**Document approval**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Name** | **Date** | **Signature** |
| **Author’s designation****e.g., Quality Specialist** |  |  |  |
| **Reviewer’s designation****e.g., Quality Management Director Deputy** |  |  |  |
| **Approver’s designation****e.g., Quality Management Director** |  |  |  |

|  |  |
| --- | --- |
| **Effective Date** |  |

**Table of Contents**

[1 Purpose 4](#_Toc126138727)

[2 Scope 4](#_Toc126138728)

[3 Responsibilities 4](#_Toc126138729)

[4 Definitions, terms and abbreviations 4](#_Toc126138730)

[5 Workflow 5](#_Toc126138731)

[5.1 General 5](#_Toc126138732)

[5.2 Annual planning 5](#_Toc126138733)

[5.3 Report preparation 6](#_Toc126138734)

[5.3.1 Cover Page 6](#_Toc126138735)

[5.3.2 General Information 7](#_Toc126138736)

[5.3.3 Summary 7](#_Toc126138737)

[5.3.4 Activities from previous APQR 7](#_Toc126138738)

[5.3.5 Conclusions and recommendations 8](#_Toc126138739)

[5.3.6 Material Sources 8](#_Toc126138740)

[5.3.7 Manufacturing 8](#_Toc126138741)

[5.3.8 Data analysis and trending 9](#_Toc126138742)

[5.3.9 Deviations and Nonconformities 9](#_Toc126138743)

[5.3.10 Out-of-Specification results 10](#_Toc126138744)

[5.3.11 Process and Analytical Changes 10](#_Toc126138747)

[5.3.12 Qualification status of relevant equipment and utilities 10](#_Toc126138748)

[5.3.13 Validation 11](#_Toc126138749)

[5.3.14 Quality agreements 11](#_Toc126138750)

[5.3.15 Stability program 11](#_Toc126138751)

[5.3.16 Medical complaints (Adverse Events) 12](#_Toc126138752)

[5.3.17 Technical Complaints (Supply Chain) 12](#_Toc126138753)

[5.3.18 Returned Products 12](#_Toc126138754)

[5.3.19 Recalls and Rapid Alert Notifications 12](#_Toc126138755)

[5.3.20 Marketing Authorization variations and post-marketing commitments 12](#_Toc126138756)

[5.4 Documentation 13](#_Toc126138757)

[6 Applicable documents 13](#_Toc126138758)

[7 Appendices 13](#_Toc126138759)

[8 Document revision history 13](#_Toc126138760)

# Purpose

The purpose of this Standard Operating Procedure (SOP) is to outline Annual Product Reviews (APR) and/or Product Quality Reviews (PQR). It covers current regulatory requirements and expectations. PQR and APR requirements are merged into one document, which is then referred to as Annual Product Quality Review (APQR).

# Scope

This SOP is valid at Company CDE for the whole Organization. The respective training shall be given in accordance with **SOP-10 Training Management**.

# Responsibilities

Responsible for the content of this SOP is e.g., Quality Management Director.

|  |  |
| --- | --- |
| **Role** | **Definition/Task** |
| Quality Organization employees | * compiles all information from the relevant stakeholders and completes the APQR Report.
* provides a final overall opinion on the quality of the product based on the information provided in the reports on the previous stages of production
 |
| e.g., QC Heade.g., Manufacturing Heade.g., Regulatory Affairs HeadQualified Person | * verify, review APQR Annual Plan, APQR Report
* provide information for APQR Report preparation.
 |
| e.g., Quality Management Director | * Approves APQR Annual Plan, APQR Report
 |

# Definitions, terms and abbreviations

|  |  |
| --- | --- |
| **Term/abbreviation** | **Definition at LenioBio** |
| APR | Annual Product Review |
| APQR | Annual Product Quality Review |
| ERP | Enterprise Resource Planning |
| FP | Finished Product |
| HVAC | Heating ventilation and conditioning system |
| IPC | in-process controls |
| MAH | Marketing Authorization Holder |
| OOS | Out-of-Specification |
| OOT | Out-of-Trend |
| PQR | Product Quality Review |

# Workflow

## General

A company performing the final stages of product manufacturing, i.e., providing a Finished Product (FP) ready for distribution, is responsible for ensuring that all stages of production are reflected in the appropriate APQR. APQR Report must contain a final overall conclusion on product quality based on the conclusions available in the APQR of the components that make up the finished product.

