**Document approval**

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# Purpose

The purpose of this **Quality Manual** is to describe the Quality Organization and Quality Management System (QMS) including management responsibilities associated with it.

It is the responsibility of e.g., Quality Management Director to ensure compliance with the requirements of this **Quality Manual** at the function/entity level.

# Company Profile

Grau Pharma GmbH is GRAU is a trade organization engaging in wholesale, import and export operation of pharmaceuticals and active pharmaceutical ingredients (API).

e.g., CEO establishes, implements, and maintains a quality policy that includes Grau Pharma GmbH’s Quality commitments. Our Quality commitments are reflected in MD-01 Quality Commitment Appendix to this Quality Manual.

Current Grau Pharma GmbH’s organizational structure is reflected in MD-01 Organigram Appendix to this Quality Manual.

# Quality Organization

Grau Pharma GmbH has a developed, implemented, properly functioning, and continually improving Quality Management System in place.

Grau Pharma GmbH’s Quality Management System provides a systematic, risk-based approach to consistently and effectively ensure control of the distribution chain and consequently maintain the quality and the integrity of medicinal products.

The Grau Pharma GmbH’s Quality Organization is an independent function responsible for the development, implementation, and maintenance of the QMS. It consists of a formal organization with defined lines of accountability, as well as advisory and decision-making bodies, and is responsible for Quality Assurance (QA), Quality Management (QM) throughout the organization. In cases when all parts of Quality are impacted the term Quality Organization may be used, and until Quality Management is formally separated QA and QM are effectively used interchangeably.

The Quality Organization is headed by e.g., Quality Management Director. e.g., Quality Management Director act as Responsible Person in Grau Pharma GmbH according to Article 79 (b) of Directive 2001/83/EC.

Responsibilities of the Responsible Person include:

* ensuring that a QMS is implemented and maintained;
* focusing on the management of authorized activities and the accuracy and quality of records;
* ensuring that initial and continuous training programs are implemented and maintained;
* coordinating and promptly performing any recall operations for medicinal products;
* ensuring that relevant customer complaints are dealt with effectively;
* ensuring that suppliers and customers are approved;
* approving any subcontracted activities which may impact on GDP;
* ensuring that self-inspections are performed at appropriate regular intervals following a prearranged program and necessary corrective measures are put in place;
* keeping appropriate records of any delegated duties;
* deciding on the final disposition of returned, rejected, recalled or falsified products;
* approving any returns to saleable stock;
* (xii) ensuring that any additional requirements imposed on certain products by national law are adhered to

Quality Organization has the right to:

* enter all areas of Grau Pharma GmbH's facilities and gain access to all records necessary to fulfill Quality Organization’s responsibilities,
* suspend product distribution, if necessary, until quality or compliance issues are resolved, implement mandatory market action up to and including product Recall,

Responsible Person may delegate their duties, but the primary responsibility remains with delegator. The responsibilities may not be delegated to any person performing tasks that could create any conflict of interest.

# Governance

Our top management continuously demonstrates leadership and commitment to the QMS. The e.g., CEO is the chief executive officer of Grau Pharma GmbH, whose primary responsibilities include setting the vision, policies, making major company’s decisions, managing the overall operations and resources of the company, acting as the primary point of communication between key internal and external stakeholders, and being the public face of the company.

Quality oversight and governance is achieved through several committees across Grau Pharma GmbH.

## Leadership Team

Consists at a minimum of the C-Level representatives, the highest-ranking Quality representative, and may be amended as appropriate. In terms of quality and compliance, the Executive Committee ensures that the following are in place and visible:

* long-term planning and strategy for quality and compliance.
* the quality plan and strategy for Quality Organization is in place.
* compliance with applicable laws, regulations, and corporate policies.
* quality plan that includes review, approval and monitoring of implementation effectiveness.
* ensuring compliance with the requirements of this Quality Manual,
* ensuring that Quality Objectives are included in the overall company strategy, communicated and supported by all relevant functions/levels
* establishing a quality commitment that outlines the company's overall intentions and direction regarding quality
* demonstrating strong and visible support for the QMS,
* ensuring that customer requirements and applicable regulatory requirements are identified and met, and

# Management Review

The continued suitability, adequacy, and effectiveness of the QMS is ensured through periodic reviews of the Quality Plan(s), key performance indicators, and provided operations quality.

Key persons and stakeholders of Management Review processes are defined in   
**SOP-04** **Management Review.**

Multiple functions may be held or represented by a single person.

