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RESEARCH ARTICLE

COMPARITIVE EVALUATION OF ANNUAL PRODUCT QUALITY REVIEW WITH RESPECT TO US AND EUROPE

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ABSTRACT

Annual Product Quality Review (APQR) is basically an evaluation conducted annually to determine if there are any possible changes in the process or manufacturing of the pharmaceutical product or any change in the specifications of the product or any change in the manufacturing process. It is designed to minimize the product defects and also the risks associated with the manufacturing of the pharmaceutical product. This article gives brief overview of the general procedure for the preparation and documentation of the Annual Product Quality Review and also focuses on the regulations and the regulatory requirements as per US and Europe. It also includes the comparative evaluation basically about similarities and differences of requirements associated with the manufacturing of the drug product in these two countries. These will help to minimize the step involved in the manufacturing of the pharmaceutical. It is also necessary to know that the regulatory requirements of different countries are different and hence this will further guarantee the quality of the pharmaceutical product.. Thus the article is based on the comparative evaluation and regulatory requirements for manufacturing of the pharmaceutical product and which will help to maintain the quality of the product.

INTRODUCTION

To Annual Product Quality Review [1, 2, 3]

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 and to highlight any tends in order to determine the need to change any drug product specifications or the manufacturing processes or control procedures.

Annual Product Quality Review verifies the consistency of the existing manufacturing processes and determines the quality and process defects of the products. It also determines possible improvements of the methods and process and the trend of yield, analytical results, and manufacturing parameters of the product are also highlighted.

This makes it possible to retrospectively verify conformity to rules and observance of limits of specifications and the out of specification (OOS) parameters for the pharmaceutical product. It also determines the possible defects and the prospective actions based on trend analysis to be defined for protection from possible risks. Through the implementation of the regulatory guidelines of annual product quality review, risks of pharmaceutical product can be minimized which will be helpful for the pharmaceutical companies to develop their products consistently of best quality on yearly basis.

Implementation of regulatory requirements of Annual Product Quality Review will make pharmaceutical companies' application and approval of new drug easier and will help export of pharmaceutical product to the international market. An ideal real-time assessment would contain a constant, on-going system review that is available to the person granting the release.

Need Of Annual Product Quality Review For Manufacturing And Control Of Pharmaceutical Products And Active Pharmaceutical Ingredients [3]

- 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.
- This requirement was published as final current good

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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 the 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.

General Procedure For The Preparation And Documentation Of Annual Product Quality Review [4]

Regulatory Requirements For Preparing Annual Product Quality Review [5,6,7,8,9,10,11,12,13,14,15,16,17,18,19]

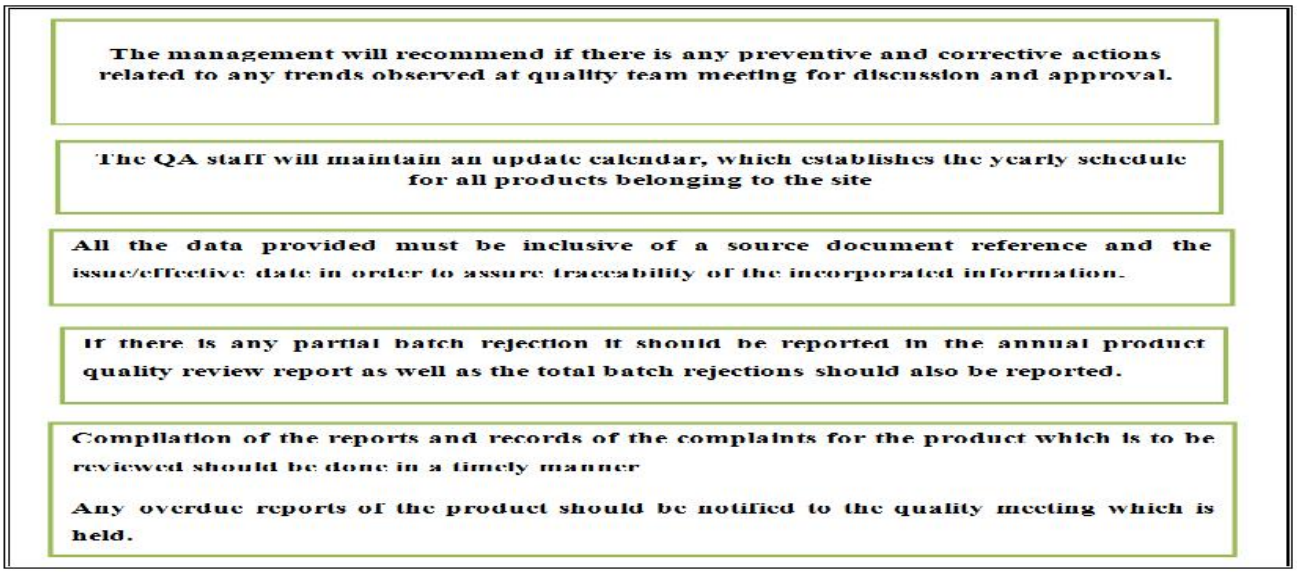
The annual product quality review will determine if there is any need of revalidation of processes or methods, control procedures for the manufacturing of the pharmaceutical product and changes in product specifications, their manufacturing and their evaluation for regulatory notification for the regulatory submissions to different regulatory authorities.

