MANUFACTURING & QUALITY AUDIT DIVISION
CENTRE FOR DRUG ADMINISTRATION

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GUIDANCE NOTES ON PRODUCT QUALITY REVIEW

GUIDANCE NOTES

Subject: PRODUCT QUALITY REVIEW

1.0 INTRODUCTION:

The purpose of this guidance is to communicate the expectation with regard to the conduct of Product Quality Review. Product Quality Review is a GMP requirement listed under Chapter 1 of the PIC/S GMP Guide for Medicinal Products, effective since 1 Jan 2006.

2.0 WHAT IS A PRODUCT QUALITY REVIEW?

Product Quality Review is regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, which are conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements.

The Product Quality review (PQR) is an effective quality improvement tool to enhance the consistency of the process and the overall quality of the product. The PQR will capture a broader view of product data, capturing trends and will help determine the need for revalidation and changes, if any.

3.0 BACKGROUND

European Union (Eudralex):

The additional text "Product Quality Review" for Chapter 1 to the EU GMP Guide has been adopted by the Ad hoc GMP inspectors Working group at their first meeting in July 2003. The proposal of Product Quality Review arises from the experience of Member States' inspectorates where quality problems with products on the market leading to recall could have been anticipated if the manufacturer/marketing authorization holder had operated a system for formally reviewing process consistency and trends.

US Food and Drug Administration (FDA):

The code of federal regulations (CFR) of Food and Drug Administration in their 21 CFR – Parts 210 & 211 dictated the requirements of reviewing the products annually. It is clearly stated under Subpart J - Records and Reports 211.180(e) that written

records required by the part shall be maintained so that data can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.

International Conference on Harmonization (ICH)

ICH Q7A GMP Guide for Active Pharmaceutical Ingredients requires manufacturers to conduct annual quality review of the active pharmaceutical ingredients in order to know the consistency on the quality of products manufactured through out the year.

Basically, product quality review (PQR) is a natural progression of GMP quality system implementation by manufacturers and this requirement is also not new to begin with, however it (product quality review) is just that the requirement is now clearly specified/mandated in the PIC/S Guide to Good Manufacturing Practice for Medicinal Products. It is believed that manufacturers might have done some sort of informal review of their manufacturing processes over the years, but it has not been documented or announced.

4.0 PROCEDURE:

4.1 Product Quality Review should typically be carried out for each product manufactured in the previous year. In the case of campaign manufacturing, the review period can be extended beyond a year. Such extensions shall be for a limited number of months and as described in a procedure. Along with PQR, implementation of preceding years' recommendations shall be reviewed.

The Product Quality Review Report should contain at least the following details:

(i) A review of starting materials and product contact primary packaging materials used for the product, especially those from new sources.

(a) Summary of all batches of starting and packaging materials received in a year and their approval status;
(b) Summary of the suppliers/manufacturers of the materials;
(c) Compilation and analysis of the results of analytical tests for key quality attributes such as description, identification, loss on drying/water content by Karl Fisher, particle size, related substances and assay;

(d) Compilation of the Certificate of analysis (COA) results obtained from supplier/manufacturer, if the batch is released based on supplier's COA.
(e) Summary of details related to any significant deviations observed such as rejection of vendor lots.

(ii) A review of critical in-process controls and finished product results.

(a) Compilation(s) and analysis of in-process test results obtained from the total number of batches manufactured in that particular year e.g. weight variation, dimension, friability, hardness, disintegration time, fill volume variation (such as for ampoules, vials, bottles), pH, etc
(b) Compilation(s) and analysis of finished product test results such as description/appearance, identification, pH, loss on drying/Water by KF, viscosity, dissolution test, impurities and related substances, degradation product (if any) and assay.

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

(a) Summary of the number of failed batches/products. The list will identify the batches that failed specifications and the root cause for this failure, if identified
(b) Summary of the reasons for failure (assignable or non-assignable causes)
(c) Summary of the completed investigation report(s) and corrective actions taken.

(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.

(a) Summary of all deviations or non-conformance, together with causes of the non-conformance, sorted based on data trending
(b) Compilation (using trend analysis) of corrective and preventive actions (CAPA) taken

(v) A review of all changes carried out to the processes or analytical methods.

(a) Summary of the changes, if any, made to the process e.g. change of mixing time, blending time, drying time, changes in coating process, changes in compression speed/time, changes in filling speed etc
(b) Summary of the changes made to the analytical methods, e.g. change of solvents, buffers, reagents, pH, change in composition of mobile phase, change in HPLC/GC method parameters i.e. flow rate, temperature, wavelength, run time, and change of HPLC/GC column etc
(c) Review/report of the impact of the changes on the quality of the product.

(vi) A review of Marketing Authorization variations submitted/granted/refused, including those for third country (export only) dossiers.

(a) Summary of the number of products registered with local and overseas authorities that were covered in the review document, if grouping by product type are done.
(b) Summary of the changes made to the product specification and their status of approval. Document the regulatory decision.
(c) Summary of the number of products submitted but not approved/refused by the local and overseas authority

(vii) A review of the results of the stability monitoring programme and any adverse trends.

(a) Summary of the number of batches included for stability studies during the review period and the reasons for their selection.
(b) Summary of stability study report and results, i.e. out of specifications for each conditions (real time/long term and accelerated studies), together with a review of the results obtained for stability indicating analytical tests.

(viii) A review of quality-related product returns, complaints and recalls and the investigations performed at the time.