In the case where a manufacturing site carries on last manufacturing stages APQR Report shall refer to another valid and most recent APQR Reports prepared by manufacturing sites on previous manufacturing stages (for example, a pharmaceutical manufacturer would be expected to refer to the most recent approved APQR Report of a pharmaceutical substance in the pharmaceutical manufacturing process).

The generalized process is displayed in ***Figure 1.***

***Figure 1: Process Flow***

## Annual planning

The APQR Annual Plan shall be prepared according to **APQR Annual Plan Form** and shall contain the following features:

* Time frame: The default period covered by the site plan is one (1) year. The "From/To" date must be documented using a clear date format (e.g., 01.01.2022 to 31.12.2022).
* instances of the APQR that provide complete coverage of the products (e.g., drugs, intermediates, Active Pharmaceutical Ingredients (APIs), FPs, combination products, etc.) produced at the facility/organization.
* products, even if their production is not planned or planned in small volumes during the review period, to ensure that relevant issues are addressed (e.g., complaints, stability, changes, CAPA).
* If a product has been discontinued, the APQR must be conducted within the expiration date (or retest period, if applicable) of the last commercial lot and through the end of the stability program.
* If the product has been sold to another MAH, appropriate quality agreements with such legal entity should be made to ensure that APQR requirements are met throughout the product lifecycle.
* Any changes must be reviewed and approved by e.g., Quality Management Director (e.g., change the review period, or add additional products/intermediates to the program).
* Amendments to APQR Annual Planshould be made in a timely manner so that these amendments are reflected in the affected APQRs. In the event of a discrepancy between the approved APQR Annual Plan and the actual plan for a particular report, an APQR may be initiated prior to formal approval of the updated version of APQR Annual Plan. Document change reasons should be reflected in the updated version of APQR Annual Plan.

Each instance identified in APQR Annual Plan must contain at least:

* product information: e.g., product name, dosage form, strength, material identifier (e.g., ERP material number),
* review period.
* Review period rules:
* The default review period is twelve (12) months.
* Reduction of the review period is allowed and must be justified in the report itself.
* For a new commercial product, the APQR review period must include the production date of the first commercial batch. The review period begins on the production date of the first assigned commercial lot.
* APQR approval deadline: ninety (90) calendar days after the end of the review period.

## Report preparation

Quality Organization employees prepare particular reports according to approved APQR Annual Plan and schedule.

Each particular APQR Report shall be prepared according to **APQR Report Form**. The following points shall be included:

### Cover Page

Cover page may present the following information:

* product information (if available): product name, API name, dosage form, strength, material identifier (e.g., ERP material number),
* uniqueAPQR Report reference number,
* period of examination,
* list of author(s), reviewers, and approvers

### General Information

General information Indicates relevant product information: for example, product name, applicable product code(s)/numbers (e.g., ERP material code), manufacturing location(s), review period covered by this APQR Report, and (if applicable) justification of why the review period was shortened or extended.

### Summary

A summary of the information contained in the APQR Report should be provided at the beginning of the document. If the APQR Report is in the local language (e.g., German), an English translation of the summary should also be provided.

The executive summary should:

* contain a statement of the current status of the product or pharmaceutical substance/chemical intermediate in terms of control status (if the process is validated), process performance levels and compliance,
* include a statement that either the CAPA is not required or the CAPA(s) are deemed necessary as a result of the APQR (with brief description of each CAPA). Whenever CAPAs are needed, each CAPA must be traceable (e.g., CAPA IDs).
* confirm current specifications for both raw materials and product,
* identify useful opportunities for product and process improvement based on trends, Deviations, Nonconformities, and process performance. If the process is stable and performing well and there are no trends or problems, then no improvement action is required.
* For any problems identified, a reference to the corrective actions initiated as a result of the APQR should be included. Where necessary, further advice to CAPA on returning the product to audit or any revalidation action should be identified and justified.
* In addition, the author of the APQR Report of the finished product is responsible for providing a final overall opinion on the quality of the product based on the information provided in the reports on the previous stages of production, as appropriate.