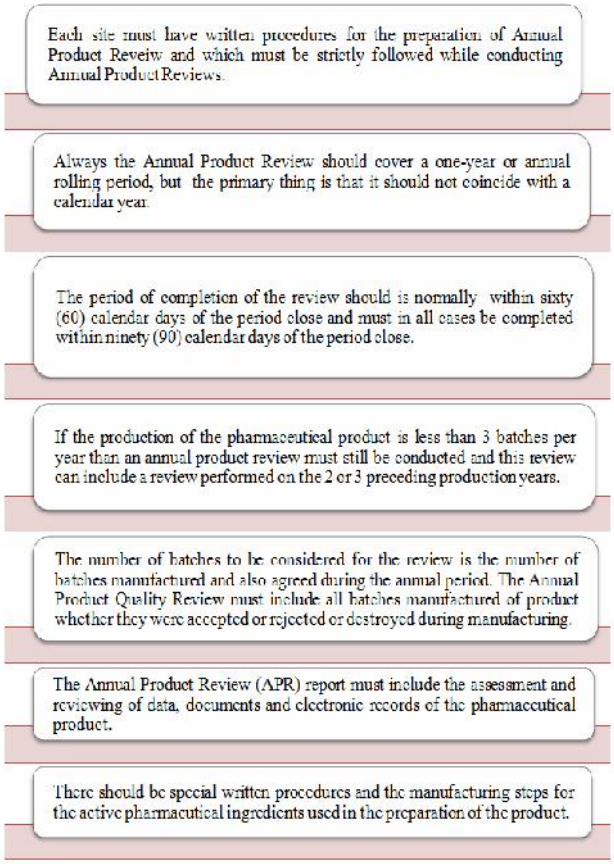
The evaluation of all the in-process control results, the finished product laboratory results for the analysis of the pharmaceutical product from all lots manufactured or tested during the evaluation period should be considered until and unless the total number of lots of manufactured product is equal to or exceeds fifty.

If this is the case the data to be evaluated should be a representative sample of the lot of the manufactured product.
The selection of lots for the evaluation should be basically based on a pre-determined frequency for e.g. first four lots manufactured each month and this should be done to eliminate or minimize the effect of the seasonal changes on product characteristics and also allow the inclusion of released batches as well as rejected batches of the product.

If for a particular product for which the review is to be performed, the batches manufactured are less than 3 batches, than the annual product quality review will be delayed until at least 3 batches are available for the review or until the next review period where two years of data will be available for the review.

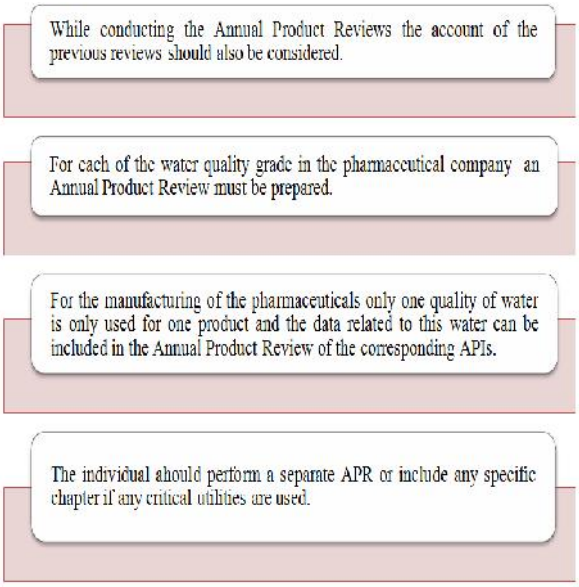
The department of Quality Assurance will select the batches to be included for the review and they will send the list of batches to the other departments also. The last batch and the first batch in the review period will be determined by the final disposition date of each batch.