Management Review meetings shall be conducted by the Quality Organization on at least an annual basis to assess the ongoing suitability and adequacy of the QMS and to identify risks and/or opportunities for continuous improvement.

The purpose of Management Review is:

* review and measurement of the achievement of quality system objectives;
* identification of emerging regulations, guidance and quality issues that can impact the QMS;
* to demonstrate operations compliance with regulations/standards, customers, suppliers requirements,
* ensure that the products do not put patients at risk due to lack of safety, quality, or efficacy
* identify and evaluate trends and risks to promote continuous improvement of the QMS,
* ensure that QMS is effective, appropriate, adequate, and efficient,
* address resources necessary to support the QMS,
* assessment of performance indicators that can be used to monitor the effectiveness of processes within the quality system, such as complaints, deviations, CAPA, changes to processes; feedback on outsourced activities; self-assessment processes including risk assessments and audits; and external assessments such as inspections, findings and customer audits,
* review changes in business environment and objectives.
* review the quality plan, and quality commitment to ensure alignment and continued applicability to the company's strategy,
* review follow-up actions from previous Management Review meetings.

Management Review shall be documented and shall include a conclusion on the adequacy of the QMS and a list of appropriate actions. The results of Management Review shall be used as input into the review and revision of quality plans, objectives, etc.

# Resource Management

Resources are provided in order to effectively support the needs of the QMS, regulatory requirements, and to meet customer needs. Resource needs are addressed during Management Review and the quality planning cycle.

# Quality Objectives

Grau Pharma GmbH strives to supply clients with high quality, easy to use and reliable products. To achieve these outputs, Quality Objectives are established related to design, execution, distribution, monitoring and continuous improvement of quality in all functions.

# Quality Strategy and Planning

According to SOP-03 Quality Plan the Leadership Team develops:

* quality plans that outline the company's quality strategy as well as the Quality Objectives and quality commitment. Quality Plans are reviewed and updated periodically.
* Quality Objectives and priorities to ensure the implementation of the quality strategy. Changing business priorities and needs are reflected in periodic reviews of the quality plans.

The planning cycle is aligned with the budget cycle to ensure that the necessary resources are allocated to implement the plan(s). Targets are set based on various inputs, e.g., risk assessments, product evaluations, quality system assessments, audit and inspection findings, industry trends, changing regulatory environments and employee/cultural surveys.

The continued suitability, adequacy, and effectiveness of the QMS is ensured through periodic reviews of the Quality Plan, key performance indicators at various levels of the organization.

The results of the Management Review shall be used as input into the review and revision of Quality Plan.

# Leadership Responsibilities

Leadership Team is responsible for:

* implementing an effective and appropriate quality system to improve the quality and availability of reliable products.
* ensure compliance with the requirements of this Quality Manual,
* ensure that Quality Objectives are defined in line with the overall company strategy, communicated and supported by all relevant functions/levels,
* establish a quality commitment that outlines the company's overall intentions and direction regarding quality,
* participate in the development, implementation, monitoring and maintenance of an effective QMS to ensure the achievement of Quality Objectives,
* demonstrate strong and visible support for the QMS, ensure its implementation in the organization and support continuous improvement,
* ensure that customer requirements and applicable regulatory requirements are identified and met,
* participate in the development of quality plans and ensure their implementation, maintenance, and review,
* define the individual and collective roles, responsibilities, authorities, and relationships of all organizational units related to the quality system,
* Ensure that these interactions are communicated and understood at all levels of the organization,
* establish and provide adequate and appropriate resources and infrastructure necessary to implement and maintain the QMS and to continuously improve its effectiveness,
* ensure a timely and effective communication and escalation process to raise quality issues to the appropriate levels of management,
* ensure that product and process knowledge is managed from development through the product's commercial life cycle to product discontinuation by applying a systematic approach to the collection, analysis, storage, and dissemination of information related to products, production processes and components,
* participate in the appointment of key management personnel.

# Quality Management System

The purpose of a QMS is to comply with applicable regulatory requirements and customer expectations and to ensure that products and/or clinical trial materials are of the required quality for their intended use.

The QMS is a structured and documented approach that outlines Grau Pharma GmbH's expectations of GxP requirements and other relevant standards/recommendations to ensure the quality of GxP processes, products, and services. It provides a systematic, risk-based approach to achieving the desired level of quality consistently and effectively.

Grau Pharma GmbH has a single QMS for all aspects of our GxP business that covers GxP processes across the entire product and service lifecycle.

A QMS promotes innovation and continuous improvement.

