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Department of Health
Therapeutic Goods Administration

Product Quality Reviews (PQRs) for listed and complementary medicines

Technical guidance on the interpretation of the PIC/S Guide to GMP

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TGA Health Safety
Regulation



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About this guidance

This guidance is for manufacturers of listed and complementary medicines manufactured according to the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* ([PIC/S Guide to GMP](#)).



This guidance is **only applicable** to manufacturers and sponsors of listed medicines and complementary medicines (including registered complementary medicines).

This guidance does **not** apply to medicines listed for export-only when the medicine would not be a listed or complementary medicine if supplied in Australia.

Purpose

This guidance is intended to clarify the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* ([PIC/S Guide to GMP](#)) in relation to conducting Product Quality Reviews for listed and complementary medicines.

Product Quality Reviews have become an accepted part of GMP requirements internationally and can provide useful information and additional controls over manufacturing processes and quality requirements for products.

Development of this guidance

This guidance was developed in collaboration with the [complementary medicine technical working group](#). Technical working groups comprise TGA and industry subject matter experts and have been established to develop, consider and review GMP guidelines.

This document is provided for **guidance only** and has been developed on the basis of current knowledge of the subject matter. It should not be relied upon to address every aspect of the relevant legislation. Please also refer to the *Therapeutic Goods Act 1989* and the *Therapeutic Goods Regulations 1990* for legislative requirements and the current version of the *PIC/S Guide to GMP*.

Disclaimer

This guidance is not mandatory or enforceable under law. It is not intended to be restrictive. We recommend following this guidance document to facilitate regulatory obligations being met. The guidance describes a way that a manufacturer may operate to demonstrate compliance with the relevant manufacturing principles (*PIC/S Guide to GMP*).



Guidance documents are not intended to establish a minimum standard of practice for inspection purposes. Guidance documents are not enforceable.

Related guidance

The following guidance is relevant:

- [TGA interpretation and expectations for demonstrating compliance with the PIC/S guide to GMP](#)

Purpose of PQRs

Product Quality Review (PQR) is a mechanism to ensure that data captured by the Pharmaceutical Quality System (PQS) is reviewed for trends. This tool can support a continuous improvement environment.

PQRs are designed for the purpose of identifying and implementing recommendations for required improvements. The objectives of a PQR are to:

- verify the consistency of the existing manufacturing process
- verify the appropriateness of current specifications for both starting materials and finished products
- highlight any adverse quality trends
- identify product and process improvements

Using PQRs

PQRs provide:

- useful information and additional controls over manufacturing processes and quality requirements
- important information for release for supply (RFS) authorised persons



TGA inspectors will review evidence that a manufacturer has undertaken their responsibilities in regard to PQRs, as specified in the GMP or technical agreement.

The PQRs are inspected at TGA inspections of a manufacturer that conducts release for supply. TGA inspectors will be checking that the PQRs have been conducted in a timely manner.

Manufacturers should:

- document issues identified through the PQR in a corrective and preventive action (CAPA) and consider the need for revalidation
- have a management procedure in place to monitor any CAPAs and revalidations resulting from PQRs
- cover PQRs and the effectiveness of the system in internal audits

There should be standard operating procedures (SOPs) for ongoing management and review of PQRs. The effectiveness of these procedures should be verified during self-inspection.

Implementation of PQR outcomes

The data generated and evaluated in the PQR should be used to identify any items for continuous quality improvements and an action plan should be documented to manage this process. The effectiveness of the continuous improvement should be evaluated in the next PQR.

It is expected that any outcomes identified though PQRs are documented and evaluated to determine and implement corrective actions or potential revalidation as required.

Distribution of responsibilities

The sponsor and the release for supply manufacturer are both responsible for:

- ensuring that the PQR is accurate and performed in a timely manner
- evaluating the PQR

When multiple manufacturers are involved, or the sponsor is not the manufacturer, the responsibilities of each party in the PQR process will be documented in a GMP or technical agreement; the RFS authorised person will hold a copy of these agreements.

