	Business function, System Owner/Process (if applicable) and/or QA (required always in case of GxP-related change)
	Multiple Approvers can be selected	

5.2.3 Impact assessment

All the potential affected GxP functions, processes, analysis must be identified and the any potential risks related to patient safety, product quality and/or data integrity must be assessed.

A structured impact assessment of the change is performed via driven checklists assigned to the SMEs of the areas potentially affected by the change (e.g., EHS, Manufacturing, Quality, Regulatory Affairs, Medical, IT, etc.). This shall ensure that appropriate science- and knowledge-based impact assessments are carried out, and are adequately and consistently documented for a change. During the impact assessment the points below are taken in account:

- Potential risks linked to the proposed change
- The level of accuracy, effort (e.g., testing, validation, review, training) and documentation corresponds with the level of risk aligned with the type of proposed change.
- Change plan in detail included if apply
- Data to support the change by requesting and attaching additional documents.

The impact assessment is managed by the NRP who is responsible to launch the assessment request and review the outcome.

The outcomes of the assessments drive the definition of the implementation strategy, the classification of the change level and the effectiveness check criteria (including the proposed EC plan).

Step	Role	Activity	
1	NRP	<ul style="list-style-type: none">Identify the functional area(s) that must perform the assessment by applying the following rule according to the change type:	
		Product Changes	Technical Changes

Step	Role	Activity
		<ul style="list-style-type: none"> Regulatory Affairs CMC compliance Quality Assurance <p>Note: in some cases an external assessment can be provided and attached (e.g. CMB)</p>
		<ul style="list-style-type: none"> Validation IT (in case of CS changes) Quality Assurance (only for all GxP-related changes) (in case of assessment synergies, the input can be documented in one check list only, e.g. Validation and QA assessment).
		Any additional assessment needed, based on the potential functional area(s) affected.
		<ul style="list-style-type: none"> Assign the impact assessment task to the SME of the relevant area. Select a due date within the assessment must be completed. Initiate all the respective checklists.
2	SME	<ul style="list-style-type: none"> Receive the impact assessment checklist completion task. Involve further experts to assess the impact of the change, if needed. Perform the assessment in the respective section "Checklist" considering all risks related to the proposed change. Select the NRP of change for the checklist review task (if needed additional user(s) with the proper role of NRP and Approver can be added to perform the Checklist review task as well - e.g QA Function for GxP- related changes to CS). Provide the action plan for implementation/verification (if needed) in the respective section "Change Plan". Attach any relevant document if applicable in the respective section "Attachments". Sign-off the Checklist Completion.
3	NRP	<ul style="list-style-type: none"> Review the assessment performed by each functional area. Sign-off the checklist review. In case of rejection, provide a reason and ensure that respective modifications are implemented (if applicable).

Step	Role	Activity
4	NRP	<ul style="list-style-type: none"> ▪ Select the proper option if the change can be approved for implementation based on the assessment outcome from the SMEs (Note: In case the NRP evaluates that the change cannot be implemented, a rationale must be provided) ▪ Enter the relevant information needed <ul style="list-style-type: none"> ▪ The implementation strategy (e.g., for a CS change, NRP must define the release of the system) ▪ Depending on the definition in the Quality Agreement, confirmation <ul style="list-style-type: none"> ▪ That the customer was informed ▪ That the customer approved or acknowledged the change ▪ Customer notification or approval must be attached to the change in the system ▪ The level of the change ▪ The Effectiveness Check Evaluation and Plan (if applicable) by specifying the acceptance criteria. ▪ Sign-off the Impact Assessment.

5.2.4 Change approval

The defined change approver(s) approve the GxP-related change proposal based on the information provided in the change proposal, the impact assessment outcome, implementation strategy and the effectiveness check evaluation/plan.

The change approver(s) can request more details to be included in the change proposal or impact assessment in order to make a proper decision.

Step	Role	Activity
1	Approver	<ul style="list-style-type: none"> ▪ Review the information inserted in all previous steps (e.g. proposal of the change, impact assessment, implementation strategy) ▪ Approve the change for implementation. In case of rejection, provide a reason and ensure that respective modifications are implemented (if applicable) <p>Note: In case of multiple approvers, the final rejection of the change can occur when only one of the approvers select the rejection option.</p>

5.2.5 Implementation

As soon as the change proposal, impact assessment outcome (including implementation strategy) and effectiveness check evaluation/plan are approved by the responsible Approvers, the implementation activities of the change can start according

to the change plan proposed by the group of SMEs and the defined implementation strategy.

All the actions for implementation are created by the responsible person of the Implementation step (automatically assigned by the system to the NRP). However, the responsibility of the implementation step can be shared with multiple users who are trained on the NRP role.