(a) Summary of batches returned due to potential quality defects, together with the reasons.
(b) Summary of market complaints received in a year, together with the nature of complaints.
(c) Summary of batches recalled, together with the reasons.
(d) Compilation of investigation reports prepared following market complaints and the actions taken to prevent recurrence.

(ix) A review of adequacy of any other previous product process or equipment corrective actions.

Summary of all corrective actions from previous product quality review reports (other than those already listed in points **(iii)** and **(iv)**, indicating the implementation status of each of the corrective actions, and their effectiveness in addressing the problems.

(x) For new marketing authorizations and variations to marketing authorizations, a review of post-marketing commitments.

(a) Summary of any changes, in terms of the specification, registered with drug regulatory authority, including overseas drug regulatory authorities.
(b) State any post-marketing commitments and review the status of these commitments.

(xi) The qualification status of relevant critical equipment and utilities, e.g. HVAC, water, compressed gases, etc.

(a) Summary of the number of equipment / instruments in production and laboratory department.
(b) Summary of the qualification/re-qualification status (policy) of equipment / utilities used in the production processes and QC laboratory indicating whether it has been qualified and it's next qualification due date/policy. The actual results of qualification, maintenance and calibration etc. would not be required in the PQR.

The Product Quality Report should cross reference to the respective validation reports. Information available in the validation report need not be repeated in the PQR.

(xii) A review of Technical Agreements to ensure that they are up to date.

(a) Review of written contract covering the technical requirements on periodic maintenance of production and laboratory equipment between the manufacturer and supplier. A summary report would be sufficient.
(b) Review of written contract covering the technical requirements between contract giver and contract acceptor (if any). A summary report would be sufficient.
(c) These technical agreements need to be annually reviewed to determine whether is there need to further revise/update the technical agreements.

The attached Annex 1 shown at the end of this document is meant to provide an overall summary at a glance on the corrective and preventive action undertaken while compiling the data for Product quality review.

5.0 HOW TO IDENTIFY TRENDS, INTERPRET DATA, AND DRAW CONCLUSIONS FROM THE DATA

5.1 The data generated from the batch or product shall be trended using the appropriate statistical techniques such as time series plots, control charts, etc to draw the conclusions, if any. This will help the manufacturer to take any corrective or preventive action, should manufacturer find the process to be out of control.

5.2 The data should be trended and analyzed to determine if (i) the process is in control; and (ii) the process is capable. Control limits should be established through trending. The appropriateness of current specifications for both starting materials and finished product should also be determined. In addition, it is important to highlight any trends observed and to identify product and process improvements. Improvement plans and actions should be initiated and taken if the process is found to be out of control or has low capability indices.

5.3 The data may be analyzed using the following techniques:

(a) Control Charts
Processes should be demonstrated to be in control, and one of the ways to demonstrate this is the use of charting techniques commonly known as the Shewhart Control Charts. The use of such charts (example: X-bar charts, R-charts and Moving Range charts etc.) enables the manufacturer to determine upper and lower control limits, and identify trends (examples: upward trend of data, shift in mean etc.) so that appropriate actions may be taken before out-of specification occurs.

(b) Process Capability Study
A process capability study is used to determine whether a process is stable and capable. Process capability indices are used to measure how well the data fits into the specification limits. Frequently used process capability indices include Cp and Cpk. Cp is used to evaluate the variation of the process, and Cpk is used to evaluate the centering of the process.

It is important for manufacturers to calculate and analyze the values of Cp and Cpk for their processes and understand the interpretation of such data. It is recommended that the Cp / Cpk values be targeted at 1.33 or above. Process capability studies assist manufacturers in determining if the specifications limits set are appropriate, and also to highlight processes that are not capable. Manufacturers would then be required to take necessary improvement plans / actions.

5.4 Other types of statistical techniques may also be used, as and when appropriate in the Product Quality Review. Information derived from such statistical analysis should be interpreted and conclusions drawn, so as to ensure that processes are in control and capable.

6.0 CONCLUSION:

Product Quality Review is an important aspect of Good Manufacturing Practice. It is important for manufacturers and marketing authorization holders to conduct annual Product Quality Review. The manufacturer and marketing authorization holder, (where different) should evaluate the results of this review and an assessment should be made whether corrective and preventive actions (CAPA) or any revalidation should be undertaken. Reasons for such corrective actions should be completed in a timely and effective manner.

Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review.

The authorized person responsible for final batch certification together with the marketing authorization holder should ensure that the Product Quality Review is performed in a timely manner and is accurate. These annual product reviews should be signed by the authorized person and/or Marketing Authorization Holder.

REFERENCE

PIC/S PE 009-4 (effective 01 June 2006)

END OF DOCUMENT

ANNEX-1

In summary, following requirements need to be provided for Product Quality Review:

(a) Trend analysis of quality control parameters as committed during marketing authorization application shall be compiled product-wise and batch-wise,

(b) Market complaints investigation and planned corrective actions.

(c) Product recalls, reasons for recalls and corrective actions.

(d) Returned Goods

(e) Salvaged Goods

(f) Non conformances as per in-house Specifications

(g) Batch failures at various stages of production and their investigations

(h) Changes done in formulation, process and packaging.

(i) Results of Stability studies and retention sample review.

(j) Regulatory changes in Pharmacopoeia / drug act

(k) Changes in Vendor

(l) Changes in facility/equipment

Note: Product Quality Review may be grouped for similar product (Formulation and Primary Packing is same – brand name or market is different) and Recommendation (s) shall be made in the report based on the review, if any change is desired.

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REVISION HISTORY

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