



ANNUAL PRODUCT QUALITY REVIEW: REGULATORY ASPECT

Khushboo Mayurbhai Vora¹,
Jignesh Shah*,
Dilip. G. Maheshwari²

¹Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad, Gujarat 382210, India.

¹Assistant Professor, Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad, Gujarat 382210, India.

²Head of Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad, Gujarat 382210, India.

ABSTRACT

Annual Product Quality Review (APQR) is an evaluation which is prepared according to the cGMP requirements of different regulatory authorities. A Good Manufacturing Practice ensures that the products are consistently produced and controlled according to quality standards. Annual Product Quality Reviews not only are required by GMP but also required for robust quality improvement for manufacturing the pharmaceutical product. Annual product review is an evaluation conducted annually to assess the quality standard of each drug product with a view to verify the consistency of existing process and to check the appropriateness of current specifications and to highlight any trend in order to determine the need to change any drug product specifications or the manufacturing processes or control procedures. It is a written report is required for every drug product, based on data collected at least annually. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. It is universally accepted by the industry and contents must specify a list of manufactured batches, release data and reviews of deviations, complaints, recall and returned goods. This article gives brief overview of regulatory aspects and regulatory requirements for Annual Product Quality Review of pharmaceutical product. It mainly focuses on the documentation required for the preparation of Annual Product Quality Review. Thus the article is based on the regulatory requirements or standards to manufacture and maintain the quality of any pharmaceutical product.

KEYWORDS: Product Quality Review, Quality, Goods Manufacturing Practice, Annual Product Review

INTRODUCTION:

Annual Product Quality Review:^{1, 2, 3}

Annual product review is an evaluation conducted annually to assess the quality standard of each drug product with the view to verify the consistency of existing process and to check the appropriateness of current specifications and to highlight any trends in order to determine the need to change any drug product specifications or the manufacturing processes or control procedures. Annual product review is done for the products which are manufactured in **U. S. market.**

Product Quality Review:

It can be defined as regular periodic or rolling quality reviews of all licensed medicinal products, including products to be exported, should be 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.

Address for correspondence

Dr. Jignesh Shah*
Assistant Professor,
Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad.
E-mail: jss192@gmail.com

It is an effective quality improvement tool to enhance the consistency of process and the overall quality of the product. It will capture broader view of product data, capturing trends and will help to determine the need of any revalidation or any changes. This is done for products which are intended **for Europe market** or manufactured in Europe but intended for products to be exported.

Importance of Annual Product Quality Review:

- It verifies the consistency of the existing manufacturing processes.
- It determines the quality and process defects of the products.
- It determines the defects and possible improvements of the methods and process.
- Trend of yield, analytical results, manufacturing parameters of the product are also highlighted.
- It reviews the quality of the raw material and packaging material which is used for the product.
- Mainly it indicates the quality of material.
- To determine the consistency of the quality of the product the in-process parameters and the finished product results are reviewed.
- Quantity of the final product is reviewed by trending the yield of every batch.

- Out of specification parameter helps to determine the product defects.
- If any of the batch is failed, then it is also included in the Annual Product Quality Review to determine the batch rejection of the product.
- For the determination of the stability of the product, stability study and its trend are performed.
- It also helps to determine if there is any re-validation of the process and the effect of any improvement made previously.
- The determination of the Corrective and preventive actions and their impact on product quality are also reviewed.

NEED OF ANNUAL PRODUCT QUALITY REVIEW FOR MANUFACTURING AND CONTROL OF PHARMACEUTICAL PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS⁴

- The US Food and Drug Administration proposed a requirement to prepare written summary for each product in its February 13, 1976 by rewriting the good manufacturing practices (GMPs) for drug products.
- The purpose for this proposed GMP requirement was to provide reliable procedures for a drug manufacturer to review the quality standards for each drug product.
- After numerous comments from industry objecting to the preparation of written summaries, FDA revised the proposal to allow each company to establish its own procedures for the evaluation of product quality standards, by reviewing the records required by the GMPs on an annual basis.
- This requirement was published as final current good manufacturing practices (CGMP) regulations for drug products (21 CFR 211.180(e))
- Since its publication, 21 CFR 211.180(e) has been commonly referred to—by FDA and the pharmaceutical industry—as the "**Product Annual Review**" (PAR) or the "**Annual Product Review**" (APR).
- In August 2001, FDA also adopted and published the guidance for industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.
- This guidance was developed within the Expert Working Group of the International Conference on

Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

- This guidance was then incorporated as Part II of the European Community Guide to GMP (EU GMP Guide) in October 2005.
- Sections 2.5 and 12.6 of this guidance specify and refer to the performance of a **Product Quality Review (PQR)** for active ingredients.
- The EU GMP Guide is the document that provides the details supporting the principles of GMPs within the EU.

