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Title:

Title (EN):

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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 Product Quality Review Process within the Grünenthal Group. Regular periodic quality reviews shall be conducted annually (unless differently specified and supported by risk assessment) to verify the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product and to identify product and process improvements to ensure complete oversight on the quality of the medicinal product and safety of the patient. Moreover, based on the review outcome, any trends are highlighted to identify possible product and process improvements.

2 Scope

This document applies to all Grünenthal entities which are involved in the Product Quality Review Process. It is covering all products manufactured by the Grünenthal group or by a CMO where Grünenthal or a customer is the MAH or has a specific responsibility according to local requirements within the purview of technical agreement in place between the parties.

3 Responsibility

Grünenthal is responsible for conducting the Product Quality Review of all products manufactured by Grünenthal Group and for which Grünenthal is the Marketing Authorization Holder or acting as CMO for a customer.

Where Grünenthal acts as the Marketing Authorisation Holder and the manufacturing steps are performed by a CMO, the respective responsibilities in performing the Product Quality Review are defined in the technical agreement in place between the parties.

The Senior Management has the ultimate accountability of the overall process whose outcome is regularly evaluated during the management review.

The main responsibilities of function/roles listed in this document are as follows:

Function/Role	Responsibility
Global Quality Assurance	<ul style="list-style-type: none"> • Ensure compliance with the Quality Management System at Grünenthal and external guidelines/ standards/ regulations applicable • Ensure Global Oversight on the process
Internal Manufacturing Quality Assurance	<ul style="list-style-type: none"> • Implement the process on a local level and ensure adequate documentation management according to this SOP • Ensure compliance with Quality Management System and applicable local regulations • Alignment of identified need for further CAPAs included in the evaluation of the adequacy of process validated with the releasing QP and assessment of effectiveness check of any actions. • Provides respective PQRs as per plan • Creates PQRs or parts of a PQR whenever the local site is involved in manufacturing activities • Perform a content check of CMO PQR as soon as received from ESQ after formal check when Grünenthal perform manufacturing steps.
Commercial Quality Assurance	<ul style="list-style-type: none"> • Planning of MAH reviews of the PQRs • Perform a content check of CMO PQR as soon as received from ESQ after completeness check only if all manufacturing steps including batch certification are performed by a CMO. • Review the PQR results as Marketing Authorization Holder (MAH) or according to specific local responsibility and assess the necessity for further corrective and preventive actions • Add any national information as required
External Supply Quality Assurance	<ul style="list-style-type: none"> • Implement responsibilities for PQR creation in technical agreements with external CMOs • Request PQR on timely manner to external CMOs • Perform a formal check of CMO PQR before forwarding the PQR to GO -CQA and/or GO- IMQ • Responsible for the completion of annex 1 with regard to the qualification status of supplier
Contributing Departments	<ul style="list-style-type: none"> • Creation of relevant PQRs annexes

Function/Role	Responsibility
Qualified Person	<ul style="list-style-type: none"> • Approve the PQR • Evaluate with CQA – during the MAH review - any national amendments and/or CAPA needed

The responsibilities are described in more details (step per step) in section 5.

4 Terms and Definitions

Term/Abbreviation	Definition
API	Active Pharmaceutical Ingredient
CAPAs	Corrective Actions and/or Preventive Actions
CMO	Contract Manufacturing Organization
CQA	Commercial Quality Assurance
Contributing departments	e.g. but not limited to: Quality Control, Production, Regulatory Affairs
Cluster of affiliates	Group of countries operating under the same CQA organization
ESQ	External Supply Quality Assurance
EU	European Union
GLS	Grünenthal local subsidiaries
GMP	Good Manufacturing Practices
CMC	Chemistry Manufacturing and Controls Quality Assurance
GQA	Global Operation – Global Quality Assurance - GxP
IMQ	Internal Manufacturing Quality Assurance
GRT	Grünenthal
IPC	In-Process-Control
LIMS	Laboratory Information Management System
Local Quality Assurance	QA in manufacturing sites (IMQ/CMC) and CQA in Grünenthal local subsidiaries (GLS)
MAH	Marketing Authorization Holder

