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## Annual Product Quality Review

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### ABSTRACT

Annual Product Quality Review (APQR) is an estimation prepared according to the Current Good Manufacturing Practice (CGMP) requirements of different regulatory authorities. A Good Manufacturing Practice (GMP) ensures that the products are constantly produced and controlled according to quality standards. APQR is not only required for GMP but also required for the quality improvement of the pharmaceutical product. APQR is an evaluation carried out annually to measure the standard of quality of each drug with an intention to verify the constancy of current process and to check the correctness 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 that is required for every drug, based on the data that was collected in the previous year. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the finished product. The APQR is globally accepted by the industry and the contents should 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 focusses 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.

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### INTRODUCTION

The APQR (Annual Product Quality Review) is an estimation carried out yearly or to be conducted at

regular period of time to evaluate every drug product's quality standard or quality assessments of all registered medicinal pharmaceutical products, with the vision to justify the constancy of the current method and to check the correctness of the existing qualifications and to focus on any trends in order to decide the necessity for modification of any manufacturing procedures (or) the specifications of drug product (or) the control techniques.

The APQR is done for the products which are produced in Australia, Canada, and Europe, Row, U.S and U.K market.

This is a useful quality development tool to improve the constancy of manufacturing procedure and complete characteristic of the product. This is done

by taking into account the comprehensive review of product information and capturing styles that will help to conclude the deficiencies and possible developments of the process and Procedures and will reveal if there is no significant modification should be done to the manufacturing procedure (or) to the system. The Annual Product Quality review approves that the process (or) the system is constantly producing material (or) Product meeting its qualifications; normally revalidation is not needed. (Pandey, 2018; Pazhayattil, 2012)

### Product Quality Review

It is defined as a rolling quality (or) the regular periodic reviews of all approved medicinal products, which include the products to be shipped. The annual product review should be organized with the objective of confirming the constancy of current process, the correctness of existing specifications for both starting materials and the finished products to highlight any trends and to identify the product and process improvements.

### Role of Annual Product Quality Review

#### Annual Product Quality Review should

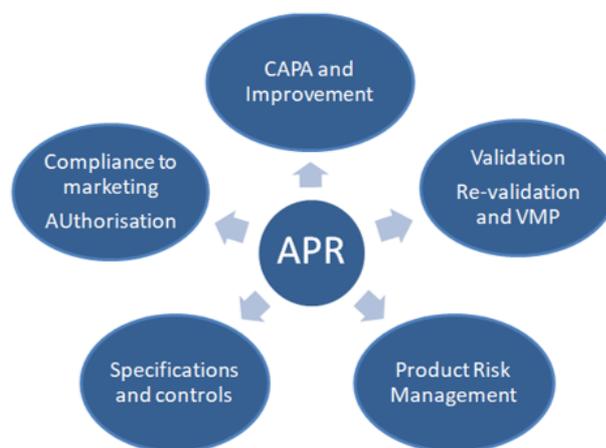
1. Verify the constancy of the current manufacturing processes.
2. Determine the quality and process faults of the products.
3. Regulate the faults and possible developments of the methods and procedures.
4. Determine analytical results and trend of yield
5. Highlight the manufacturing parameters of the product.
6. The quality of raw materials and packing materials which is used for the product.
7. Specify the material quality.
8. Help to determine the quality and the consistency of the product.
9. Review the results of finished products and in-process parameters.
10. Review the final product quality by using trend of yield for every batch.
11. Determine the product defects by using out of specification parameter.
12. determine the batch rejection of the product if any of the product batches have failed.
13. Be helpful in the determination of stability study, trend analysis and the product stability.
14. Determine the process revalidation and if there is any improvement made previously.
15. Review the corrective and preventive actions and their impact on the quality of the product.

### Significance of APQR

1. The annual product quality review should verify the current manufacturing process consistency and minimizing the risks for the pharmaceutical products which are helpful for Pharmaceutical companies for the consistent development of product quality for yearly basis.
2. The annual product quality review should determine the process defects and the quality of products. It should also determine the improvements that are possible for the manufacturing processes and the analytical methods.
3. The annual product quality review should highlight the product's manufacturing parameters, yield trend and the analytical results. It is also helpful in the identification of the product or the process defects.
4. The annual product quality review should analyse the raw material and the packing material quality which are used for product. Mainly the APQR should indicate the material quality.
5. The annual product quality review should verify the current qualifications, appropriateness for both starting materials and the finished products to identify the improvements in the product and the process and to highlight any styles.
6. The product defects should be determined by using OOS (out of specification) and the actions that are prospective then the possible risks which should protect the product quality.
7. The annual product quality review should contain information regarding the batches that are rejected.
8. The annual product quality review should contain the results of stability study for on-going and the long term stability of the marketed product and the bulk product that should be done.