### Activities from previous APQR

The Author provides a list of all actions/CAPAs identified during the current review period. These activities must be referenced to the relevant section of the APQR Report from which the CAPA was opened and a reference to the CAPA monitoring system must be provided with the appropriate record identifier.

The Author reviews the findings, recommendations, and related actions as specified in the previous APQR Report for the same product. Author provides a brief summary and status of all such activities. Any gaps or open activities must be clearly addressed and/or justified.

The Author should ensure that consideration is given not only to the actions formally documented in a previous APQR Report, but also to any other subsequent APQR/CAPA actions associated with that report (e.g., actions agreed upon and identified as a result of a MAH review that are not necessarily documented in the report itself).

### Conclusions and recommendations

This section will include a brief statement about the product, whether it can be produced according to specifications and GMP. The statement is the result of an executive summary. Basically, there are three possible outcomes:

* The product is suitable for further production and distribution.
* The product is suitable for further production, provided that appropriate actions are taken to eliminate the significant problems identified during APQR.
* The product is not suitable for further production and distribution due to issues identified during APQR.

### Material Sources

This section should provide a brief description of the quality of raw materials. A list of the relevant product components (e.g., pharmaceuticals, excipients, primary packaging and intermediates) should be provided. The following rules shall apply:

* Materials that are pharmaceutical substances should be specifically identified.
* For each ingredient listed, the supplier/manufacturer must be documented with qualification status and control information.
* Any change in supplier/manufacturer status should be noted and commented on.
* Any material from a new source should be noted and briefly explained.
* In addition, APQR Report for Finished Product should confirm the revision of related APQR Report for the pharmaceutical substance, indicating the document number and/or title and the dates of the review period.

### Manufacturing

This module should include:

* Number of lots produced during the period under review that were intended for commercial use and provide comments on lots not yet released.
* The number of lots released during the reporting period.
* Number of lots rejected during the review period, reference to the relevant investigation and decision on the part.
* Number of lots that were reprocessed during the review period (where reprocessing steps are not part of the approved process) and a reference to the relevant rationale.
* Number of reworked and reprocessed batches during the reporting period.
* A list of batch numbers or a summary of the number of batches may be provided.

At a minimum, a list of all materials covered (drugs, pharmaceuticals, combination products, and finished products) should be provided to clearly document the materials that fall within the scope of this APQR Report.

A reference should be provided for the last batch from the previous APQR Report and the first batch from the current APQR. A statement that all batches intended for commercial use are included should be provided.

For a list of batches produced during the period under review, any missing batches should be explained and justified, e.g., due to validation batches pending approval, orders cancelled/cancelled prior to the start of production, etc.

A flow chart or a brief description of the manufacturing process may be included in this section.

### Data analysis and trending

Analytical data from release tests and in-process controls (IPC), if they replace release tests, for all lots placed during the reporting period should be reviewed. The following Information on the statistical method can be used for the evaluation:

* information on the statistical method used to determine the statistical method used for the evaluation,
* appropriate summaries and aids for data evaluation and interpretation (e.g., trend charts),
* Any trends considered relevant should be discussed, including comparison with data from previous reporting periods, particularly in the context of demonstrating the effectiveness of CAPA.
* It is necessary to provide an opinion on this review and make recommendations if CAPAs are required. The applicable monographs or test specifications should be cited.
* All related CAPAs should be documented through the **SOP-07 CAPA Management** and realized under Changes in processing methods and/or analytical methods and specifications according to **SOP-05 Change Management**.

### Deviations and Nonconformities

All product related Deviations and Nonconformities closed during the review period must be submitted with reference to the investigation, root cause, the relevant CAPA and the effectiveness of the CAPA. For critical Deviations and Nonconformities a summary should be included.