Term/Abbreviation	Definition
MAH Review	A review performed on finished products (PQR) by the MAH according to regulatory standards applicable This may also include a review according to specific local responsibilities.
OOS	Out of Specification
PIC/S	Pharmaceutical Inspection Co-Operation Scheme
PQR	Product Quality Review
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
QP	Qualified Person

5 Process

5.1 General

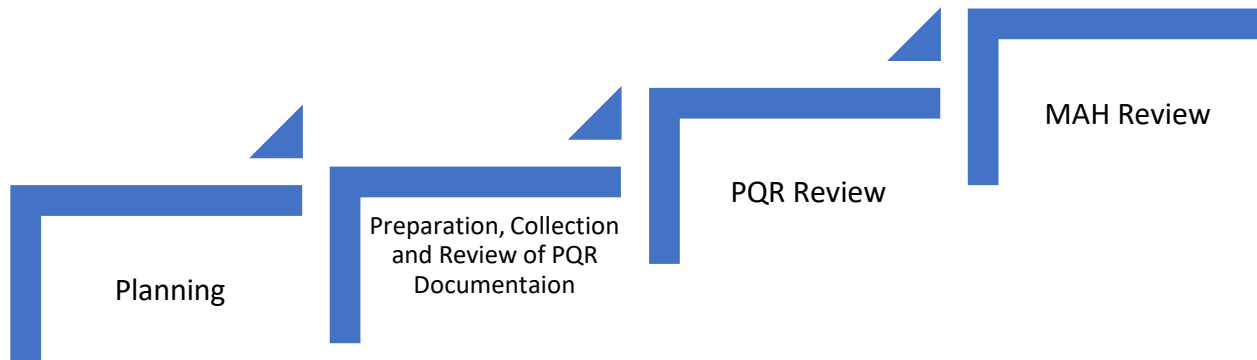
Regular periodic quality reviews of all authorized medicinal products shall be conducted and documented annually (unless differently specified and supported by risk assessment).

Similar products, e.g. such with a similar composition (e.g. different strengths of a product) or a comparable production process, can be grouped and assessed together in one PQR.

If so, common properties shall be assessed together and specific features shall be pointed out.

Any CAPAs necessary shall be documented and adequately tracked according to the relevant procedure applicable. The need of any effectiveness check of such actions shall be evaluated, monitored and documented accordingly.

The general process flow from the planning to the final MAH Review is described below:

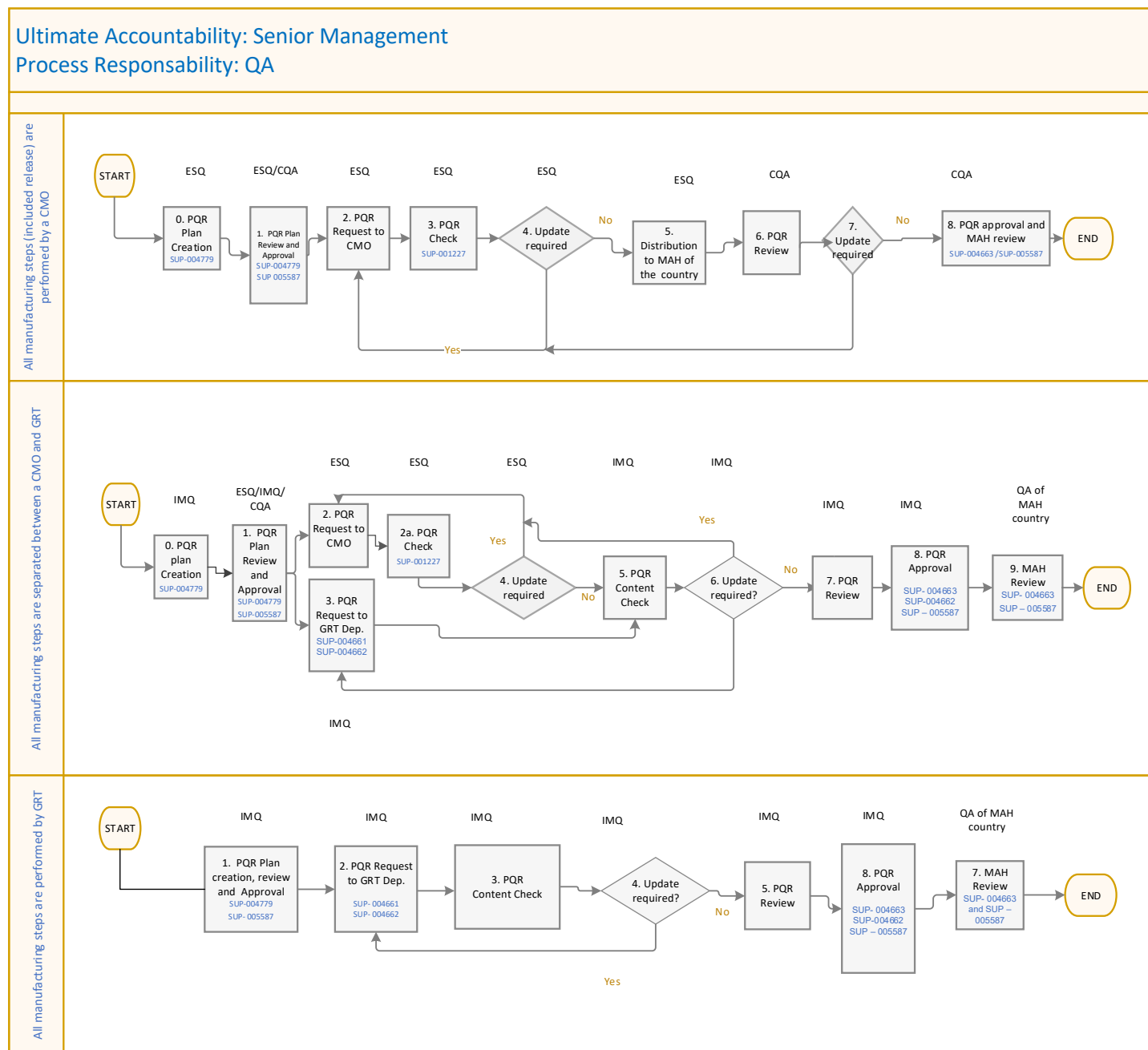


The responsibilities and the detailed steps needed for conducting the Product Quality Review and the subsequent MAH Review are described in the following sections depending on:

- All the manufacturing steps (including release) are performed by CMO
- The manufacturing steps are separated between CMO and Grünenthal
- All the manufacturing steps (including release) are performed by Grünenthal

The PQR review and the subsequent MAH review shall be planned according to the SUP 004779: the PQR plan shall be created and approved within Q1 of each year and any delays to the PQR plan must be properly documented by a deviation according to the internal processes in place.

5.2 Process Flows



5.3 Filing of PQR plan, PQR review and MAH Review

PQR Plans, PQR and MAH reviews shall be filed according to SUP-005587.

5.4 Content of Finished Product PQR

The Product Quality Review shall be conducted for API and Finished Products.
The PQR report shall contain a review of all the critical cGMP aspects related to the production of the API and/or Finished Product in subject to the assessment and document the outcome carried out during the evaluation/reporting period.
In order to focus the review on the relevant factors for the final quality of the product, the critical parameters to be monitored (Critical Quality Attributes) are preliminarily selected with a "risk based" approach.

The PQR review shall be documented by using:

- the SUP 004661 Product Quality Review API
 - the SUP 004662 - Product Quality Review Finished Product
- depending if it deals with API or Finished Product PQR.