Grau Pharma GmbH uses a QMS approach based on a system aiming to meet regulatory requirements related to specific GxP processes, including elements such as organization, management, standards, procedures, training, IT tools and respective metrics.

All quality subsections with the associated systems have a designated owner who is responsible for developing and maintaining an appropriate, purposeful, effective quality system. The owner ensures the effective and efficient implementation of regulatory requirements in applicable areas at Grau Pharma GmbH. Changes in regulations, enforcement trends and inspection results are monitored for their impact on quality systems, gaps are evaluated, and the owner determines the need for new or revised documentation.

Each owner is responsible, at a minimum, for:

* defining the quality strategy for the respective system and its implementation in cooperation with all affected functions,
* defining, developing and maintaining procedures for the implementation of the quality system strategy,
* defining, develop and maintain an appropriate level of harmonization within the systems., and
* monitoring performance and evidence of continuous improvement.

# Documentation of the QMS

The QMS and its requirements are outlined in the formal QMS documentation. The documentation system consists of four (4) levels of documentation, as described in [***Figure 1***](#_bookmark17) below.

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Description automatically generated

***Figure 1: Grau Pharma GmbH documentation system***

## Tier One - Master Documents

The first tier documents like Master Documents define Grau Pharma GmbH's key principles based on the regulatory requirements for quality system. The quality system Owner is responsible for overseeing the content of the Quality Module.

First tier documents are no working documents. Other QMS documentation e.g., Standard Operating Procedures (SOP) describe how principles are applied to operations.

The Quality Manual is a Master Document and describes the QMS, its scope, the fundamental processes, procedures, and the responsibilities of management. The Quality Manual may be shared on request, for example, with external stakeholders like Health authorities or inspectors.

The Quality Manual is defined by e.g., Quality Management Director, approved and signed by e.g., CEO, and reviewed during Management Review. The Quality Manual is revisited least every three (3) years to ensure alignment with the Grau Pharma GmbH's strategy.

## Tier Two – Policies

Policies are not working documents and describe the general policies which apply within the company.

## Tier Three – Operating Procedures (SOPs, Working Instructions)

Standard Operating Procedures (SOP) describe overarching general technical standards or Grau Pharma GmbH policies related to the QMS. Working Instructions (WI) describe how to conduct processes, methods, or activities. Their aim is to achieve a certain tier of standardization in an organization. Whenever a standardized process is described, the standards define the key steps of the process and the roles involved in performing the process, as well as their respective responsibilities. SOPs and WIs include templates for forms or other documentation required by legislation, such as protocols, master files or specifications.

## Tier Four – Records, Reports

Quality Tier four documents include filled quality records, reports are evidence, plans, forms, and checklists indicating that procedures and related instructions have been followed to achieve the expected results. These documents shall be managed by the relevant body in which the process is carried out.

## Applicability of QMS documentation

The Grau Pharma GmbH Master Documents and Policies applies to all GxP sectors and organizations.

The quality modules, SOPs and WIs apply to all relevant Departments depending on the processes and/or technologies applied in them.

Grau Pharma GmbH operations using specific technologies that require compliance with certain regulatory requirements will apply the Grau Pharma GmbH, Policies, SOPs and WIs on an individual assessment basis. Such specific regulatory requirements will be included in respective documents of Grau Pharma GmbH.

# Fundamental Quality Systems and Processes

## Quality Risk Management

The quality management and governance system cover the definition of the QMS strategy and its documentation, as well as the quality monitoring and planning processes and Quality Risk Management. The continued suitability, adequacy, and effectiveness of the QMS shall be monitored and evaluated through periodic Management Review.

A Quality Risk Management process is to be established to provide a proactive approach to identifying potential risks to the quality, safety, and effectiveness of products and processes. As part of the assessment, the quality risk assessment considers the severity and impact of the event. Results and decisions of risk assessments are implemented, as necessary, in Quality Plan or CAPAs.

## Data and Records

A Grau Pharma GmbH Document Management System has been implemented that defines the creation, control, distribution, periodic review, storage, and destruction of GxP documents and records. This includes documents related to the execution (e.g., SOPs, WIs, protocols), recording (e.g., forms, worksheets), and evaluation (e.g., reports) of quality-related actions and decisions.

Records and data must be managed to ensure their accuracy, completeness, consistency, and security (ALCOA principles). Established standards applicable to printed or electronic records must be followed. Data must be attributable, legible, current, original, accurate, and complete, consistent, permanent, and accessible (ALCOA). Data integrity must be maintained throughout the product lifecycle. Record retention times must be defined and aligned with Regulatory.