A trend analysis of rejections should be conducted, and any observed trends or recurrences should be discussed along with the effectiveness of the CAPA (if the effectiveness of the CAPA cannot yet be assessed, it should be reviewed in the next reporting period). If a site periodically (for example, quarterly or semi-annually, but not annually) analyzes trends in Deviations and/or Nonconformities for a particular product and this evaluation is documented in an approved report, it is acceptable for the site to reference these reports rather than conducting an analysis of trends in the APQR itself. In this case, the relevant reports should be referenced, and the findings copied to the APQR. If any trends and/or issues are identified during APQR, further CAPA measurements shall be proposed. If the review period is not fully covered by the available trend reports (for example, the last quarterly report is prior to September and the APQR period is prior to November), confirm that the unassessed months will be covered in the next APQR.

### Out-of-Specification results

All lots with an Out-of-Specification OOS confirmed outcome that closed during the review period must be submitted, including a summary and references to relevant research, root cause, relevant CAPAs, and CAPA effectiveness. If the OOS was not closed within the review period, this should be reported and will be discussed in the next report.

Such events should be reviewed, and any observed trends or recurrences should be discussed along with CAPA effectiveness (if CAPA effectiveness cannot yet be assessed, this should be considered in the next review period e.g., quarterly or bi-annually, but not annually). OOS trends for a specific product and this assessment are documented in an approved report; it is acceptable for the site to refer to these reports rather than making the trends in the APQR itself. In this case, the relevant reports should be referenced, and the findings copied to the APQR Report. If any trends and/or issues are identified in the APQR, the CAPA reviewing the issue should be contacted. If the review period is not fully covered by the available trend reports (for example, the last quarterly report is prior to September and the APQR period is prior to November), confirm that the unassessed months will be covered in the next APQR.

### Process and Analytical Changes

All changes that may affect the quality of the product approved for implementation by Quality Organization, including those from previous review periods that were implemented and/or closed or cancelled/terminated during the review period, should be reported (changes that are open and never approved should not be reported).

These changes include:

* process changes (related to manufacturing and/or packaging processes),
* changes in analytical methods and/or specifications (including changes in starting materials where appropriate),
* changes in any raw materials (including chemical intermediates, pharmaceuticals, excipients and primary packaging materials),
* changes in sources of raw materials (applicable to new suppliers and changes of location for raw materials within the same company). This requirement also applies to changes in supplier status, such as downgrading or withdrawal of supplier certification or promotion from any status.
* changes in equipment.

The list should include a brief description, milestone, and regulatory compliance. If a particular country requires the first batch of product to be recorded at the time of sale, the batch number may be provided or, if this is not possible, the date of sale should be provided in the APQR Report.

### Qualification status of relevant equipment and utilities

A list of equipment (manufacturing and packaging) and utilities associated with the product shall be included in the APQR. This list shall include:

* a list and description of the equipment (for example, asset number)
* year of certification and/or qualification review
* any change with a reference to change management.

A conclusion should be provided on the suitability status of the equipment and utilities, and that they are acceptable or unsuitable for further production of the product in question. For any nonconformity, justification should be provided and adequate CAPAs should be identified.

The review of utilities should include all processing water types (e.g., for injection, purified, etc.), Heating ventilation and conditioning system (HVAC) and compressed gases, if present and used in the production process. The APQR must confirm that the equipment is within the adequacy test period. Note that the review must take into account the qualification of any automation inherent in the equipment itself.

### Validation

An overview and status of the validations associated with the product (e.g., process validation, packaging validation, analytical method validation) (including any revalidations that may have taken place during the review period) should be provided.

If a problem with a product's validation status is identified during APQR, it should be documented and addressed in the Conclusions and Recommendations section of the APQR Report.

### Quality agreements

All quality (technical) agreements with contractors, manufacturers and service providers that have a direct impact on the product (i.e., work outsourced to external partners such as contract manufacturers, contract warehouses, contract laboratories,) should be listed, reviewed and confirmed.

### Stability program

A summary of the stability data for all batches representing the stability of the manufactured batches intended for distribution must be provided.