Step	Role	Activity	
1	NRP	<ul style="list-style-type: none">Create the implementation tasks (via AIs) according to the implementation strategy defined Note: Additional Approvers can be included, if neededMonitor all the dependencies of the AIs in order to ensure the proper starting of implementation activities (e.g. some AI must be implemented first) <p>Depending on the change type, the following action creation approach can be processed according to the implementation strategy defined in the impact assessment step:</p>	
		Product Change	Technical change
		<ul style="list-style-type: none">Actions that can be implemented before submission to Health authorities, including changes that do not require any submission to any Health authority.Actions that can only be implemented after submission or approval to Health authorities.	<ul style="list-style-type: none">Actions that must be implemented before the equipment/ utility/ facility/process is released for use.Actions that must be implemented in case a CS change: actions for the Validation and Productive environment, including the authorization to implement in Production.Actions that can be implemented after the release for use of a system/ equipment/ utility/ facility/process.
2	MOC Task Assignee	<ul style="list-style-type: none">Perform all assigned action items within defined timelines (if needed justify the delay and inform the NRP)Provide appropriate documentation, if applicableSign-off all action items. In case of rejection, provide a reason and ensure that the respective modifications are implemented (if applicable)	

Step	Role	Activity	
3	NRP	<ul style="list-style-type: none">▪ Monitor the progress of all change implementation actions to ensure each action is completed on timely manner and in the required time sequence▪ Track any significant information regarding the adherence to the implementation plan in the relevant field▪ Approve completion of all action items and document the completion date, including upload of related documentation, if applicable▪ Check the completion of all action items▪ Enter the implementation date. <p>Within the framework of this procedure some examples of the implementation date can be considered as follows:</p>	
		Product Change	Technical Change
		<ul style="list-style-type: none">▪ Activation of the respective bill of material (if affected) and therefore enabling the company in manufacturing of finished products displaying the respective change▪ The first release in the last country	<ul style="list-style-type: none">▪ The release of system/ Equipment/ Utility/ facility/Process for the use in a productive environment (e.g., after validation or testing activities are successfully completed and approved)▪ The closure of last action item
		Note: In case of specific local regulatory requirements, an agreement with the Quality Assurance function is mandatory about the implementation date.	
		<ul style="list-style-type: none">▪ Document any modification from the original change plan or any additional impact/result in the implementation summary▪ Sign-off the implementation step	

The implementation is completed when all the defined actions in the implementation are completed regardless the outcome itself.

The change at this stage is considered as implemented (the MOC form is still open to perform post activity and/or effectiveness check actions.)

5.2.6 Verification

Verification phase is used to perform post implementation activities if they are defined in the implementation strategy and/or to carry out actions to perform the effectiveness check of the change implemented if planned and approved in the respective previous steps.

Step	Role	Activity
1	NRP	<ul style="list-style-type: none"> Create any verification task (via AIs) as defined in the implementation strategy.
2	MOC Task Assignee	<ul style="list-style-type: none"> Perform all assigned action items within defined timelines (if needed justify the delay and inform the NRP) Provide appropriate documentation, if applicable Sign-off all action items. In case of rejection, provide a reason and ensure that the respective modifications are implemented (if applicable)
3	NRP	<ul style="list-style-type: none"> Monitor the progress of all change verification actions to ensure each action is completed on timely manner and in the required time sequence Track any significant information regarding the adherence to the implementation plan in the relevant field Approve completion of all action items and document the completion date, including upload of related documentation, if applicable.
4	NRP	<ul style="list-style-type: none"> Check the completion of all action items Evaluate if the verification is successful (e.g., effectiveness checks result are successful, post implementation tasks are completed successfully, etc.) Report a summary of the verification action results or any significant information, when appropriate (e.g., any modification from the original change plan or any additional impact/result) Set the verification date as the latest action item completion date Sign-off the Verification step. In case of rejection, provide a reason and ensure that respective modifications are implemented (if applicable).

5.2.7 Change Close Out

The change is considered closed once all implementation and verification actions (including Effectiveness Check, if applicable) are completed, reviewed and approved on the change control form.

The change form is closed once all the approvers for the step have signed off the change close-out step.