Basic Contents of Annual Product Quality Review:

Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

- i. A review of starting materials including packaging materials used in the product, especially those from new sources.
- ii. A review of critical in-process controls and finished product results.
- iii. A review of all batches that failed to meet established specification(s) and their investigation.
- iv. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
- v. A review of all changes carried out to the processes or analytical methods.
- vi. A review of Marketing Authorisation variations submitted/granted/ refused, including those for third country (export only) dossiers.
- vii. A review of the results of the stability monitoring programme and any adverse trends.
- viii. A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- ix. A review of adequacy of any other previous product process or equipment corrective actions.
- x. For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments.
- xi. The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

REGULATORY ASPECTS FOR PREPARING ANNUAL PRODUCT QUALITY REVIEW^{5, 6, 7, 8, 9, 10, 11, 12}:

Table 1: Regulatory requirements for the preparation of Annual Product Quality -Review

PARAMETERS	DATA TO BE REVIEWED
Starting material: A review of starting materials including packaging materials used in the product, especially those from new sources.	STARTING MATERIALS: Firstly identify all starting and packaging materials received in the year and used for manufacturing of the product. It should then contain the name of the suppliers/manufacturers of the materials. It should contain suppliers certificate of analysis (CoA) or certificates of compliance

	<p>All analytical tests should be performed for the starting materials such as linearity, range, LOD, LOQ, robustness, ruggedness and the test results obtained after testing should be included.</p> <p>If there are any changes to process for production of the product or any changes related to specifications for the starting materials should also be included.</p> <p>If there are any significant deviations observed in the results or any trending done, then it should also be mentioned in the annual product quality review.</p> <p>FOR PACKAGING MATERIAL:</p> <p>It should include all the written procedures describing sufficient detail about identification, storage, handling, sampling, examination, and/or testing of labelling and packaging materials.</p> <p>All the labelling and packaging materials shall be representatively sampled and examined before using it for packaging or labeling of a drug product.</p> <p>Any labeling or packaging materials which meet the appropriate written specifications should be approved and then only released for use and if it does not meet the specifications then they shall be rejected to prevent their use in operations for which they are unsuitable and these all results should be clearly mentioned in annual product quality review.</p> <p>All the record should be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected and the result should be reviewed and included in APQR.</p> <p>Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification.</p> <p>The use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations should also be included.</p> <p>If any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling is used for product development then the name of the technique should also be included.</p> <p>It should also contain the inspection rejection rate.</p>
<p>In-process controls and quality control testing: A review of critical in-process controls and finished product results</p>	<p>This part of APQR should include the written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.</p> <p>These written procedures, including any changes in the procedures should be drafted, reviewed, and approved by the appropriate</p>

	<p>organizational units and also by the quality control unit and then only mentioned in the APQR.</p> <p>The trend in-process tests results and also the QC tests results in both manufacturing and packaging processes and microbiology considerations should also be included.</p> <p>The trending should include the following test results:</p> <ul style="list-style-type: none"> • Physical variations such as weight/dimensions, friability, hardness, uniformity of content, disintegration time, fill volume/overage, hardness, dissolution time. • Rejected products such as breakages, particulates, etc. should also be included in the APQR. • The yield obtained during the manufacturing process using
<p>Manufactured batches (intermediates, bulk, finished products and campaign batches) :</p> <p>A review of all batches that failed to meet established specification(s) and their investigation.</p>	<p>The list of deviations and non-conformances observed with the product when it is reviewed should be mentioned.</p> <p>Then the next is to identify the deviations associated with the product and also the reports of Corrective and Preventive Actions (CAPA) taken.</p> <p>The reasons for the failure of the batches should be included.</p>
<p>Process or testing changes:</p> <p>A review should be done for all changes carried out to the processes, and if any change is carried out for the analytical methods.</p>	<p>If there is any change in the process to manufacture the pharmaceutical product, then the changes should be clearly mentioned in this section of annual product quality review.</p> <p>The changes in any of the manufacturing processes, analytical methods, labelling, packaging, etc. should be mentioned in this section.</p> <p>The steps include:</p> <ul style="list-style-type: none"> • First identify the batches which are affected. • Then provide a justification for the change. • Review the effectiveness/impact of the change on the batch under review.
<p>Marketing authorisations: A review of Marketing Authorisation variations which are submitted or refused or granted and also those for third country (export only) dossiers.</p>	<p>This section of Annual Product Quality Review should include the list of marketing authorisation variations found including the third country export only dossiers.</p> <p>It should also include the number of products submitted/granted/refused.</p> <p>If any changes are made to the product then it requires submission of variations to the marketing authorisations.</p> <p>The number of products registered locally or overseas should be sent to the marketing authorisation.</p> <p>The above variations should be submitted and if not submitted then a conclusion should be documented.</p>
<p>Stability programme:</p> <p>A review of the results of the stability monitoring programme and any if any adverse trends found should be reviewed and included.</p>	<p>The review of the results of any long term and on-going stability of the bulk product and the marketed product should be done.</p> <p>And the results of long term stability and on-</p>