### Preparation of APR (Annual Product Review)

1. All companies should have a written procedure for APQR process and should recommend that the review should be done for all batches that are manufactured from 1st January to 31st December. Then all batches should include both approved and rejected batch products. This is the written procedure and made mandatory by majority of the GMP regulatory bodies.
2. The annual product review report configuration should be different based on specific documentation of the company and different types of products.
3. A standard template should be followed by the company to ensure that all the required aspects should be evaluated.
4. Since annual product review is a progressing document, it must contain only few sections consisting of nominal necessities to elaborate the document with an agenda consisting of data or information appropriate to the product.
5. The report of an APQR should contain the following information.
6. The testing results of finished and half finished products should contain the following information.
7. The review of a reworked/reprocessed batch and then the reason for the rework/reprocess of the batches.
8. Critical in-process controls.
9. Yield review and quality review of the failed batches CAPA & OOS should be taken.
10. Changes are proposed, and then certified and further implemented that would indirectly or directly related to the product, in-case if a change control is raised related to a multi-product facility should be mentioned in the APQR review report of all the products that are manufactured in the facility.
11. Effectiveness of CAPA, deviations, and Corrective and preventive actions are taken against each deviation on the later manufactured batches.
12. It involves the issues regarding the previous year APR and unresolved issues.
13. It contains information regarding the recalls, return of goods and complaints which are noted for the products.
14. The review of a retained sample.
15. The CAPA effectiveness should be mentioned in the previous year records of APR.
16. The analytical (or) process Validation methods should get caused if any changes are made.
17. The updates (or) the regulatory filings should be made in current drug master file (DMF) with the changes made.
18. Repacking made
19. The qualifications of the critical equipment.
20. In any station, if any investigation outcomes related to stability studies found, it should be addressed properly.
21. The quality agreements should be made for product.
22. The review of a starting packaging materials and starting materials which are used for the product.
23. A comment must be there after every numbered sub-section followed by an overall summary of the report.
24. The annual product review document should be finally reviewed by each department, approved by the quality and authorized by the management. Figure 1 explains The Relationship of Annual Product Review to Quality System.



**Figure 1: The Relationship of Annual Product Review to Quality System**

**Need of APQR for the manufacture and controlling of pharmaceuticals and API's**

1. The USFDA recommended a necessity for preparation of printed summary for every drug product. This was done on Feb 13th, 1976 by modifying GMP of products.

2. The intention behind this suggested GMP necessities were to deliver consistent processes for the drug industrialist for the purpose of reviewing required standards for quality regarding every drug products.
3. Later FDA received many comments from companies regarding objection to printed summary preparation. This made FDA to revise its proposal which allowed every industry to launch processes that helped to evaluate the quality standards of drug products, by revising the records which are required by the GMP on a yearly basis.
4. This led to publication of CGMP regulations for the drug products.
5. From the time of this publication, the 21 CFR Part 211.180(e) is being referred as PAR (Product Annual Review) or the APR (Annual Product Review).
6. FDA proposed Q7A GMP Guidance for API in August 2001.
7. These regulations were proposed by the Expert team of ICH.
8. In October 2005, these regulations were introduced as part of EU GMP Guidelines.
9. A section 2.5 and 12.6 of the above regulation specifies the PQR (Product Quality Review) for API.
10. European Union Good Manufacturing practices Guidelines offer information that supports GMP principles in EU. ([Lee and Grazal, 2008](#))
4. The review should contain information related to results of adverse trends and stability monitoring programme.
5. The review should contain information regarding the results of critical in-process parameters and finished products.
6. A review which contains all recalls, complaints, investigations and quality-related returns should be performed at the time of review
7. A review should include all non-conformances (or) significant deviations, the effectiveness of the CAPA should be taken and related investigations.
8. A review should include marketing authorised variations which are granted (or) submitted (or) refused for the third person (country)/ for export only.
9. The condition of relevant utilities and the relevant equipment, e.g. compressed gases, HVAC and water, etc.
10. A review should contain an adequacy of corrective actions of equipment (or) any other process done for the product previously. .
11. A review which contains commitments for Post-marketing, authorisations which are used for the new marketing and variations due to marketing authorities.

### Contents of APQR

The annual product review should be annually organized and recorded, by taking information of earlier reviews, and should include the following information.

1. The review should include raw materials and packing materials which are used for the product, especially which are bought from the new sources.
2. The review should include all information regarding the batches that are unsuccessful to meet the specification
3. The review should contain an information regarding all changes should be carried out to the analytical methods or the procedures.

