Number:	
Title:	
Title (EN):	
Type:	**Scope:**
Area:	
Country:	
Previous Number:	

Document Information

Revision:	**Status:**
Effective Date:	

1   OBJECTIVE

The objective of this document is to define how the Product Quality Review Process must be managed for Medicinal Products or Drug Substances manufactured by Grünenthal or where Grünenthal acts as Marketing Authorization Holder.

2   SCOPE

This document applies to all Grünenthal employees which are involved in the Product Quality Review Process.

3   RESPONSIBILITIES

Function/Role	Responsibility
Global Quality Management System department	Ensure compliance of the Quality Management System at Grünenthal with external guidelines/ standards/ regulations applicable; Ensure global oversight on the process.
Internal Manufacturing Quality Assurance	Implement the process on a local level and ensure adequate documentation management according to this SOP; Create PQRs according to the Annual PQR Plan; Align with contributing departments to create annexes timely to fulfill the Annual PQR Plan; Alignment with the releasing QP the need for further CAPAs/revalidation as an outcome of the evaluation of the consistency of the existing processes, the appropriateness of current specifications for both starting materials and finished products; Notify CQA that approved PQRs are ready for MAH Review; Share PQRs with customers whenever requested.
Contributing departments	Create PQR annexes (as defined in SUP-013083 "Overview and Responsibilities of API and FP PQR Annexes")
Commercial Quality Assurance	Planning of MAH reviews of the PQRs; Approve the PQR plans;

Function/Role	Responsibility
	Review the PQR results as Marketing Authorization Holder (MAH) or according to specific local responsibility and assess the necessity for further CAPAs, revalidation or amendments to the PQR;
	If applicable, create the PQR of in-country GMP activities (e.g. QC Testing);
	If all manufacturing steps including batch certification are performed by a CMO, involve responsible Regulatory Affairs department to create Annex 6 and/or 10 and attach these annexes to the MAH Review document
External Supply Quality Assurance	Prepare and approve the PQR plan if all manufacturing steps including batch certification are performed by a CMO and/or ESQ;
	Approve the PQR plan of products where CMOs are involved;
	Implement responsibilities for PQR creation in TQAs with external CMOs;
	Request PQR timely to external CMOs;
	If batch certification is done by IMQ, forward CMO PQR to IMQ for review and approval;
	If all manufacturing steps including batch certification are performed by a CMO, review and approve CMO PQR;
	If batch certification is done by ESQ, prepare, review and approve the PQR;
	Notify CQA that approved PQRs are ready for MAH Review;
	When needed, escalate issues related to CMO PQRs.
Qualified Person for batch certification	Review the PQRs whenever batch certification is done by GRT QP and evaluate (also if raised by CQA during the MAH review) any need for further CAPAs and/or revalidation;
	Approve the PQRs whenever batch certification is done by GRT QP.
	Notify CQA that approved PQRs are ready for MAH Review

4   TERMS AND DEFINITIONS

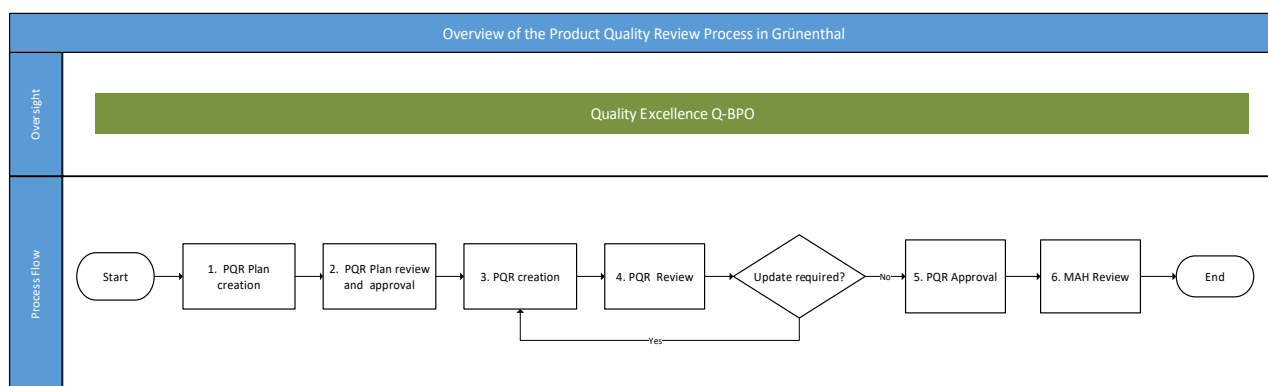| Term/Abbreviation	Definition
API	Active Pharmaceutical Ingredient
CAPAs	Corrective Actions and/or Preventive Actions
CMO	Contract Manufacturing Organization
CQA	Commercial Quality Assurance
Contributing departments	e.g. but not limited to: Quality Control, Production, Regulatory Affairs
Cluster of affiliates	Group of countries operating under the same CQA organization
ESQ	External Supply Quality Assurance
GMP	Good Manufacturing Practices
CMC	Chemintry, Manufacturing and Controls
GQA	Global Quality Assurance
IMQ	Internal Manufacturing Quality Assurance
GRT	Grünenthal
IPC	In-Process-Control
MAH	Marketing Authorization Holder
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 DESCRIPTION