The PQR report shall include the sections described in the following table:

Section	Section description
Table of content	<ul style="list-style-type: none">- List the main topics covered in the Product Quality Review document with the indexing and reference page number- Refer to the batch listing- Include any local additional requirements if needed (each site shall add the name of the item as a complementary in the relevant SUP - 004661 – e.g: Annex "Complaints" shall be named as "Complaints & Adverse Events" in case Adverse Events must be listed
Summary and Conclusion – Approval	<ul style="list-style-type: none">- Summarize and make reference to each single annex by giving the overall picture of the assessed product quality and highlighting any negative observation/trend during the PQR review period and/or any interruption of product distribution.- Report an assessment of the validation status and compliance of the process controls and product with regard to concerned changes
Annexes	<ul style="list-style-type: none">- All annexes of the PQR shall be created in the English language for global products and preferably in English for local products. For local products a PQR shall be created in that native language.- See § 5.4.1 for the details related the content of annexes and Part II of SUP 004779 for approximate timelines reference

The naming convention to be used for the product description in the header of the SUP - 004662 is:

Main Bulk/API name + galenic form + strength + unique identifier (if different types exist)

e.g. Tramal capsules 50mg (yellow/yellow)

The PQR shall be created by Internal Manufacturing Quality Unit, reviewed by the Functional Heads (e.g Manufacturing Head, QC Head) and approved by the Qualified Person.

The signature cycle of the PQR shall be started once all annexes are available and the summary and conclusion is finalized.

5.5 PQR Annexes

5.5.1.1 API PQR Annexes

Annex	Activity	Responsability
0 - Description of the Production Process and batch listing	A description of the production process for the relevant manufacturing steps for the considered APIs	IMQ
1A - QC of Finished API 1B - In-Process-Control	A review of critical in-process control and critical API test results.	QC
2 - OOS in QC	A review of all batches that failed to meet established specification(s).	QC
3- Deviations	A review of all critical deviations or non-conformances and related investigations.	IMQ
4A– Changes in Analytical Methods - QC 4B - Changes in Analytical Methods - In Process Control 4C - Changes in Production Process 4D - Changes in Specification	A review of all changes carried out to the processes or analytical methods.	IMQ
5 - Stability	A review of the results of the stability monitoring program.	QC
6- Complaints, Returns and Recalls	A review of all quality-related returns, complaints and recalls.	IMQ

Annex	Activity	Responsability
7- Previous Actions	A review of adequacy of corrective actions.	IMQ

5.5.1.2 Finished Product PQR Annexes

Annex	Activity	Responsability
1 - Starting Material	A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances	IMQ/ ESQ
2A - QC of Finished Products 2B - In-Process-Controls	A review of critical in-process controls and finished product results	QC
3 - OOS in QC	A review of all batches that failed to meet established specification(s) and their investigation	QC
4- Deviations	A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken	IMQ
5A – Technical Change Controls 5B – Product Change Controls	A review of all changes carried out to the processes or analytical methods	IMQ/ CMC
6 - Variations	A review of Marketing Authorisation variations submitted, granted or refused, including those for third country (export only) dossiers	RA
7 - Stability	A review of the results of the stability monitoring program and any adverse trends	QC/IMQ

Annex	Activity	Responsability
8 - Complaints, Returns and Recalls	A review of all quality-related returns, complaints and recalls and the investigations performed at the time	IMQ
9 - CAPAs	A review of adequacy of any other previous product process or equipment corrective and preventive actions	IMQ
10 - Post-marketing Commitments	For new marketing authorizations and variations to marketing authorizations, a review of post-marketing commitments	RA
11A - Qualification Status – QC 11B- Qualification Status – IPC 11C - Qualification Status Production – Formulations – Bulk Product 11D - Qualification Status - Production – Packaging	A review of the qualification status of relevant equipments and utilities, e.g. HVAC, water, compressed gases, etc.	IMQ/QC
12 - Technical Agreements	A review of any contractual agreements as defined in Chapter 7 (of EU GMP Guideline, Part I) to ensure that they are up to date	ESQ/IMQ

5.6 Manufacturing, Testing and Release on behalf

If a product is manufactured, tested and/or released externally on behalf, the responsibilities for creating the PQR shall be regulated in accordance to the corresponding Quality Agreement.

