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Short Communication

A SHORT COMMUNICATION ON PREPARATION AND APPLICATION OF ANNUAL PRODUCT QUALITY REVIEW IN BIOPHARMACEUTICAL INDUSTRIES

SEETHA RAM K[1#*], DIVYA JYOTHI G[2#], NITHIYAA JS[3], SATISH BABU K[4#], ATULYA KUMAR NANDA[5], KVC CHAKRAPANI[6]

[1]Department of Biotechnology, Acharya Nagarjuna University, Guntur – 522510. [2]Department of Microbiology, Acharya Nagarjuna University, Guntur – 522510. [3]Department of Biotechnology, Anna University, Chennai – 638401. [4]Department of Biotechnology, Vignan University, Guntur – 522213. [5]Department of Biotechnology, Fakir Mohan University, Odisha – 756020. [6]Department of Chemistry, JRNRVU, Rajasthan – 313001. # Authors have equal contribution. *Email: kotraseetharam@gmail.com

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ABSTRACT

In regulatory scope of biopharmaceutical industries, annual product quality review (APQR) is a structured and exhaustive summary of a licensed human pharmaceutical or biopharmaceutical product, which provides insights about the consistency and robustness of the process. APQR / PQR facilitate to highlight the trends of process parameters of product/s or for process improvements for all commercial products. APQR is essential for good manufacturing practices and also important for improvement to fill gaps in manufacturing system for compliance. It is a comprehensive document prepared annually for each licensed medicinal product based on the data generated for a financial year for respective product/s with a window time of four months. The main philosophy behind the need of APQR is risk reduction, productivity, compliance & verification of validation status. This article provides ideal regulatory requirements for APQR preparation, with focus on data analysis requirements to analyze the batch data to draw meaningful insights on the process for improvement. As of now, this is the first review on annual product quality review as per regulatory requirements in view of current good manufacturing practices.

Key words: Annual Product Quality Review, current good manufacturing practices, compliance.

INTRODUCTION

Every year pharmaceutical industries will produce lot of drugs and the production method should be in compliance state in view of patient safety. All the data for a particular period should be documented. In general, Annual Product Quality Review (APQR) has to be prepared in view of cGMP/ GMP requirements of different health regulatory agencies across the globe [1]. According to ideal industrial quality systems, good manufacturing practices make certain products are produced in a controlled manner in view of patient safety, system performance and compliance requirement. Different regulatory systems require APQR as a part of GMP and also for continuous process improvements conducted annually [2]. It is also one of the tool useful to measure the quality standards of the each and every critical quality parameters (CQP) of manufacturing process. A report to be prepared post to financial year for every product manufactured based on the data generated for the product in that particular financial year with all CQP's. In ideal industries, cross functional departments like Engineering, Instrumentation, Regulatory Affairs (National and International), QC Microbiology, QC Analytical, QC Raw materials, Production, manufacturing sciences and warehouse shall be the part of APQR review which is duly prepared by QA, end user.

Quality to be built in

Quality is not an inbuilt characteristic feature of any pharmaceutical product. All regulatory systems of pharmaceutical industries set minimum standards in manufacturing of quality products. For this, quality management system is in place for every biopharmaceutical industry. But effective quality management systems in pharma / biopharma industries avoid drug shortage and recall that are linked to quality issues. Hence clean room operators who are working in manufacturing area should have quality mind set to carry out the operations in right way even no body observes, because quality is not an in built activity. Operators built the quality through aseptic operations. So all quality parameters to be considered in APQR preparation.

Importance of APQR

1. To understand the consistency of current process
2. It helps to review the annual number of batches for every specified commercial product and its non-compliances in short time.
3. It helps to understand the risks associated with the product.
4. It improves the quality of the product in annual timelines.
5. Verifying compliances with different regulatory systems/ market authorizations in view of manufacturing
6. Comparing the current manufacturing process with executed process in view of risk minimization.
7. It helps to identify the required major activities i.e., Requirement of revalidation, adverse trends, etc.
8. Trending the product yield, CQP's of manufacturing, analytical and stability data (long term and accelerated) will help to identify the areas of improvement of manufacturing process.
9. All batch rejections or batch contaminations or batch terminations should include in APQR and reasons to be verified and documented.
10. All raw materials/ packing materials/ critical consumables which will be used in the process to be reviewed for its quality.
11. All types of non-compliances for quality parameters will help to avoid the recurrences by taking respective actions by top level management of particular industry in view of cGMP.
12. It helps to identify the critical steps in process controls and finished product results.