5.1   General

Regular Periodic Quality Reviews (PQRs) of Finished Products and APIs must be conducted for products manufactured by Grünenthal and/or where Grünenthal acts as Marketing Authorization Holder, to verify the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished products. Additionally, PQRs allow to identify product and process improvements, ensuring complete oversight on the quality of the medicinal product and safety of the patient.

The process flow (figure 1) describes the end-to-end process steps that must be followed when planning, creating, approving and executing the MAH review of PQRs. Compliance with applicable local legislations and existing agreements with license partners must be ensured.

Figure 1: End-to end PQR Process

The responsibilities of each step of the PQR process are described in table 1 and depend on the following scenarios:

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

Table 1: PQR Process Responsibility Matrix

Manufacturing Process Step	All manufacturing steps (incl. release) are performed by a CMO	Manufacturing steps split between CMO and GRT site	All manufacturing steps are performed by GRT site(s)
1. PQR Plan creation	ESQ	ESQ/IMQ	IMQ
2. PQR Plan Review and Approval	ESQ, CQA	IMQ, ESQ and CQA	IMQ and CQA
3. PQR creation	ESQ (request to CMO)	ESQ (request to CMO) IMQ (creation in GRT site)[1]	IMQ
4. PQR Review and Approval	ESQ	ESQ[1]/IMQ	IMQ
6. MAH Review	CQA	CQA	CQA

Whenever more than one entity is involved in the creation and review of the PQR (e.g. MAH is not the manufacturer, or manufacturing/testing is split between different manufacturing sites), a TQA must be in place between the various parties defining their respective responsibilities in producing the PQR.

5.2 Creation, Review and Approval of PQR Plans

Regular periodic quality reviews of all authorized medicinal products must be conducted and documented annually (unless differently specified and supported by risk assessment). An annual plan for PQR creation must be generated by the responsible department (see table 1).
The planning of PQR creation, approval and MAH review must consider the timelines outlined in 5.3 and 5.4 (see below). When applicable, the timelines must be adjusted to ensure timely provision of the PQR as agreed with suppliers and/or customers in the respective Technical Quality Agreements.

In case of products with manufacturing steps split between manufacturing sites, the IMQ department of the manufacturing site performing the last manufacturing step is the leading site and must coordinate the planning of PQR with the other affected IMQ department (in case of GRT site) or ESQ (in case of CMO).

The PQR plan must be created and approved by the responsible departments outlined in table 1 within the first quarter of each year. A PQR Plan template is provided in SUP-004779 "Product Quality Review Plan Template". Any delays to the PQR Approval and MAH Review as stipulated in the PQR plan must be appropriately documented by a deviation (see PROC-004019 – "Global Process for Deviation Management").

---

[1] When batch certification is done by ESQ QP, ESQ must create/approve the internal PQR

PQR Plans must be approved and stored as described in the WIN PROC-008741 "Managing PQRs in MasterControl".

5.3　Creation, Review and Approval of PQRs

Products with 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 must be assessed together and specific features must be pointed out.
Whenever more than one manufacturing site is involved (internal or external) and batch certification is done by a GRT QP, the respective department/site in GRT responsible must:

- Coordinate the collection of the PQRs of the other manufacturing site(s)[2] and other annexes by GRT functions[3]
- Prepare a consolidated PQR report, including a "Summary and Conclusion" section, with reference to all annexes.