The summary shall contain:

* + study reference number
	+ sample storage date
	+ planned duration (for example: 36 months, 48 months, etc.) and conditions (for example: 25 °C/60% relative humidity (RH), 30 °C/70% RH, etc.)
	+ Current condition or most recent test interval (e.g., 12 months, 24 months, etc.)

Data should be reviewed to identify and evaluate any trends. The review shall include any confirmed OOS/OOT (Out-of-Trend) results against the recorded specification limits obtained during the review period.

The conclusion of this review should include an assessment of trends and a statement confirming whether the stability data support the reported expiry date (in the case of a medicinal product) or review period (in the case of an API) or whether there is a need to update the stability data, registered specification limits or changes to the shelf life.

The Stability Report detailing the overall stability status of the product in the conclusion should be referenced to its identifier and explicitly where it can be found so that any interested party can easily access it.

### Medical complaints (Adverse Events)

This section is related to drug product.

The drug safety/pharmacovigilance service shall continuously monitor adverse reactions reported on the product related to a potential decrease in the quality of the medicinal product (for example, complaints of lack of efficacy, analysis of treatment errors possibly related to drug/formulation quality issues, wrong application of the medical device and/or combination product, etc.).

For the reporting period on drug safety/pharmacovigilance, an overall conclusion on whether the nature of the adverse event reports indicates a defect in the quality of the medicinal product should be provided. A comparison should be made with data from the previous reporting period to identify any trends.

If the APQR review period is not fully covered by available drug safety/pharmacovigilance trend reports, confirm that the months not evaluated will be covered in the next APQR.

### Technical Complaints (Supply Chain)

All supply chain complaints closed during the review period must be reviewed. For critical complaints, a list should be provided that should include, if possible: complaint number, country, lot number, nature of the complaint, and a summary. The investigation, root cause, and associated CAPA should be mentioned clearly as well. Non-critical supply chain complaints should also be listed. If reasonable, similar complaints may be grouped and summarized.

All data should be reviewed and compared with previous assessments. Any recurrence should be commented on, and recommendations should be made to address the underlying causes of the recurring complaints and eliminate or reduce them. All such recommendations and actions should be properly documented and monitored. The effectiveness of CAPA resulting from complaints should be verified.

### Returned Products

A list of returned batches for the review period must be provided. In this list, for each return, material and batch information, reason of the batch return should be provided.

### Recalls and Rapid Alert Notifications

List and overview of all recalls, regulatory notifications (e.g. Rapid Alert Notifications), feedback from the market or any other market action taken during the review period for the product should be provided.

A summary of each such case should include the serial number, lot numbers affected, and a reference to the relevant investigation and related CAPAs (if any).

### Marketing Authorization variations and post-marketing commitments

An overview, summary, and status of all relevant regulatory changes and Marketing Authorization options shall be provided for all countries where the product is authorized, whether submitted granted/approved or refused/rejected during the period audits.

Pharmaceutical manufacturing facilities involved in packaging and/or technical/production batch should also provide information on the status of any changes to the safety label.

An overview, summary and status of all post-marketing commitments submitted, opened, executed or closed during the review period should also be provided.

## Documentation

After completion APQR Annual Plan or APQR Report all related stakeholders (e.g., QC Head, e.g., Manufacturing Head, e.g., Regulatory Affairs Head, Qualified Person) review such documents.

e.g., Quality Management Director approves APQR Annual Plan, APQR Report.

Quality Organization properly retains and then archives such documents according to **SOP-16 Archiving.**

# Applicable documents

SOP-01 Documentation Management

SOP-02 Good Documentation Practice

SOP-05 Change Management

SOP-06 Deviation and Nonconformity Management

SOP-07 CAPA Management

SOP-10 Training Management

SOP-12 Complaints and Recalls Management

SOP-14 Material Management

SOP-13 Supplier Management

SOP-15 Computerized Systems Management

SOP-16 Archiving

# Appendices

The following appendices are integral part of this SOP:

Appendix APQR Annual Plan Form

Appendix APQR Report Form

# Document revision history

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