Guidance for Industry: Product Quality Review

Version 1.1

Pharmacy and Poisons Board

Contents

1. Introduction

This guideline is intended to provide general guidance on the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* (PIC/S Guide to GMP) with respect to implementing Product Quality Review (PQR).

There may be other acceptable approaches that provide an equivalent level of quality assurance. This guideline is not intended to create additional requirements and is not intended to form the basis for GMP inspections.

2. Purpose of this document

To provide guidance to industry on how to implement Product Quality Reviews (PQRs).

3. Scope

PQRs are a requirement in PIC/S Guide for GMP, Clause 1.4.

Regular periodic or rolling quality reviews of all registered pharmaceutical products, including export-only products, should be conducted to highlight any overall trends (not necessarily visible with other quality systems) and to identify product/process improvements by verifying and identifying:

- the consistency of the existing process(es);
- trends in product data;
- the appropriateness of current specifications for starting materials, intermediates and finished products;
- to verify compliance of the registered particulars of pharmaceutical products (Marketing Authorisation);
- deficiencies not detected by routine testing, monitoring or performance metrics; and
- identify opportunities for product and process improvements.

4. Scheduling product quality reviews

PQRs should typically be:

- carried out for each product manufactured in the previous year;
- take into account reviews from previous years; and
- use a risk-based approach, refer to *PIC/S Guide to GMP Annex 20: Quality Risk Management*.

A PQR schedule is documented (typically annually) for each product/group of products within a PQR register (or equivalent management tool).

Manufacturing circumstances	PQR scheduling requirements
Low batch numbers	If very few batches (for example, less than three) are manufactured within 12 months, a PQR could be conducted every two years. In this case the justification should also consider the risk associated with the type of medicine and should be documented.[1]
Prioritising specific PQRs	Consider the following to assist with the prioritisation of products for review: • recurring deviations on critical parameters; • recalls, complaints and returns; and • process changes.

[1] http://www.tga.gov.au/industry/manuf-medicines-cgmp-qa.htm#ch1 Question 20.

5. Grouping Products

PQR may be completed by grouping products by a particular characteristic/type.

Product groupings must be scientifically justified. For example, products selected within a group must be similar enough so that the parameters being reviewed in the PQR are representative of the group. Manufacturers should review every batch within the grouping.

The justification for the groupings selected must be documented in the PQR report, or alternatively, within the PQR procedure if groupings/approach will remain the same across successive PQRs.

Important: Groupings should not be justified based on commercial factors.

The grouped products should be of the same pharmaceutical form containing the same or very similar active ingredients and excipients, and manufactured using the same type of equipment.

Example of appropriate groupings:	Example of inappropriate groupings:
Groupings relevant to the facility's finished products could include: • final presentations are the same but different pack size or different brand name; • ingredients and primary packaging is the same, but different strengths; and • final presentations are the same but different marketed regions and/or product registrations.	The following groupings are unlikely to be appropriate because of factors such as significantly different excipients, chemical/physical interactions, different type of equipment used to manufacture etc.: • products with the same API but very different excipients; and • liquid vs. solid preparations of the same API (e.g. cream vs. topical ointment, tablet vs. gel-cap vs. capsule).

The number and name of all finished products manufactured will vary from year to year and as new licensed products come onto the market. Therefore, the number and name of each product manufactured during the period of review for the PQR must be included within the PQR report and within the PQR register.

6. Preparing product quality reviews

A PQR report should be prepared for every scheduled review using a controlled report template to ensure a standardised documentation approach. The report should include the following:

- product name(s);
- batch size(s) and presentation(s);
- review date;
- references to source data;
- comparison of the review from previous PQRs;
- date that the next review is required;
- groupings and scientific justification;
- identification of issues or trends;
- summary of findings, conclusions and recommendations;
- proposed actions; and
- names and signatures (with date) of the persons responsible for preparing, reviewing and approving the report.

7. Conducting anddocumenting a PQR

PIC/S Guide to GMP (Clause 1.4) requires the following parameters (at minimum) to be assessed when conducting PQR.

Parameter	Examples of information to be reviewed
Starting materials: A review of starting materials including packaging materials used in the product, especially those from new sources.	• Identify all starting and packaging materials received in the year and used in product manufacture • Name of the suppliers/manufacturers of the materials • Supplier's Certificate of Analysis (CoA) or Certificates of Compliance (CoC) or analytical results • Significant deviations or trends • Inspection rejection rate • Changes to production process or specifications by suppliers • Results of analytical tests
In-process controls and quality control testing: A review of critical in-process controls and finished product results.	Trend in-process test results and QC test results in the manufacturing and packaging process from both chemistry and microbiology aspects: Trending may take into consideration: • Physical variations – e.g. weight/dimension, friability, hardness, disintegration time, fill volume/overage, uniformity of content • Chemical variations – e.g. assay, related substances/manufacturing related-impurities, pH, residual solvents • Rejected units – e.g. breakages, particulates, etc. Yield reconciliation from stages of the manufacturing process using data from the associated batch records.
Manufactured batches (intermediates, bulk, finished products and campaign batches): A review of all batches that failed to meet established specification(s) and their investigation.	• List deviations and non-conformances associated with the product under review • Identify deviation/CAPA reports and the associated batches • Identify current status of investigations providing a summary of the: – reason for the failure – completed investigations – corrective actions taken – effectiveness of the action
Deviations and CAPA: A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.	• List the following relating to *significant* deviations and non-conformances: – reason for the failure – completed investigations – corrective actions taken • Assess corrective actions for significant deviations and non-conformances from previous PQRs, indicating the status of each of the corrective actions, and their effectiveness