When performing the PQR review, if significant quality issues are identified for the first time, these must be evaluated and if necessary, documented in Grünenthal's eQMS (MasterControl) and properly escalated.

Compiled PQRs must be reviewed/approved and stored as described in the WIN PROC-008741 "Managing PQRs in MasterControl" by the department(s) described in table 1 "PQR Process Responsibility Matrix". Whenever batch certification is done by GRT QP, the responsible QP must be one of the approvers.

The department responsible for PQR approval, as described in table 1 "PQR Process Responsibility Matrix", must notify CQA that approved PQRs are ready for MAH Review.

The tables below describe the timelines for the preparation, review and approval of the PQR by the respective Quality department (see table 1 – "PQR creation" and "PQR review and approval"). While the periods PQR delivery/creation are indicative, the date of the PQR approval (as outlined in the annual PQR plan) must be respected. When applicable, the timelines may be adjusted to respect agreements stipulated in Technical Quality Agreement with CMOs.

---

[2] Whenever a CMO is involved, the coordination with the CMO is done through ESQ
[3] Annexes by other GRT functions include e.g. Annex 6 and 10 (Regulatory Affairs) (see SUP-013083 "Overview and Responsibilities of API and FP PQR Annexes")

Table 2: Timelines - All manufacturing steps (incl. release) are performed by a CMO

Weeks after end of review period	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
PQR delivery by CMO	███	███	███	███	███	███	███	███	███	███	███	███				
PQR Review and Approval													███	███		

Table 3: Timelines - Manufacturing steps (incl. release) in GRT site or split between Manufacturing Sites (CMO and/or GRT sites)

Weeks after end of review period	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
PQR delivery by CMO (if applicable)	███	███	███	███	███	███	███	███	███	███	███	███				
PQR creation by GRT manufacturing site(s) (if applicable)	███	███	███	███	███	███	███	███	███	███	███	███				
Summary and Conclusion by (last) GRT site (if applicable)													███	███		
PQR Review and Approval by GRT manufacturing site															███	███

5.3.1 Content of Finished Product PQR

The PQR report must contain a comprehensive and systematic review of all aspects related to the quality of a Finished Product and/or API over a defined period.
The templates outlined in SUP-004661 "Product Quality Review API (Template)" and SUP-004662 "Product Quality Review Finished Product (Template)" must be used to when creating the PQR for internally manufactured APIs and Finished Products.
Annexes include the GRT and EU GMP regulatory requirements. If special requirements by customers or local regulations exist, these must be added and listed in the Table of Contents.
Annexes must be signed outside of MasterControl.

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

Table 4: Sections of the PQR

Section	Section description
Summary and Conclusion	- 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. - Assess whether corrective and preventive action or any revalidation should be undertaken
Table of contents	- List the main topics covered in the Product Quality Review document with the indexing and reference page number - Include any local additional requirements if needed (each site shall add the name of the item as a complementary in the respective template SUP-004661/SUP-04662 – e.g: Annex "Complaints" shall be named as "Complaints & Adverse Events" in case Adverse Events must be listed
Description of the Production Process and Batch Listing	- Description of main production process steps (incl. testing) and location(s) - Released batches during review period
Annexes	- All annexes of the PQR must be created in the English language for global products and preferably in English for local products. - A high-level description and responsibility for creation of each annex of API and FP PQR is described in SUP-013083 "Overview and Responsibilities of API and FP PQR Annexes"

5.4 MAH Review and Amendment of PQRs

A MAH Review must be conducted for Finished Product PQRs and must take place within 20 working days after the PQR Approval. The MAH review must be documented in SUP-004663 "MAH Review (Template)" or, if required by local authorities, an alternative approved template.

The MAH is accountable for performing the MAH review, which includes an evaluation of:
- whether corrective and preventive action are required

- any revalidation should be undertaken

- PQR of in-country GMP activities (e.g. QC Testing) is needed [4]

- Products from CMO: Annex 6 and 10 by GRT Regulatory Affairs is needed

---

[4] If needed, SUP-004662 "Product Quality Review Finished Product (Template)" must be used. At least the changed annexes and a new summary and conclusion chapter must be added.