	going stability of the bulk product and finished product should be included. Also include the product information such as its manufacturing date, shelf-life, etc.
Returned product: A review should be done for the quality-related returns and the salvaged products and also the investigations should be performed at the time.	The batch number(s) which are returned should be mentioned. The reason for the return should be mentioned. The associated investigation report number should be written.
Complaints and/or adverse events reported: A review should be done for the quality related complaints and also the investigations should be performed at the time.	The batch number of the product should be identified and written. The reason for complaint should be noted. The complaints obtained should be reported and the manufacturing should be stopped. The associated investigation report number should be written. Current status of the product should be mentioned.
Recalls: A review of all quality related recalls should be performed.	The number of batches/product recalled should be written. The reason for recall should be mentioned. Associated investigation report number should be mentioned. The Current status of the product is mentioned.
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
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/requalification 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 requalification and assess for subsequent impact to product quality
Contractual agreements: A review is done for any contractual arrangements made to ensure that they are up to date.	The contracts should be reviewed for the services associated with the product in review and report: The Name and address of the contract acceptor should be written. The availability and details of the written contract is mentioned. The types of services provided, For e.g. testing or maintenance and calibration services.

CONCLUSION:

Thus Annual product Quality Review is an evaluation conducted annually to assess the quality standard of each drug product with the view to verify the consistency of existing process and to check the appropriateness of current specifications to manufacture the pharmaceutical product. Thus it is necessary to study

the regulatory requirements for the preparation of Annual Product Quality Review to manufacture the pharmaceutical product according to the GMP requirements and which is safe and effective to the public. Hence to study the regulatory requirements is essential.

ACKNOWLEDGEMENT

Authors are heartily thankful to Dr. Kilambi Pundrikakshudu, Director of, L. J. Institute of Pharmacy, Sarkhej, Ahmedabad for providing all facilities to carry out this research work.

REFERENCES:

1. Pharmaguideline, "Importance of Annual Product Quality Review", <http://www.pharmaguideline.com/2013/11/importance-of-annual-product-quality-review-apqr-apr-pqr.html> (Last accessed on 8/1/2015)
2. Health Sciences Authority, "Guidance notes on Product Quality Review", January 2013, http://www.hsa.gov.sg/content/dam/HSA/HPRG/Manufacturing_Importation_Distribution/Overview_Framework_Policies/GUIDE-MQA-024-004.pdf. [accessed on 8 January 2015]
3. PharmaManufacturing.com, "Annual Product Reviews: How to Conduct an Effective Annual Product Quality Review", February 2012, <http://www.pharmamanufacturing.com/articles/2012/018/> (Last accessed on 9/1/2015).
4. Pharmatech, "Product Annual/Quality Review: US–EU Comparative Analysis and Interpretations", <http://www.pharmtech.com/pharmtech/Peer-Reviewed+Research/Product-AnnualQuality-Review-USndashEU-Comparative/ArticleStandard/Article/detail/500406> (Last accessed on 9/1/2015)
5. Pharmaceutical Inspection co-operation scheme, "Guide to Good Manufacturing Practice for Medicinal Products PE 00910" Part I and II. . [accessed on 16 January 2015]
6. Pharmaceutical Inspection co-operation scheme, Guide to Goods manufacturing practice Annex 20, Quality Risk Management. (Last accessed on 17/1/2015)
7. Commission of the European Communities. The Rules Governing Medicinal Products in the EC., Vol. IV, (Last accessed on 17/1/2015)
8. Good Manufacturing Practice for Medicinal Products. Luxembourg: Office for Official Publications of the EC, 1992. ISBN 92-826-3180-X. (Last accessed on 17/1/2015)
9. European Commission, "Medicinal Products for Human and Veterinary Use," in EU Guidelines for GMP, Chapters 1–9, Dec. 2005. (Last accessed on 17/1/2015)
10. European Commission, Enterprise and Industry, Pharmaceuticals, Documents, "New GMP Provisions for Product Quality Review," website announcement, Nov. 8, 2005. (Last accessed on 18/1/2015)
11. Food and Drug Administration, Department of Health and Human Services. 21 CFR 210, 211. Washington: Office of the Federal Register National Archives and Records Administration, 1997. (Last accessed on 19/1/2015)
12. FDA, "Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; Amendment of Certain Requirements for Finished Pharmaceuticals," *Fed. Regist.* **60** (13), 4087–4091. (Last accessed on 19/1/2015)

How to cite this article:

Khushboo Mayurbhai Vora, Jignesh Shah, Dilip Maheshwari*: Annual product quality review: regulatory aspect, 6(1): 2345 - 2350. (2015)

All © 2010 are reserved by Journal of Global Trends in Pharmaceutical Sciences.