Regulatory Requirements For The Preparation Of Annual Product Quality Review As Per Us [4, 5,6,7,8,9,10]

- The regulatory requirements and the written procedures for the preparation of the Annual Product Quality Review are published in the Code of Federal Regulations (CFR) code and the final regulations are published in the Federal Register which includes the daily published record of the proposed rules, final rules, meeting notices, etc.) are collected in the CFR.
- The CFR is divided into 50 titles which represent broad areas subject to Federal regulations.
- The FDA's portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. All the regulations related to the drugs and foods are included in the Section 21 of the CFR. The regulations that are required under Federal law are:
- **21 Code of Federal Regulations Part 210** is about the Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.
- **21 Code of Federal Regulations Part 211** is about the Current Good Manufacturing Practice for Finished Pharmaceuticals.
- The relevant Annual Product Reviews are generally requested in the advance in preparation of every FDA inspection, if we keep in mind that the relevant APRs are generally requested in advance in preparation for every FDA inspection for this the significance of the APR becomes clear.
- The review offers a simple point of entry for every inspection.
- The requirements for the preparation of the Product Annual Review are described in the 21 CFR 211.180(e).
- The other chapters are also cited in 21 CFR (e.g. Section 211.192 which includes the Production Record Review, Section 211.198 which contains all the Complaint Files related to the product, then section 211.204 is about the Returned Drug Products etc.).
- Just because of this, it is not always clear exactly what is expected by the regulatory authority. So it is presently a standard FDA practice to make additional and quite reasonable demands that make it possible to improve the evaluation possibilities for products.
- This development is then consistent with the requirements of the Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations published in September 2006.
- The USFDA regulations describe very limited the contents for the review and evaluation of the product but as per EUROPE the contents for the preparation of the Annual Product Quality Review are well described.



Frequency and procedures for Annual Product Quality Review

- FDA requires an annual frequency for the Annual Product Quality Review (APQR), which is stated in all three GMP regulations and the guidance document.
- FDA and EU require an annual frequency for the PAR/PQR, which is stated in all three GMP regulations and the guidance document.
- FDA does not allow the extension of the review frequency beyond an annual basis, regardless of the number of batches produced in the preceding 12-month period.
- FDA expressed the concern that "Potential problems with product quality standards could go undetected and thereby delay recognition of a need to revise specifications or manufacturing or control procedures"
- The Product Quality Review requires that the account should be kept of the previous reviews and also as the part