### Regulatory characteristics for the preparation of APQR

#### Parameters to be reviewed

1. Ware house review
2. Production review
3. Quality control review
4. Quality assurance review

#### Data to be reviewed

##### Ware house review

1. During the ware house review identify all the starting materials and the packing materials which are used for product.
2. The review should include the approval of packing material and their release and the rejections.

3. The review includes all the deviations, analytical tests and the changes that are made for the specifications.

### Production review

1. The review which contains the product description and the master formula record description.
2. The review which contains information regarding the equipment's which are used for the manufacturing and for packing purpose.
3. The review which contains information regarding the classification of the manufacturing area and the flow diagram for the process.
4. The review which contains information regarding the qualification status of utilities, equipment's and the processes.

### Quality control review

1. The review which contains information regarding the written procedure should be there for the process and the production controls and to assure the quality, purity, strength and the identity of the drug product. If there should be any procedure changes then it should be reviewed and approved by quality units.
2. The review which contains information regarding the out of specifications, out of trend and the laboratory incidents of the drug products.
3. The review which contains an on-going (or) the long term stability for the marketed drug products and the bulk products.

### Quality assurance review

1. The review which contains information regarding the corrective and preventive actions that are taken, investigations and the process deviations.
2. The review should be done for the market complaints, quality related returns, product recalls, rejected batches, repacking batches, control samples, post marketing commitments and the marketing variations (Tribe, 2002; PICOS, 2009).

### Six Areas are listed below

1. Legal: The regulatory notices and Market authorisation.

2. External: Returns, recalls, complaints and the adverse events.
3. Processes: Process validation, changes and controls.
4. Product: Failures, OOS, Product testing, stability and retention samples.
5. Quality Control: Test methods, changes and product specification.
6. Events: Product related Corrective and preventive action and the incidents

All the six areas listed above are mentioned in Figure 2 in the form of flowchart



**Figure 2: Six Areas for Specific Reviews of product**

### Product Quality Review by Various Regulatory Agencies

#### European Commission

The quality reviews of an active pharmaceutical ingredient should be regularly organized with an objective to verify the process constancy. Such type of reviews would be annually organized and should be recorded which include following information.

1. A review which includes the test results of critical active pharmaceutical ingredients and the critical in-process parameters.
2. A review which includes the information regarding the adequacy of corrective actions.

3. A review which contains the information related to complaints, recalls, and all quality related problems.
4. A review which contains information regarding any changes are made to the analytical methods (or) processes.
5. A review which includes that batches that are unsuccessful to meet the established specifications.
6. The review which includes the stability monitoring program results.
7. A review which contains information regarding the non-conformances (or) the critical deviations and their related investigations.

The results which are obtained from the review which should be evaluated and made an assessment whether there should be undertaken any revalidation (or) corrective action. The reasons which are documented for the revalidation and the corrective actions which are taken. Those corrective actions that are agreed should be completed in an effective and timely manner.

#### **Periodic Review of the Validated Systems**

The systems and the processes that will be evaluated regularly to confirm that the systems or the processes which should still be operated in an effective way. The Significant variations are not made to the processes and the systems. The quality review should also confirm that the system (or) the process is consistent and product is meeting its requirements. Thus, normally there is no need for the revalidation ([Eudralex and Commission of the European Communities, 2015](#); [Kroes, 2014](#))

#### **Frequencies and the procedures for APQR**

1. The FDA requires annual frequency for APQR, which should be mentioned in all the three guidance documents and the Good Manufacturing Practice regulations.
2. The APQR should require an account which should be maintained for previous reviews.
3. The European Union and Food and drug administration should require the yearly frequency for PQR/PAR that information should be mentioned in three guidance document and the GMP regulations.
4. The FDA should not allow the review frequency which may go on an extension annually, regarding the number of batches that are produced during the period of 12 month's

#### **WHO**

The rolling quality (or) regular periodic reviews are conducted with an objective and with a view to verify the existing process consistency and to check that the current specifications appropriateness, then to identify the improvements which are made for both process and the product.

The quality review of a product should be considered as a tool and helps in surveying the quality status of the manufacturing processes, including collection of the starting materials. Such type of reviews should be conducted every year and must be documented. According to the NRA and the international recommendations and requirements may include:

1. All changes made
2. The starting materials
3. The results of quality monitoring and the quality control
4. The in-process controls which are critical
5. The complaints and the recalls
6. The content of information regarding the findings that are obtained during the inspections and the internal audits and corrective actions that are implemented
7. Review of the information regarding the errors, significant deviations and all non-conformances and corrective actions that are implemented.
8. Review of all the look-back cases ([Food and Drug Administration, HHS, 2012](#)).