The GMP or technical agreements will normally specify in each particular situation which party will be responsible for each of the twelve items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP.

Sponsor responsibilities

The sponsor needs to ensure that agreements are in place to enable production of PQRs. This is particularly important when there are multiple contract manufacturers.

Sponsors:

- have access to all PQRs
- contribute to PQRs

The sponsor's contribution needs to ensure that the product complies with the marketing authorisation.

Sponsors and the twelve specified items

The table below contains a list of the items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP that are likely to be the responsibility of the sponsor. These are suggestions only and you may allocate these responsibilities as you see fit.

Suggested sponsor responsibilities


Item	Description
6	Review the marketing authorisation variations submitted, granted or refused, including those for third country (export only) dossiers
7b	Review the results of the initial long term stability of the market product monitoring program and any adverse trends
7c	Review the results of the ongoing stability of the market product monitoring program and any adverse trends
8	Review all quality-related returns, complaints and recalls and the investigations performed at the time
10	Review post-marketing commitments to new marketing authorisations and variations to marketing authorisations
12a	Review any contractual arrangements relating to the manufacture of the bulk product as defined in Chapter 7 Part I of the PIC/S Guide to GMP to ensure that they are up-to-date
12b	Review any contractual arrangements relating to the manufacture of the market product as defined in Chapter 7 Part I of the PIC/S Guide to GMP to ensure that they are up-to-date

Manufacturer responsibilities

Manufacturers:

- prepare the data for the PQR related to their manufacturing steps
- list significant non-conformances, deviations and CAPAs for equipment, process and products
- submit data and lists to the PQR compiler
- retain a copy of the data and lists, for provision to TGA inspectors
- hold objective evidence that demonstrates that responsibilities have been undertaken

Make relevant objective evidence available for review by TGA inspectors at the time of inspection of licensed or certified premises. The evidence should demonstrate that you have undertaken your responsibilities in regard to PQRs as defined in the GMP or technical agreements.

 Licensed manufacturers must not delegate to unlicensed parties, responsibilities that are inherent to the manufacturing steps that they are licensed to undertake.

The [RFS authorised person](#) has specific responsibilities in relation to PQRs.

Bulk manufacturer

The table below contains a list of items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP that are likely to be the responsibility of the bulk manufacturer. These are suggestions only and you may allocate these responsibilities as you see fit.

Suggested bulk manufacturer responsibilities

Item	Description
1a	Review starting materials used in bulk manufacture, especially those from new sources and in particular the review of supply chain traceability of active substances
2a	Review critical in-process controls in bulk manufacture
2b	Review finished product results <ul style="list-style-type: none"> The bulk manufacturer would normally do this unless QC testing is carried out on the packed product
3a	Review of all bulk batches that fail to meet established specifications and their investigation
4a*	Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant CAPAs taken regarding bulk manufacture
4b*	Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant CAPAs taken regarding testing
5a	Review all changes carried out to the bulk manufacturing processes
5b	Review all changes carried out to analytical (and other testing) methods
7a	Review the results of the initial long term stability of the bulk product monitoring program and any adverse trends
9a	Review the adequacy of any previous product process or equipment corrective actions relating to manufacture of the bulk product
11a	Review the qualification status of relevant equipment and utilities e.g. HVAC (heating, ventilation and air conditioning), water, compressed gases relating to manufacture of the bulk product <ul style="list-style-type: none"> You can review the qualification of equipment and utilities as part of the Validation Master Plan schedule and do not need to do this for each PQR
12a	Review any contractual arrangements relating to the manufacture of the bulk product as defined in Chapter 7 Part I of the PIC/S guide to GMP to ensure that they are up-to-date

*: For item 4, when reviewing the effectiveness of CAPAs, also assess the need for revalidation.