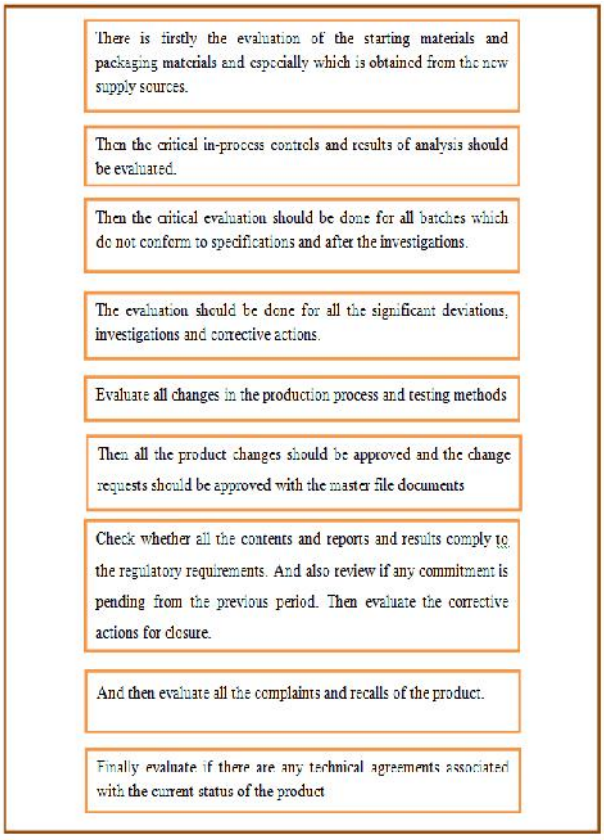
SR. NO.	Parameter	US	EUROPE
1.	Annual Product Quality Review (APQR) – In US and Europe	It is known as Annual Product Review (APR) / Product Annual Review (PAR) in US.	It is known as Product Quality Review (PQR) in Europe.
		Regulatory Authority	
2.	The regulatory authority for the preparation and documentation of the APQR	U.S. Food and Drug Administration (USFDA) Centre for Drug Evaluation and Research (CDER)	European Medicines Agency (EMEA) The Committee for Medicinal Products for Human Use (CHMP) Pharmacovigilance Risk Assessment Committee (PRAC) Committee for Medicinal Products for Veterinary Use (CVMP)
		Regulations And The Regulatory Requirements Required To Prepare The Annual Product Quality Review	
3.	The regulations required for the preparation of the APQR.	21 CFR 211.180(e)	EMEA- Part I of the EU GMP , Chapter-1
		Items For Review	
4.	Study and review of all the quality related data, returned products, if any complaints and recalls are there for the product and the investigations performed at that time during the review.	It is specified under the 211.192	It is specified in the European guidelines
5.	The review of adequacy of any other previous product processes or corrective actions of the equipment	It is not specified	It is specified
6.	The qualification status of the equipment's and utilities used for that product for e.g. HVAC. Water, compresses gases, etc.	Not specified	Specified
7.	The study and review of the starting materials used for the preparation of the product	It is not specified	It is specified in EU
8.	The review of any contractual agreements signed for that pharmaceutical product which is well defined in the chapter 7 to ensure that they are up to date.	Not specified	Specified
9.	The evidence and information related to the salvaged products and the review of the same.	It is specified	Not specified
10.	The review and data related to the in-process controls	It is not specified	It is required and specified
11.	The reviewing of the packaging materials used in the preparation of the product.	It is not specified	It is specified
12.	The critical insignificant deviations and the non-conformances observed	Not specified	It is specified
13.	The reviewing of of the data of stability results of the product.	Not specified	Specified
14.	The study and reviewing of any adverse trends found during product development.	Not specified	It is specified
15.	The study and review of any marketing authorization variations which are submitted, granted or refused	Not specified	It is specified
16.	The data of post marketing commitments if any	Not Specified	Specified
17.	The inclusion of review of the exported products only	Not Specified	They are specified
18.	The data of total no. of batches whether they are approved or rejected	Specified	It is not specified
19.	The analyzed data of the batches that failed to meet the specifications should be included in the APQR report.	Not specified	It is specified
20.	The adequacy of any equipment's corrective actions taken or any previous processes corrective actions taken (from the previous product quality reviews).	Not specified	Specified
		Responsibilty, Documentation, Review, Follow-Up And Approvals	
21.	The responsibility of the QA personnel to ensure the accurate review and in the timely manner	It is not specified	It is required as per the European guidelines (it is done by the qualified QA person and in the doc. cell of the pharmaceutical- industry who is qualified for the batch certification and who is the holder marketing authorization.
22.	The written reports of all the data.	Not specified	Specified
23.	The documented data for the reason of corrective actions taken.	Not specified	Specified
		Frequency Of Review And Procedures For Review	
24.	The frequency of the review of all the manufactured batches.	It is annually done	It is annually done
25.	The account of the previous reviews to be kept.	Not specified	Specified
26.	Procedure or SOP for the preparation of the APQR of the product.	There is a written procedure of the preparation of the APQR of the pharmaceutical product.	There is no such written procedure for the preparation of the APQR of pharmaceutical product.
27.	Total number of review requirements	The total number of review requirements as per US is only 11.	The total number of review requirements as per EUROPE is 34.
28.	The total number of review requirements which are not specified in the guidance document.	The total number of review requirements which are not specified in the guidance document is found to be only 12.	The total number of review requirements which are not specified in the guidance document is found to be 1.

of the current review. This is also expected by the FDA and is also indicated by the many FDA 483 observations but it is not mentioned in the FDA GMPs or other guidance documents. This requirement is also not mentioned in the ICH Q7A.

Regulatory Requirements for Preparation of Annual Product Quality Review as Per USFDA

Regulatory Requirements As Per Europe[12-19]

- The preparation or documentation and the written procedures for the Product Quality Reviews should be specifically referred to the objectives to determine and justify the areas which are selected for review and the extent to which they are reviewed.
- The area or any of the review parameter that is not relevant or which is not fulfilling the objectives should be excluded from the PAR/PQR.
- The EU PQR has many additional required objectives and the review parameters which are not mentioned in either the FDA PAR or in the Q7A PQR.
- These include the identification of product and process improvements, highlighting trends, and determining the appropriateness of starting material specifications.
- The procedure for the preparation of the Annual Product Quality Review is clearly mentioned in the FDA but it is not mentioned clearly in the European guidelines.
- In the EU GMP the contents for the preparation of the Product Quality Review (PQR) are well described and no such procedure is described for the documentation of the Product Quality Review (PQR).



Procedure for preparation of Annual Product Quality Review as per Europe

Comparitive evaluation of regulatory requirements of annual product quality review (apqr) as per us and europe

CONCLUSION

The regulations, regulatory requirements and the procedures mentioned as per US and Europe should be strictly followed to prepare and document the Annual Product Quality Review of the pharmaceutical product this should be done to avoid the dissatisfied or false results.

On comparison of regulation between the US and Europe it was found that the regulations and requirements for Annual Product Quality Review in Europe are stringent as compared to US. European regulations have more number of basic requirements to be fulfilled and it strictly follows GMP to maintain the quality of the pharmaceutical product and to make consistent good quality batches of the product after reviewing the results.

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