5.7 MAH Review and Amendment of PQRs

5.7.1 MAH Review

The MAH is accountable for performing the PQR review (MAH review) according to the plan (SUP-004779) and evaluating the results of the review.

The MAH review shall be performed by the relevant Commercial Quality Assurance of the sale affiliate/cluster¹ of Grunenthal, when the sales affiliate is appointed as MAH of the product in the country.

The MAH review shall be done after 2 weeks from the approval of PQR review and the outcome of the MAH review shall be documented in the respective part 2 "MAH Review" of the relevant Supportive Document SUP - 004663 – PQR Evaluation Sheet".

The QA representative (CQA) of the MAH is requested to give a statement whether:

- Further corrective and/or preventive actions are required

and/or

- Further revalidation is required

and/or

- Nationalization of the PQR is required (e.g. adding extra PQR annexes for local stability studies or QC data from local product testing)

If the QA representative (CQA) of the MAH identifies:

- any corrections/adjustments necessary to the relevant PQR report already approved
- any need for further CAPAs
- any need for revalidation

he/she shall be accountable to align this with the product releasing Qualified Person.

5.7.2 Amendment of PQRs according to national Requirements

PQR data shall also enable the MAH to identify the need for improvement in its own regulatory affairs processes that operate in conjunction with the manufacturing sites.

If a PQR needs to be nationalized, this shall be done by using the template "Product Quality Review Finished Product SUP - 004662.

¹NOTE : in case of a cluster of affiliates, the CQA is legally accountable to maintain the QMS and ensure compliance with regulatory requirements in all countries under the relevant cluster.

At least the changed annexes and a new summary and conclusion chapter need to be added.

5.8 Distribution and Archive

The PQR and MAH reviews shall be accessible at least to the responsible Qualified Person, Head of Quality Assurance, Head of Production, Head of Quality Control and to all country Quality Assurances where Grunenthal is the marketing authorization holder. The PQR and MAH reviews shall be archived and retained for the period as prescribed by the Grunenthal procedure for the data retention requirements.

6 References

- EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Part I, Chapter 1.10
- EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Part II, Chapter 2.6
- PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I
- PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part II (API)
- Reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders EMA/457570/2019
- ICH Q7 Note for guidance on good manufacturing practice for active pharmaceuticals ingredients (CPMP/ICH/4106/00)
- Regulation (EU) 2017/745 (MDD)

7 Historical index

Revision/ document no.	Description of changes
01	Migration to MasterControl
02	<ul style="list-style-type: none">• §3 Updated Responsibilities• §4 Updated table• §5 Completely reviewed as follows:<ul style="list-style-type: none">○ §5.1 reviewed in order to describe better the general process○ §5.2 replaced with the Process Flows and the references to the relevant supportive document for the creation of the PQR Plan – SUP 004779)○ §5.3 completely reviewed with the reference to the relevant supportive document SUP 005587○ §5.4 replaced with the description of PQR content

Revision/ document no.	Description of changes
	<ul style="list-style-type: none">○ §5.5 replaced with the description of PQR annexes (§5.5.1 and §5.5.2)○ §5.6 changed numbering of the section (in the previous version "The manufacturing, Testing and Release on behalf" was reported in the section §5.8)○ §5.7 reviewed the description of the MAH review and amendments of PQR and changed numbering of the section respect with the previous version<ul style="list-style-type: none">▪ Updated the section with the new supportive documents numbers migrated in MC○ Removed the section of Customized PQR (previous §5.9)○ §5.8 Updated the section related the Distribustion by changing the title with "Distribution and Archive" and adding the information regarding to the archive (this section corresponds to the section 5.10 of the previous version)• §6 Updated the references
03	<ul style="list-style-type: none">• Updated template version• §5.2 Process Flows: removed the reference to the PROC-005047