Packaging manufacturer

The table below contains a list of items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP that are likely to be the responsibility of the manufacturer undertaking packaging steps or release for supply. These are suggestions only and you may allocate these responsibilities as you see fit.

Suggested packer responsibilities

Item	Description
1b	Review starting materials used in packing activity, especially those from new sources
2c	Review critical in-process controls in packing and QC testing (if applicable)
3b	Review of all packed batches that fail to meet established specifications and their investigation
4c	Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant CAPAs taken regarding packing activities
5c	Review all changes carried out to the processes involved in the packing activity
9b	Review the adequacy of any previous product process or equipment corrective actions relating to packing of the market product
11b	Review the qualification status of relevant equipment and utilities e.g. HVAC, water, compressed gases relating to packing of the market product. <ul style="list-style-type: none"> You can review the qualification of equipment and utilities as part of the Validation Master Plan schedule and do not need to do this for each PQR
12b	Review any contractual arrangements relating to the manufacture of the market product as defined in Chapter 7 of the PIC/S Guide to GMP to ensure that they are up-to-date

RFS authorised person responsibilities

The release for supply (RFS) authorised person or delegate:

- holds appropriate documentation, as described in the [release for supply guidance](#) (which TGA inspectors may inspect during an inspection)
- has a copy of all the GMP and technical agreements between parties involved in PQRs
- ensures the accuracy and timely completion of PQRs
- has access to appropriate information in regards to PQRs and the ongoing stability program
- makes the PQRs available to TGA inspectors

The authorised person must consider release for supply in the context of PQR findings.

Producing PQRs

There are three pathways available to produce PQRs.

1. [Product-specific pathway](#)
2. [Product grouping pathway](#)
3. [Review by exception pathway](#)

Frequency of PQRs

PQRs are normally conducted and documented annually (stated in the Product Quality Review section of Chapter 1, Part 1 of the [PIC/S Guide to GMP](#)).

Where a small (statistically invalid) number of batches of a product have been manufactured in the year:

- a review can be conducted every 2 years
- products may be grouped with other similar products
- products may be included in the review using the 'by exception' option

Content of a PQR

The review should:

- capture product quality events
- investigate and thoroughly document any potential impacts on the process or systems as a whole
- be intended to result in continuous product improvement

Where reports are already generated from the PQS for purposes such as management review, this analysed data can also be used to feed into the PQR report.

One-off adverse quality events may not indicate that a process is out of control, but may require further investigation to demonstrate the manufacturing process remains in a controlled state. Include in the report significant events that have not been identified as a trend.

Include a summary of the batches released during the review period, relevant to the approach taken.

There is more detailed information below on what to include when conducting a [review by exception](#).

1. Product-specific pathway

The product-specific pathway involves:

- a product-specific PQR for all batches manufactured during the review period
 - The PQR should include a documented review on all batches of a specific product manufactured during the review period of all applicable items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP.
- a report for each product
 - The report should highlight and discuss any identified adverse trends for the purpose of implementing improvements to ensure that systems and processes remain in a validated and controlled state.

The product-specific pathway is available for any medicinal product.

2. Product grouping pathway

Grouping of products is when one PQR is prepared for a group of products. The grouping process should be appropriate for conducting a PQR and reporting cannot be based on a representative product.

Prepare a scientific justification for how you group products for PQRs. This justification will be assessed for the acceptability of grouping products for PQRs during TGA inspections.



Both the sponsor and the manufacturer should agree to the grouping.

Grouping for any medicines

Grouping (sometimes referred to as bracketing or matrixing) can be acceptable for any medicinal product (Product Quality Review section of Chapter 1, Part 1 of the [PIC/S Guide to GMP](#)) when the number of batches manufactured annually for each product within the group is low and the grouped medicines are both:

- of the same pharmaceutical form containing the same or very similar active ingredients
- manufactured using the same equipment

Grouping for listed and complementary medicines

For listed and complementary medicines, grouping can be based on products that have **similarly constructed** formulations and a **similar method** of manufacture.