The MAH review must be performed by the relevant Commercial Quality Assurance of the sale affiliate/cluster[5] of Grünenthal, when the sales affiliate is appointed as MAH of the product in the country.

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 is accountable to align this with the product releasing Qualified Person/equivalent function (or ESQ, when all manufacturing steps incl. batch release are done at CMO).

For CMO products, if Annex 6 and/or 10 are required, CQA must align this need with the responsible Regulatory Affairs department (responsible unit, as described in SUP-013083 "Overview and Responsibilities of API and FP PQR Annexes". Annex 6 and 10 must be compiled with the MAH Review and become one single document.

Compiled MAH Review documents must be approved and stored as described in the WIN PROC-008741 "Managing PQRs in MasterControl" by the GDP-RP of the respective MAH (see table 1 "PQR Process Responsibility Matrix").

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
04	• Overall: Reformulation of text for better clarity • § 1 Objective: Reduced to describe only objective of the document. Objective of the process moved to § 5.1 General

---

[5] 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.

Revision/ document no.	Description of changes
	• § 2 Scope: Reduced to describe scope of the document. Scope of the process moved to § 5 Process Description • § 3 Responsibilities: Step-by-step responsibilities moved to § 5 Process Description • § 5 .1 General: Generic process flowchart deleted (newly created flowchart serves the same purpose); Topics related to PQR planning and creation moved to § 5.2 Creation, Review and Approval of PQR Plans and § 5.3 Creation, Review and Approval of PQRs • § 5.2 Process Flows: Process flowchart simplified to common steps and placed in § 5 .1 General; Responsibilities of three scenarios depicted in table 1 • § 5.3 Filing of PQR plan, PQR review and MAH Review: Deleted since filing is done in MasterControl (described in the newly created WIN PROC-008741 "Managing PQRs in MasterControl") • § 5.4 Content of Finished Product PQR: Changed to § 5.3.1 Structure and Content of PQR Report; Addition of section "Description of the Production Process and Batch Listing" to reflect PQR structure; Removed "and/or any interruption of product distribution."; Sections related to the creation, review and approval steps of the PQR moved to § 5.3 Creation, Review and Approval of PQRs; Sections related to details to be evaluated in the PQR removed, since they are covered in the annexes/related procedures.; Naming convention details moved to WIN PROC-008741 "Managing PQRs in MasterControl" • § 5.5 PQR Annexes: table with overview of annexes and responsibilities moved to newly created SUP-013089 "Overview and Responsibilities of API and FP PQR Annexes" • § 5.6 Manufacturing, Testing and Release on behalf: Requirement moved to section § 5.3 Creation, Review and Approval of PQRs • § 5.7 MAH Review and Amendment of PQRs: Addition of requirement (CMO products) for CQA to evaluate the need for creation of Annex 6 and/or 10 by the responsible Regulatory Affairs department • § 5.7.2 Amendment of PQRs according to national Requirements: Merged with § 5.7 MAH Review and Amendment of PQRs

Revision/ document no.	Description of changes
	• § 5.8 Distribution and Archive: Deleted since this step is covered by MasterControl system (described in WIN PROC-008741 "Managing PQRs in MasterControl")
	• SUP-004779 "Product Quality Review Plan Template": Renamed to "PQR Plan (Template)" and changed to Excel format to facilitate usage; Instructions moved to section § 5.2 Creation, Review and Approval of PQR Plans of main SOP (PROC-004198); Simplification of timelines which were moved to section § 5.3 Creation, Review and Approval of PQRs of main SOP (PROC-004198)
	• SUP-005587 "Filing PQR plan, PQR and MAH review": Deleted (archived); Newly created process of upload, approval and storage of PQRs in MC described in WIN PROC-008741 "Managing PQRs in MasterControl"
	• SUP-001227 "ESQ review of CMO PQR": Deleted (archived) as responsibilities of ESQ are described in main SOP (PROC-004198)
	• SUP-004663 "PQR Evaluation Sheet" renamed to "MAH Review (Template): Reduced to elements needed to document MAH Review
	• SUP-004661 "Product Quality Review for API (Template)" and SUP-004662 "Product Quality Review for Finished Products (Template)": Changes to templates