Product quality reviews

Document valid from:	**24.03.2025**	
Document number:	**I-SMI.TI.14e**	**Version 7.0**
Classification:	**Public**	
Replaced document:	**I-SMI.TI.14_06**	dated: 30.09.2019
Root SMI documents:	**--**	
Referenced QMI documents:	**--**	

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1. Purpose and scope

The importance and requirements for performing annual Product Quality Reviews (PQRs) are described and defined in the Guide to Good Manufacturing Practice for medicinal products, part I and part II, PIC/S document PE 009 respectively Eudralex volume 4. The PQR is considered a key document for verifying the consistency of the existing production process.
This technical interpretation describes the minimal expectations as well as recommendations for establishing and evaluating a PQR, that inspectors of the competent regulatory authority can have when assessing compliance with the guidance during an inspection of a manufacturer of medicinal products, a manufacturer of Active Pharmaceutical Ingredients (APIs) for medicinal products or a marketing authorisation holder, in order to assure a harmonized conduct of inspections.

2. Basics

- MPLO (SR 812.212.1)
- Guide to GMP, PIC/S PE 009, part I chapter 1.10 and 1.11 (product quality review for finished products)
- Eudralex volume 4, Part I, chapter 1.10 and 1.11 (Product Quality Review)
- Guide to GMP, PIC/S PE 009, part II chapter 2.6 (Product Quality Review for Active Pharmaceutical Ingredients)
- Eudralex volume 4, Part II, chapter 2.6 (Product Quality Review)

3. Definitions and abbreviations

API	Active Pharmaceutical Ingredient
FP	Finished Product
Marketing authorisation holder (MAH)	The company or other legal entity that has the authorization of Swissmedic to market a medicine in Switzerland or in other countries where he holds the authorisation. The Marketing authorisation holder is responsible for ensuring that he and any parties working for him comply with all relevant standards set out in Swiss legislation and guidelines. Compliance with these standards ensures the quality, safety and effectiveness of medicines once on the market.
Product Quality Review (PQR)	Documented regular periodic or rolling quality reviews of all licensed medicinal products or APIs with the objective of verifying the consistency of the existing manufacturing process to highlight any trends and to identify product and process improvements or weaknesses. For licensed medicinal products the appropriateness of current specifications for both starting materials and finished products is included
Responsible Person	Responsible Person according to Art. 5 and 6 (Manufacturer) Art. 17 and 18 (Marketing Authorisation Holder) of the MPLO. The RP is responsible for the quality of the medicinal products manufactured and ensures compliance with the legal provisions governing medicinal products. In this function the RP decides on the technical release (the final batch certification) and/or on the market release of a product batch.
TPA	Therapeutic products act (SR 812.21)

4. Interpretation

The PQR must be written in a defined language which can be understood by all involved parties (manufacturer, marketing authorisation holder, responsible person and competent regulatory authorities).

4.1 Content of the PQR

The Guide to GMP requires conducting PQRs for APIs and for all licensed medicinal products (including export only products) and lists the topics, which need to be taken into account (for finished products in the Guide to GMP, part I and for APIs in the Guide to GMP, part II).

It is expected that all topics listed in the Guide to GMP are explicitly addressed in the PQR. The extent (i.e. selection of the parameters to be reviewed, e.g. critical in-process controls) and depth of data review for each of these topics should be defined in a risk based way and should be suitable to highlight any trends in relevant quality characteristics and enable to identify the necessity for product and/or process improvements. The justification for the chosen extent and depth should be science based and documented. The justification can be described in a separate document. In general, the PQR has to cover all products and all the batches of a product produced during the review period. Grouping of products is acceptable but a scientific justification for the grouping must be part of the PQR.

To be able to verify the consistency of the existing production process, the number of batches produced should be as large as possible. Therefore, the PQR should include all the batches of a product produced and not only the batches supplied to one customer. For example, if a certain product is registered in several countries or produced for multiple customers (this means the products has multiple marketing authorisations), but the production process, the in-process controls and finished product specifications are the same, only one PQR covering all batches should be established and made accessible to all customers.

If a product is registered in several countries (multiple marketing authorisations) or produced for multiple customers, and the production process is essentially the same, with only minor variations in process controls and finished product specifications, only one PQR based on the most stringent criteria may be established and made accessible to all customers.