#### **PIC/S - Quality Management**

The given inherent variability in many of the products and the biological substances, having the steps that helps to raise the process robustness and thereby decreasing the process variability and should improve the reproducibility at various stages of lifecycle of product and should be reassessed by the product design during the review of a product quality.

The rolling quality reviews (or) the regular periodic reviews of all the certified medicinal products, including the transport products, the review should be organized with an objective to verify the constancy of the current process, and to check the correctness of the existing specifications for both the starting materials and the finished products, to identify the improvements in the process and the product. Such type of reviews should be organized and

should be recorded yearly, taking into consideration of the earlier reviews, which should include the following information.

1. The review which includes the starting materials and the packing materials which are used for the product, particularly those are bought from the different sources.
2. The review which includes any contractual arrangements ensures to check that if they are up to date.
3. The review which contains the results of in-process controls and the finished products.
4. The review which contains information regarding the changes which are carried out for the analytical methods (or) the processes.
5. The review which contains information regarding all the batches that are unsuccessful to meet the established requirement and should be their examination.
6. The review which contains information regarding the non-conformances (or) the significant deviations and their related investigations, and their effectiveness of the resultant CAPA which are taken.
7. The review which includes the information regarding the results of adverse trends and stability program monitoring.
8. The review which includes the variations in the marketing authorization that is granted (or) submitted or rejected, and including for the third party (export) dossiers.
9. The review which includes all the information regarding the complaints, recalls, and returns, quality related problems and then the investigations that are done.
10. The review which includes an adequacy if any of the previous product (or) the process (or) the corrective actions which are taken for the equipment.
11. The review which contains information regarding the new marketing authorization and the changes in the marketing authorizations, and a review should be done for the post marketing.
12. The review which includes the qualification status of the relevant equipment and their utilities, e.g. water, compressed gases and HVAC. (Tribbe, 2002)

### Annual Product Quality Review by ICH Q7

The quality reviews for the active pharmaceutical ingredients should be done regularly and the reviews should be organized with an objective to verify the process constancy. These types of reviews should be annually organized and should be recorded which includes the following information.

1. The review which includes the results of Active pharmaceutical ingredient tests and the in-process controls which are critical.
2. The review which includes that what are the corrective actions that are taken for the adequacy.
3. The review which includes all the information regarding the complaints, recalls, returns which are related to quality related problems.
4. The review which includes the stability monitoring program results.
5. The review which includes the information regarding the batches that are unsuccessful to meet the established specifications.
6. The review which includes the information regarding the changes that are carried out for the analytical methods (or) the processes.
7. The review which contains information regarding the nonconformances (or) critical deviations and their related investigations.

The results which are obtained from the review that should be assessed and evaluated. Whether the corrective actions (or) the re validations those are undertaken. The reasons for the corrective actions that are undertaken that are documented. Then the agreed actions that are taken are completed on time and in an effective manner (Organization, 2004).

### Annual Product Review report format

The report of an APR should contain the following information

1. The cover page should include the title of APR, Products that are covered and the signatures of APR reviewers and the approvers.
2. APR subsection should contain the element reports which are documented during the analysis of each element and it acts as a document which contains data.
3. The APR summary should contain integrated analysis of APR element reports and overall rating of APR.

4. The list of corrective and preventive actions that are taken and their result.

#### Annual Product Reviews Rating's

1. Acceptable – The risk assessment may not be warrant.
2. Satisfactory – The risk assessment should not warrant.
3. Acceptable with conditions – The risk assessment should be performed.
4. Unacceptable – The risk assessment should be performed and then the notification is sent to the regulatory agencies and should consider as a part of mitigation and communication.

#### Annual Product Review report approval

The final APR report summary should be approved and signed by:

1. The Quality Assurance Manager
2. The Regulatory affairs manager
3. Production manager
4. Other groups who may be affected if any changes are occurred. (Williams, 2010).

#### CONCLUSION

Thus, Annual product Quality Review (APQR) is an estimation carried out annually to measure the quality standard of each drug product with the view to verify the constancy of current process and to check the correctness of existing specifications to manufacture the pharmaceutical product. Thus, it is necessary to study the regulatory requirements for the preparation of APQR to manufacture the pharmaceutical product according to the Good manufacturing practice (GMP) requirements and which is safe and effective to the public. Hence, to study the regulatory requirements is essential. APQR not only required for GMP and also required for the quality improvement of the pharmaceutical product. It is designed to minimize the risks involved in any pharmaceutical production. APQR is a written report which is required for every drug product based on data which should be collected annually.

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