## Events

Related process are in place to ensure that all events (e.g., Deviations, Complaints, Quality Defects, incidents) that may adversely affect the identity, potency, quality, purity, product safety, or effectiveness of a product are documented, investigated, addressed, closed, and controlled appropriately in a timely manner.

Nonconforming products and operations are closely monitored, tracked, and quarantined and contained as necessary.

## Change Management

The Change Management process ensures that changes that may affect product or operation quality, validation status, or regulatory compliance are properly managed. Changes must be evaluated for their impact on quality, reviewed, approved, implemented, and documented.

## Audits Management

A program for internal auditing, service providers is effective and continuous. This ensures ongoing compliance with Grau Pharma GmbH’s and regulatory requirements / standards.

The regulatory inspection management process is to be established to coordinate and manage regulatory inspections, including the follow-up and closure of inspection results, and to ensure communication both internally and with the appropriate regulatory agency on any findings. It should also ensure proper communication within the organization on specific compliance issues.

## Escalation Event Management

The company has established process for the necessary escalation of product and operation related events and includes:

* escalation of quality-related issues to the appropriate management levels
* assessment of the need for market action related to such issues (Complains, Recalls, product falsified products containment), and
* informing regulatory authorities of potential product, operation quality and compliance issues, as required by applicable law.

Reporting to health authorities should be done in a timely manner. The system ensures that all regulatory obligations and corrective and preventive actions (CAPAs) are implemented and adhered to.

## 

A Suppliers and Customers Qualification system has been introduced. Appropriate qualification and approval of suppliers is performed prior to any procurement of medicinal products. It’s controlled by a procedure and the results documented and periodically rechecked.

When entering into a new contract with new suppliers, Grau Pharma GmbH carry out ‘due diligence’ checks in order to assess the suitability, competence and reliability of the other party.

Grau Pharma GmbH ensure that medicinal products supplied only to persons who are themselves in possession of a wholesale distribution authorization or who are authorized or entitled to supply medicinal products to the public. Grau Pharma GmbH checks and periodic rechecks actual authorization status by requesting copies of customer’s authorizations according to national law, verifying status on an authority website, requesting evidence of qualifications or entitlement according to national legislation.

## Suppliers, Customers Management

A system has been introduced to control services suppliers (outsourced activities) related to GxP activities. These processes should include selection, evaluation, monitoring and control of 3PL service providers related to GxP area and any related decision making in line with Quality Risk Management.

Handling operations procedures are in place to ensure adequate and reliable controls of procuring, receiving, storing, returning to saleable stock, selling, supplying, destructing, picking, returning, inventorying, transporting operations according to mutual responsibilities defined in respective Quality Agreements between Grau Pharma GmbH and 3PL contracted wholesalers.

## Computerized Systems Lifecycle Management

A system is in place that outlines the requirements for validation of computerized systems and lifecycle management of computerized systems regulated by GxP to ensure patient safety, product quality, and the integrity of regulated data. Continuous Improvement of Process Efficiency, Product Quality and Quality Management System

Monitoring information at each stage of the lifecycle is used to continuously improve process efficiency, product quality and QMS performance. The results of regular Management Review meetings and monitoring of internal and external factors affecting the QMS are used to determine CAPA that improve the system and related processes, allocate or reallocate resources, and/or revise the quality plan and Quality Objectives. These reviews and results shall be documented and communicated to Leadership Team.