The PQR should contain summaries of the raw data for the reporting period, in form of tables, graphs or any scientifically sound statistical analysis to show trends and identify product and process improvements, comparing them with data of the previous reviews where appropriate. The summarized raw data of the reporting period should be included in the appendix of the PQR. The PQR should contain an evaluation of the results of the review and an assessment as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. It should also consider conclusions and preventive and/or corrective actions from previous reviews.

4.2 Responsibilities for the PQR

4.2.1 Responsibility for establishing the PQR

The overall responsibility for establishing the PQR lies with the manufacturer technically releasing the API and/or the finished product, or where different, with the Marketing Authorisation holder (MAH) releasing the finished product for the Swiss market or for export.

Where several companies are involved in the manufacture, analysis and release of the finished product, it is expected that all activities are summarized in one overall PQR. If the overall PQR

refers to PQRs, which are covering parts of the manufacturing activities, the conclusions from these partial PQRs should be included in the overall PQR and the covered partial PQRs should be listed in the PQR and be accessible to the manufacturer.

The manufacturers involved are expected to have SOPs for the preparation of the respective PQRs. These procedures should ensure that the content of the PQR is appropriate and that the necessary conclusions are drawn out of the reviewed data, documented in the PQR and necessary corrective and preventive actions are documented under their Pharmaceutical Quality System. Procedures for the application of trend analysis should be defined.

4.2.2 Responsibility for evaluating the PQR

Both, the manufacturer, and where different, the Marketing Authorisation holder, should evaluate the results of the PQR. The manufacturer should make an assessment in the overall PQR of whether corrective and preventative action or any requalification or revalidation should be undertaken. The evaluation should involve the senior management (e. g. head of manufacturing, head of quality control or quality unit) and the responsible person of the manufacturer or MAH.

The marketing authorisation holder should verify whether the product consistently fulfils the requirements as specified in the marketing authorisation. Where the manufacturer is not the marketing authorisation holder, the marketing authorisation holder should have a process described in an SOP for the evaluation of the FP PQR of the manufacturer and for performing a quality review of product specific aspects documented under the local Pharmaceutical Quality System (PQS). The review should at least include the following aspects:

a) a verification, that the reviews as defined in the Guide to GMP have been conducted
b) an evaluation of the conclusions drawn in the PQR, including a review of the trend analysis
c) a verification that the product is in compliance with the marketing authorisation
d) review of country-specific aspects documented under his PQS: number of batches rejected or released for the market, recalls, returns, complaints, quality defects, deviations, change controls, review of contractual agreements and marketing authorisation variations
e) an evaluation if corrective or preventive actions are necessary
f) review and follow up of previously defined actions
g) a general plausibility check, e. g. if batches released to the market are actually covered by the PQR and if the on-going stability program is covering the necessary batches

The results of the evaluation of the FP PQR and the review of country specific aspects should be documented. A clear link between MAH review and manufacturer's PQR should be established, for instance with a list of finished product batches dispositioned for the Swiss market during the review period. If batches have been received/released for the market during the review period which have been discussed in the manufacturer's PQR of a previous period, reference to the corresponding document(s) should be made in the MAH review report.

The evaluation of the FP PQR of the MAH and the review of country specific aspects (i.e. repackaging and quality defects) must also include batches of medicinal products that have been temporarily been authorised for use and limited placing on the market by Swissmedic according to Article 9 letter b TPA to bridge a period when an identical medicinal product authorized in Switzerland is not available.

4.2.3 Responsibility for reviewing the PQR process

The manufacturer or MAH should review the management of the PQRs, their timely preparation and approval, the implementation of defined actions and the effectiveness as part of the local Management Review process and verify these in self-inspections.

4.2.4 Technical Agreements

Technical agreements should be established between all parties involved in the manufacture and release of the API and finished product, defining who will take the overall responsibility for establishing the PQR and the way, the extent and the responsibility for providing data for the PQR. Such agreements must comply with chapter 7 of the Guide to GMP part I or chapter 16 of the Guide to GMP part II.
Where the MAH is not the manufacturer, there should be a technical agreement in place between the MAH and the manufacturer responsible for providing the overall FP PQR, signed by the responsible persons, that defines their respective responsibilities in producing the product quality review.

4.3 Review period of the PQR

The PQR should be established at least annually. The yearly periods may be set independently from the calendar year, i.e. not necessarily from January to December.
Review timeframes can be appropriately adjusted based upon manufacturing and campaign duration with adequate justification. The timeframe criteria should be established in a SOP. Where no or very few batches were produced during the year, the review period might be longer than 1 year. The chosen review period for such cases should include at least 5 batches. For those products with very few batches produced during a review period, a reasonable grouping with other products might be considered. The trend analysis can include results gathered from the previous period to ensure its robustness.