Parameter	Examples of information to be reviewed
Process or testing changes: A review of all changes carried out to the processes, or analytical methods.	• Changes assessed should consider both those closed during the review period and approved to commence but not yet implemented. The change status should be identified e.g. approved to commence, closed and associated dates • Categorise the change type e.g. component, labelling packaging materials, manufacturing process, analytical methods etc. and assess for trends and overall impact on quality • Identify the batches affected • Provide a justification for the change • Review the effectiveness/impact of the change on the batch under review
Marketing authorisations: A review of Marketing Authorisation variations submitted/granted/ refused, including those for third country (export only) dossiers.	List and review the Marketing Authorisation variations (include third country/export-only dossiers): • number of products submitted and granted/refused • number of products registers locally and overseas • any changes made to the product that require submission of a variation to the Marketing Authorisation • for the above, variations that have been submitted. If not submitted, the reasons therefore should be investigated and a conclusion documented • for variations submitted, whether or not they have been granted or refused. If refused, the impact should be assessed and documented
Stability programme: A review of the results of the stability monitoring programme and any adverse trends.	• List the number of batches of product in review included in stability studies during the review period • Review the results of any long term and on-going stability of the bulk and marketed product • Include product information such as manufacturing date, reference to the associated method, shelf-life, etc. • Review any out-of-specification results
Returned product: A review of all quality-related returns and the investigations performed at the time.	• Batch number(s) • Reason for return and classification of reason for trending • Associated investigation report number • Actions taken and batches affected
Complaints and/or adverse events: A review of all quality-related complaints and the investigations performed at the time.	• Batch number(s) • Reason for complaint and classification for trending • Previous instances over a designated time period • Associated investigation report number • Actions taken and batches affected • Current status
Recalls: A review of all quality-related recalls and the investigations performed at the time.	• Batches/product recalled • Reason for recall and classification for trending • Regulator(s) notified and required regional responses • Associated investigation report number • Actions taken and batches affected • Current status

Parameter	Examples of information to be reviewed
Review of past PQR responses: A review of adequacy of any other previous product process or equipment corrective actions.	The focus of this requirement is on previous PQRs and the status and effectiveness of associated actions: • review and report on previous PQR CAPAs and change implementation status • assess effectiveness of actions taking into account the current PQR findings
Post-marketing commitments: For new Marketing Authorisations and variations to Marketing Authorisations, a review of post-marketing commitments (if any).	• Country of commitment • Product name and presentation • Description of the commitment • Status of the commitment
Equipment qualification: The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.	List and review the following for critical equipment/instruments and utilities in production and laboratory departments associated with the product in review: • Qualification/re-qualification status and the next qualification due date of equipment used in the production processes and QC laboratory • Reference to relevant qualification reports • Review changes made to equipment and utilities which resulted in re-qualification and assess for subsequent impact to product quality
Contractual agreements: A review of any contractual arrangements to ensure that they are up to date.	Review contracts for services associated with the product in review and report: • name and address of the contract acceptor • availability and details of the written contract • type of service provided e.g. testing or maintenance and calibration services • confirmation that the services provided are aligned with the marketing authorisation Refer to PIC/S Guide to GMP, Chapter 7 for additional information on contract manufacture and contract requirements.

8. Evaluating PQR results

The manufacturer must evaluate the results of the PQR to determine whether actions are required, including:

- corrective or preventative actions;
- validation or re-validation; and
- other site or process changes.

Processes should be demonstrated to be in control by determining upper/lower limits and trends. Preventative actions must be implemented for any processes shown to be not in control before deviations or out-of-specifications occur.

8.1 Identifying trends

Appropriate statistical analysis technique should be used to review the data collected as part of the PQR.

Technique	Example
Charting	• Run chart • Control chart (e.g I and MR charts)
Process capability studies	Process capability study is a statistical method which can be used by manufacturers to establish if specification limits are set appropriately (eg. UCL and LCL). It compares process information to the upper and lower specification limits It is recommended that Cp/Cpk values are targeted at 1.33 or above

8.2 Interpreting results

Analysis must be interpreted and documented as this will assist manufacturers to identify corrective and preventative actions if required.

Proposed actions and conclusions, including justification for not implementing actions when the PQR has revealed an adverse trend on product quality must also be documented in the PQR report.

9. PQR responsibilities with contract manufacturing

When manufacturing processes are partly or wholly contracted out, technical agreements should be in place between the various parties that defines their respective responsibilities in conducting the PQR.

Refer to PIC/S Guide to GMP, Chapter 7 for additional information on contract manufacture and contract requirements.

Document Information

Version	Date	Description of Change
1.0	27 Dec 2013	First version
1.1	Sept 2024	Reformatting of version 1.0

References

Document Title
PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE 009-10: Part I and II
PIC/S Guide to GMP Annex 20: Quality Risk Management
Health Sciences Authority Regulatory Guidance: Guidance Notes on Product Quality Review

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