Product quality reviews

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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. Basis

- 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
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

4. Interpretation

The PQR must be written in a defined language which can be understood by all involved parties (manufacturer, marketing authorisation holder, 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.

Normally, the PQR should not contain endless lists with single data (raw data) but should contain overviews, graphs or tables summarising the raw data. The PQR should contain a review and interpretation of the raw data followed by a condensed summary including an assessment and conclusion.

They PQR should 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

Where several companies are involved in the manufacture or analysis and where the marketing authorisation holder is different from the manufacturer, it is expected that one overall PQR is established. 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.

There should be one overall responsible person/organisation for establishing the PQR. This can be either the manufacturer technically releasing the API and/or finished products (and being responsible for final batch certification) or, in case of finished products, the marketing authorisation holder releasing the finished product for the (Swiss) market. Technical agreements should be established between all parties involved, 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.

It is expected that the overall responsible person/organisation as well as all involved manufacturers establish procedures (SOPs) for establishing the relevant part of the PQR. These procedures should ensure that the content of the PQR is appropriate and that the necessary conclusions are drawn out of the reviewed data and documented in the PQR.

4.2.2 Responsibility for evaluating the PQR

Both, the manufacturer, and in case of finished products, the marketing authorisation holder, should evaluate the results of the PQR and both should make an assessment of whether corrective and preventative action or any revalidation should be undertaken. The evaluation should involve the upper management and the responsible person of the companies involved.

The marketing authorisation holder should verify whether the product consistently fulfils the requirements as specified in the marketing authorisation. The process for the evaluation of the PQR and for the follow up of defined actions should be described in a SOP. The SOP of the marketing authorisation holder should include at least 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 trendings
c) a verification of being in compliance with the marketing authorisation
d) review of country-specific aspects like recalls, returns, complaints, quality defects, deviations or marketing authorisation variations
e) review and follow up of previously defined actions.

Documented evidence for having evaluated the PQR should be available.

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 or should be performed after 5 years if at least 3 batches have been produced. If after 5 years less than 3 batches have been produced, a PQR should be established as soon as 3 batches have been produced. For products with very few batches produced during a review period, a reasonable grouping with other products might be considered. The trending can include results gathered from the previous period to ensure its robustness.

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. “Timely” is considered as within 6 months after the end of the review period.

An evaluation of the results and an assessment of potential actions should be performed within 3 months after the establishment of the PQR. The evaluation and assessment of the PQR should be completed at the latest before the end of the next review period or at the latest 12 months after the end of the reviewed period (e.g. in case of a discontinued production).

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.

5. Changes to the previous version

- Chapter 2: Update of the references due to the revision of the MPLO (as at January 1, 2019)
- Chapter 4.3: Adaptation of the review period of the PQR to the guidance provided by the EMA (Q&A)

6. Annexes

- None