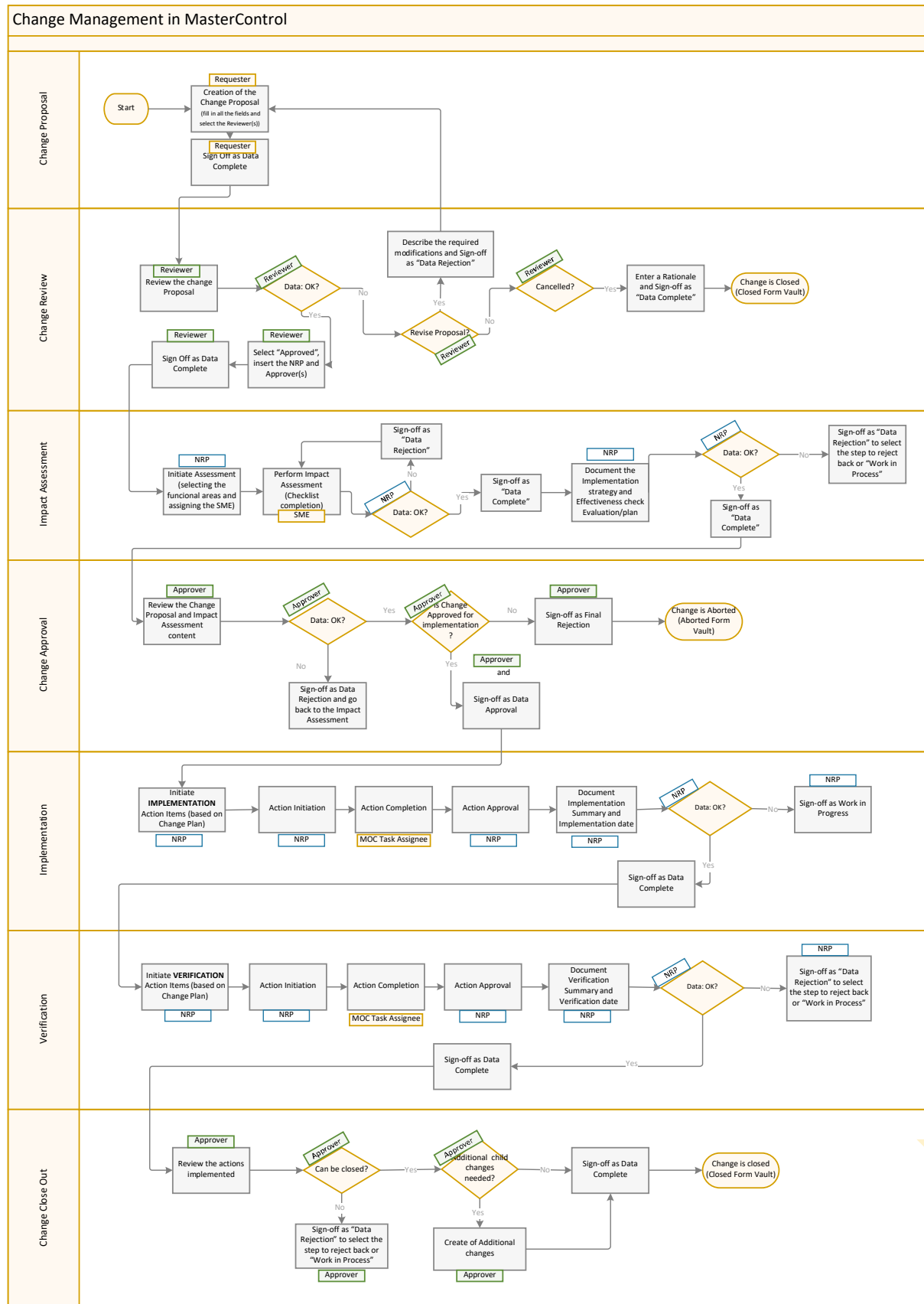
If defined in the Quality Agreement, the customers identified in the assessment step should be informed about the change close out and about the details of the first batch produced by:

- The NRP in case of a product change

- The IMQ in case of a technical change (the NRP must inform the IMQ about the change close out).

Step	Role	Activity
1	Approver	<ul style="list-style-type: none">▪ Review all the implemented actions and the verification actions (included the effectiveness check ones) when defined.▪ Evaluate if the change can be considered successfully or not successfully implemented.▪ Summarize the overall results and it is mandatory to perform and document an assessment in case the change closure is not successful.▪ Insert all the relevant information required.▪ Confirm the closure results and closure date. <p><u>Note:</u> The closure date must be entered manually and it corresponds to the same verification date.</p> <ul style="list-style-type: none">▪ Select the option to open any MOC child if needed, and fill in the relevant fields of additional MOC section as consecutive action of the selection.▪ Sign-off the change close out step. In case of rejection, provide a reason and ensure that the respective modifications are implemented (if applicable).

5.3 Process Flow



5.4 MOC Functionalities

Any meetings can be documented via the Meeting Minutes form if needed. The meeting minute functionality can be used to document meeting minutes/decisions, to track any additional tasks needed (e.g. collaboration or pre-activities before implementation) or any decision relevant for processing the change (e.g. tasks to be done before making a decision like data collection to support the assessment, definition of the implementation strategy, notification to authorities).

Anytime the functionality of the Communication Log can be used for notifications to the functions involved and/or affected by the change. For example:

- perform any escalation notification
- notify the update of some actions to the needed stakeholders
- notify the Task assignee to start the assigned action item

5.5 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 Change Control Management is not needed.

Nevertheless, in case the MasterControl 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 MOC form must be reviewed for completeness and correctness by a second person. Both people must sign the respective MOC step in MasterControl.

6 REFERENCES

- ICH Q10 Pharmaceutical Quality System
- EU GMP Chapter 4, Annex 11, Annex 15
- US-FDA 21 Code of Federal Regulations (CFR) Part 11
- PI 054-1 "How to Evaluate and Demonstrate the Effectiveness of the Pharmaceutical Quality System with regard to Risk-Based Change Management"

7 HISTORICAL INDEX

Revision no.	Description of changes
01	New Document due to the implementation of the new global process for Change Control Management in MasterControl
02	Implementation of obligation to <ul style="list-style-type: none">- to inform the customer and/or obtain customer approval for a change before the change approval step.- inform the customer about the change outcome. Merge with PROC-003164. Editorial changes to improve readability.