In any case, the PQR should be performed at latest after 3 years even if no production has taken place, or only very few batches have been produced, and should cover the relevant aspects (e. g. review of marketing authorisation variations, results of the stability monitoring programme, quality-related returns, complaints and recalls, adequacy of corrective actions, contractual arrangements).
Likewise, if during the quality and regulatory review (e. g. the Management Review) a special situation has been noticed e. g. regarding stability results, returns, recalls, negative trends with respect to complaints and/or deviations (including those arising from qualification and validation activities) or regulatory issues, a PQR should be established even if no or very few batches have been produced. A review of the defined actions of the last PQR should be included.

4.4 Timelines for establishing and evaluating the PQR

The PQR should be established in a timely manner by the manufacturer. “Timely” is considered as within 6 months after the end of the review period.
The evaluation and assessment of the FP PQR by the MAH should be completed at the latest 12 months after the end of the reviewed period and before the start of the new review period (whatever occurs before).

4.5 Products in co-marketing

The marketing authorisation holder of a product in co-marketing (art. 34-38 VAZV/OASMéd), in principle, has the same responsibilities as a marketing authorisation holder of a basic product. However, the co-marketing authorisation holder is not able to verify whether the product consistently fulfils the requirements as specified in the marketing authorisation because he does not have access to the marketing authorisation. Therefore, different requirements to the PQR are applicable.

The co-marketing authorisation holder should secure or at least verify that the marketing authorisation holder of the basic product establishes a PQR. Co-marketing-product specific aspects

like recalls, returns, complaints, quality defects or deviations must be integrated in the PQR of the basic product and must, therefore, be made available by the co-marketing authorisation holder to the marketing authorisation holder.

If the marketing authorisation holder does not establish a PQR, including co-marketing product specific aspects, the co-marketing holder is obliged to establish an adapted PQR (in line with this technical interpretation), which contains all the activities as defined in the Guide to GMP, part I, for which the co-marketing holder is responsible (e.g. primary and/or secondary packaging, changes, recalls, returns, complaints, quality defects, deviations or contractual arrangements).

The exchange of information between the marketing authorisation holder and the co-marketing authorisation holder (e. g. complaint data) should be defined in a technical agreement.

4.6 Parallel imported products

The MAH of a parallel imported product has typically no access to the PQR of the manufacturer of the product. However, as the marketing authorization holder, he should verify that the product consistently meets the requirements laid down in the marketing authorization and should have a procedure, described in an SOP, for conducting a quality review of specific aspects for parallel imported products (i.e. complaints, recalls, quality defects).

5. Changes to the previous version

- Chapter 3: FP, MAH, Responsible person and TPA included
- Chapter 4: Interpretation “responsible person” added
- Chapter 4.1: Textual adjustments. Data should be compared with data from previous reviews. Clarification that CAPAs should be documented within the Pharmaceutical Quality System
- Chapter 4.2.1: Clarification of responsibilities for establishing the PQR between the manufacturer, or where different, the marketing authorization holder. Textual adjustments. Precising that partial PQRs of the overall PQR must be accessible to the manufacturer/MAH
- Chapter 4.2.2: Clarification of responsibilities for evaluating the PQR between the manufacturer, or where different, the marketing authorization holder. Textual adjustments. Adjustment of country-specific aspects: Inclusion of number of batches rejected or released for the market, change controls, review of contractual agreements and an evaluation if corrective or preventive actions are necessary, inclusion of plausibility check and if the on-going stability program covers necessary batches. Precising that batches of medicinal products that have been temporarily been authorised for use and limited placing on the market by Swissmedic according to Article 9 letter b TPA must be included
- Chapter 4.2.3: New chapter “Responsibility for reviewing the PQR process”
- Separate chapter 4.2.4 for Technical Agreements issued (transferred from chapter 4.2.1)
- Chapter 4.3: Interval for establishment of a PQR if only a few batches have been produced or no production have taken place reduced from 5 years to 3 years
- Chapter 4.4: Clarification regarding timelines for establishing the PQR by the manufacturer and the MAH
- Chapter 4.6: New chapter “Parallel imported products”

6. Annexes

- None