# Terms and Abbreviations and Definitions

|  |  |
| --- | --- |
| **Term/abbreviation** | **Definition** |
| ALCOA | Acronym which stands for Attributable, Legible, Contemporaneous, Original, Accurate principles of data integrity. |
| CAPA | Corrective and Preventive Action. |
| Complaint | Expression of dissatisfaction with a product or service, which is filed by a consumer, customer, client. |
| Correction | Any actions immediately taken to minimize product, process and/or patient impact upon nonconformity discovery or other undesirable situation. Correction relates to containment whereas Corrective Action relates to the Root Cause. |
| Corrective Action | Action to eliminate the cause of a detected nonconformity or other undesirable situation (complaints, product rejections, quality defects, recalls, deviations, audits and regulatory inspections findings, trends from process performance and product quality monitoring).  Corrective Action is taken to prevent recurrence. |
| Customer | Person or organization that could or does receive a product that is intended for or required by this person or organization. |
| CoA | Certificate of Analysis; Indicate all parameters, associated Specifications, and methods used to test for Product release. |
| Deviation | Non-fulfilment approved instruction, procedure or established standard. Any unexpected event or occurrence where an established process was not followed.  Deviation can result in Nonconformities (Nonconforming Material, Nonconforming Product, Nonconforming Service). |
| Event | Deviations, Complaints, Nonconformities, CAPAs, or exceptions may adversely affect the identity, potency, quality, purity, Product safety, or effectiveness of a Product or Material. |
| Falsified medicinal product | Any medicinal product with a false representation of:  (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;  (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder; or  (c) its history, including the records and documents relating to the distribution channels used. |
| GDP | Good Distribution Practice is that part of quality assurance which ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacturer to the pharmacy or person authorized or entitled to supply medicinal products to the public. |
| GMP | Good Manufacturing Practices means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use. |
| GxP | Good x Practices (whereas x is a placeholder including, manufacturing, distribution, clinical, laboratory, or any other regulated environment applicable). |
| Holding | Storing medicinal products |
| Leadership Team | The Leadership Team refers to the top management at Grau Pharma GmbH and includes all Chief Executives. It provides strategic and operational leadership to the company. It sets goals, develops strategy, and ensures the strategy is executed effectively. |
| MAH | Marketing Authorization Holder |
| Nonconformity | Non-fulfilment of a requirement related to product characteristics (specifications) or results of product/condition/value/process/system monitoring, measurement, inspection, review, test, audit.  Nonconformities may arise as a result of previously occurring Deviations and may also lead to other Deviations and Nonconformities. |
| Nonconforming Product | Product that does not fulfill its specified requirements.  The Product is declared nonconforming in cases of confirmed Quality Defects, serious manufacturing process Deviations and product related Nonconformities. |
| Preventive Action | Action to eliminate the cause of a potential non-conformity or other undesirable potential situation (complaints, product rejections, quality defects, recalls, deviations, audits and regulatory inspections findings, trends from process performance and product quality monitoring). Preventive Action is taken to prevent occurrence. |
| Transport | Moving medicinal products between two locations without storing them for unjustified periods of time |
| Procuring | Obtaining, acquiring, purchasing or buying medicinal products from manufacturers, importers or other wholesale distributors |
| QA | Quality Assurance  Assures adherence to outlined processes and compliance guidelines. |
| Quality Defect | Product-related Nonconformity. Faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorization or product specification file, or any other serious quality problems which may result in the Recall of the Product or an abnormal restriction in the supply. |
| QMS | Quality Management System  Outlines the individual systems in order to tackle the strategy outlined in this Quality Manual.  It is a dynamic system providing a framework for planning, executing, monitoring and improving the performance of Quality Management activities. |
| Quality Management | Includes all Quality Processes from systems, production processes to labor and employee quality |
| Quality Objectives | The quality objectives are the main method used by companies to focus the goal(s) from the Quality Commitment into plans for improvement. |
| Supplying | All activities of providing, selling, donating medicinal products to wholesalers, pharmacists, or persons authorized or entitled to supply medicinal products to the public |
| Recall | The action of withdrawing specific batch/batches of Nonconforming Product/s (with confirmed Quality Defects) from the distribution chain for reasons related to Product quality, safety or efficacy, which could have adverse effects and compromise the health of patients. |
| RP | The Responsible Person is a designated person within the organization according to Article 79 (b) of Directive 2001/83/EC and carry out their duties in such a way as to ensure that the wholesale distributor can demonstrate GDP compliance and that public service obligations are met. |
| Root Cause | The underlying reason for or cause of one or more Deviations or events. When the Root Cause is removed or corrected, the Deviation will be eliminated. |
| SME | Subject Matter Expert  The person who possesses a deep understanding of a particular requested subject. Departments delegates, who assess for the potential impact in their domain of expertise, document the outcome and initiate appropriate actions. |

# Applicable documents

SOP-01 Documentation Management

SOP-02 Good Documentation Practice

SOP-03 Quality Plan

SOP-04 Management Review

SOP-05 Change Management

SOP-06 Deviation and Nonconformity Management

SOP-07 CAPA Management

SOP-08 Audits Management

SOP-09 Quality Risk Management

SOP-10 Training Management

SOP-11 Complaints and Recalls Management

SOP-12 Suppliers, Customers Management

SOP-13 Computerized Systems Lifecycle Management

SOP-14 Archiving

# Appendices

Appendix Quality Commitment

Appendix Organigram

# Document revision history

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Valid from** | **Description of the revision** | **Reason for the revision** |
| 1 | See header | Document created | QMS implementation |