For your scientific justification of the grouping approach, consider:

- dosage form
- packaging
- equipment train
- ingredient matrix
- quantities of active ingredients

You may use a different grouping rationale to that applied for [process validation](#) and [stability testing](#) for listed and complementary medicines.

Content of a group PQR

The PQR for a group should:

- document the grouping approach, with a scientific justification for the approach
- include a documented review of all applicable items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP
- be performed on all batches of a specific group of products manufactured during the review period

The report should highlight and discuss any identified adverse trends for the purpose of implementing improvements to ensure that systems and processes remain in a validated and controlled state.

Batches within a group

List and review all batches of all products in the group. It is unacceptable to review only a representative (or even a 'worst case') product in a group.

3. Review by exception pathway

The PQR by exception is a holistic interrogation of the PQS and quality related events as they relate to the twelve specified items in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP.

The aim of the PQR is to identify adverse, out-of-trend or unusual events that indicate potential quality vulnerabilities.

- Review by exception is a review of PQS adverse trends in each of the twelve specified items that captures all batches of all products manufactured in the review period.
- Adverse trends can be mapped back to identify products or product groups potentially impacted.
- The design of the PQR report should highlight any adverse trends detected during the review.
- A report by exception may be generated to cover:
 - all products
 - a group of products
 - a client's products
 - each specific product

The review by exception pathway is only available for listed and complementary medicines.

Content of PQR by exception

A PQR by exception must go through the twelve items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP.

For each item, the report should:

- include any exceptions identified via the review of the PQS and identify the products potentially impacted
- discuss any identified quality event
 - Quality events should be related to the products or batches manufactured over the period for the purposes of maintaining, improving or correcting the product manufacturing processes and systems
- discuss any identified out-of-trend event
- state that no quality event or out-of-trend event was observed, if this was the case

The table below outlines the quality systems to be reviewed (Column 1) and links these to the requirements in the PIC/S Guide.

Quality systems relationship to the twelve specified items in the PIC/S Guide

PQS	PQR specified items*
Deviations and non-conformances	1, 2, 3, 4, 6, 7
Change control	1, 5, 6
Complaints, recalls and returns	8
OOS and OOT	1, 2, 3, 4
CAPAs	1, 2, 3, 4, 9
Self-inspection	1, 4
Stability	3, 4, 6, 7
Vendor assurance	1
Validation and qualification	3, 4, 5, 11
Quality Risk Management	1, 3, 4, 5
Contractual agreements	10, 12

*: items specified in the Product Quality Review section of Chapter 1, Part 1 of the PIC/S Guide to GMP

Aspects of PQS to consider when conducting a PQR by exception

The list below is not exhaustive, but summarises the most common aspects of the PQS that need to be included for each of the twelve specified items in the PIC/S Guide to GMP.

1. A review of starting materials including packaging materials used in the product, especially those from new sources

Review:

- a. out-of-specification (OOS) and out-of-trend (OOT) results
- b. deviation reports
- c. non-conformances
- d. rejected materials and supplier corrective action requests
- e. vendor assurance of new suppliers, including supply chain traceability of active substances

2. A review of critical in-process controls and finished product results

Based on the assumption that exceptions are captured in relevant deviation and or out-of-specification logs:

- a. Evaluate deviation logs for in-process checks that are outside of targets
- b. Identify trends for deviations as they relate to specific products
- c. If there is a trend for any specific product, then perform a root cause analysis
- d. Review laboratories OOS log
- e. Identify trends of out-of-specifications for specific products. Perform a root cause analysis

3. A review of all batches that failed to meet established specification(s) and their investigation

- a. Review any failed batches that resulted in an OOS, deviation, incident or non-conforming product
- b. The investigations should encompass failed batches of finished product, intermediate product as well as starting materials, including raw materials and components where applicable

4. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken

- a. Evaluate the following quality systems, which impact on product quality:
 - i. the number of unplanned events (deviations and incidents), non-conformances, out-of-specifications and out-of-trends
 - ii. the number of planned deviations and number of batches manufactured or released or rejected (and reason for rejection)
- b. Analysis relating to product quality is to include, but not be limited to, the number of repeat events (planned and unplanned). Evaluate corrective actions and their effectiveness, which is linked to the evaluation for item 9

5. A review of all changes carried out to the processes or analytical methods

Review:

- a. changes (change controls) to manufacturing processes or analytical methods
- b. validation requirements derived from changes to analytical methods, process validation or grouping justifications
- c. impact of changes to ongoing stability, especially stability groupings

6. A review of marketing authorisation variations submitted, granted or refused

- a. Review section 31 requests for information
- b. Review and evaluate the reason for changes to product entries
- c. Review and evaluate the reason for changes to labels
- d. Review internal change control process
- e. Review for trend and root cause

7. A review of the results of the stability monitoring program and any adverse trends

- a. Review stability results relating to product or product grouping
- b. Review OOS and OOT investigations relating to stability testing
- c. Where manufacturer has grouped products, then document a summary of the grouping justification
- d. Review and confirm the rationale for the shelf life. Where stability data has not yet been created, confirm the justification for the interim shelf life

8. A review of all quality-related returns, complaints and recalls and the investigations performed at the time

- a. Document the number of returns, complaints and recalls
- b. Review significant trends and corrective actions implemented as part of the analysis relating to product quality issues

9. A review of adequacy of any other previous product process or equipment corrective actions

- a. Review CAPA logs for process and equipment issues
 - Pay special attention to ensure that these corrective and preventative actions have not introduced new risks for the products or process
 - Perform an effectiveness review to evaluate whether a CAPA has met its objective based on pre-defined criteria and supporting data or evidence. This review should demonstrate reduction or prevention of occurrence
- b. Review maintenance records
- c. Review equipment and process validation schedules for completion
- d. Review calibration records

10. For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments

Review new marketing authorisations or variations to marketing authorisations since the last PQR. The following may form part of this review process:

- a. Review new marketing authorisations and variations to ensure that each step of manufacture is carried out by a manufacturer licensed to complete that step, or is certified to conduct that step (for manufacturers outside of Australia), unless exempt under Part 3.3 of the Therapeutic Goods Act 1989. This may also include a partial manufacturing step, for example, review of the starting material manufacturer to confirm GMP compliance to satisfy the ARTG entry requirements
- b. Review change control system for regulatory changes

11. The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

- a. Review the summary of Validation Master Plan schedules, which will show current status of all equipment in the manufacturing and packaging facilities. This should include computerised systems and analytical testing methods
- b. The summary provided should include, but not be limited to:
 - i. maintenance records
 - ii. incident and deviation reports created as a result of maintenance issues
 - iii. calibration records
 - iv. CAPA reports relating to equipment or utilities and the root cause and effective closure of same

12. A review of any contractual arrangements as defined in Chapter 7 of the PIC/S Guide to ensure that they are up-to-date

- a. Provide a summary table of third party contractors used and GMP and technical agreement status
- b. Review GMP and technical agreements to ensure they are in place and current. Include any changes made since previous PQR
- c. Check that agreements exist with all contractors, for example, laboratories, third party manufacturers, sponsors and consultants

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication: Technical guidance on the interpretation of manufacturing standards: Product quality reviews for listed complementary medicines	Office of Manufacturing Quality	01/02/2010
V1.1	Template update	Office of Manufacturing Quality	01/07/2013
V2.0	Change in title and scope Addition of the review by exception pathway Restructured and updated to be consistent with PE 009-13, PIC/S Guide to GMP	Manufacturing Quality Branch Regulatory Guidance Team	16/01/2019

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