13. Appropriateness of specification for raw materials/ intermediates/ semi-finished products/ finished products.

APQR scope

The scope of the APQR should be broad in view of regulatory requirement. But all regulatory systems highly demand the following in APQR.

1. Documents: Ideal pharmaceutical/ biopharmaceutical industry should have to project all the documents i.e., batch manufacturing record, checklist, equipment cleaning checklist, instrument cleaning checklist, track sheets, technical information sheets, specification (in process and finished) of concern product in product quality review.
2. Risk management: Before starting the batch, if any critical changes occurred or planned, risk assessment protocol to be prepared in supervision of QA by respective cross functional teams and should be documented in product quality review.
3. Validation/ revalidation: If any of the process step/s or specification/s which will be relooked through revalidation to be documented in APQR for better understanding regarding the filings.
4. CAPA: For all major or critical non compliances, where end user with quality support may propose preventive action through CAPA to avoid the recurrences to be documented in APQR.

Elements to be considered in APQR preparation

All pharmaceutical/ biopharmaceutical industries must specify the following in the preparation of product quality review.

1. Raw materials, packing materials and consumables used for the manufacturing process (including rejections, expiry and destruction)
2. Number of batches manufactured during the financial year
3. Number of batches released and batch failures
4. Number of deviations (Critical/ Major/ Minor)
5. Number of change controls (Critical/ Major/ Minor)
6. Number of OOS (Out Of Specification), CAPA (Corrective Action Preventive Action) and OOT (Out Of Trend)
7. Number of vendor complaints (Major/Minor)
8. Number of product recalls/ Market returns/ Market complaints
9. Number of customer complaints.
10. Qualification status of equipment's/ instruments/ utilities.

Key prospects in APQR

Usage of starting materials i.e., raw materials, packing materials and consumables should be documented from first step to last step of manufacturing in APQR. All materials to be mentioned with supplier name, supplier identification code, in-house code and supplier address [3]. Ideal industry practices include the capturing of discrepancies pertaining to all raw materials, packing materials and consumables. If any non-conformance identified for the material, discrepancy need to be recorded and to be notified to QA for further actions and those discrepancies should be captured in APQR. Quantity received at warehouse for all materials should be documented for tracking and usage without fail. All the discrepancies initiated by warehouse or QC (Quality Control) raw material should be attached with APQR as a part of ideal industry practices.

As per best industry practices, APQR to be prepared for commercial products. It includes number of batches planned for commercial purpose to be documented by excluding process validation batches and batches executed prior to process validation. Information to be provided for batches that are discontinued/ contaminated/ terminated during execution. Monthly wise batches have been captured for trending purpose. If any major changes/ critical changes implemented those quality attributes to be mentioned in APQR. Number of batches manufactured last year to current financial year should be stated clearly. In APQR, number of batches that are released in a financial year has to be documented along with batch failures. All non-compliances/ deviations/ OOS/ OOT/ complaints including critical/ major/ minor pertaining to that product shall be furnished with root cause and impact on product quality [4]. CAPA and change controls with classification should be documented with necessary information. If any of the product recall happened, that should be documented [5]. Product recall should be considered as major non-conformance. Likewise, customer complaints duly received by customers/ partners/ hospital administration will be duly investigated and should be documented in APQR. During investigation all the parameters to be verified to sort out the root cause. Number of equipment's and instrument's available in the facility to be documented with internal code and equipment/instruments with their preventive maintenance status and next due date. APQR should be prepared by IPQA/ QA, but not by other department persons. All the required information should be provided to IPQA (InProcess Quality Assurance)/ QA (Quality Assurance) by cross functional teams.

If any pharmaceutical or biopharmaceutical, manufacturing of same product/s at different sites, a separate APQR should be preferred in view of regulatory aspects for better understanding and to avoid conflicts. It should not have recommended a single APQR for same product manufactured at different sites. APQR should be product specific. It is recommended to capture all the process stages of respective product for the batches initiated during the financial year. Hence APQR preparation will take 6 months of time after financial year.

Average of each critical parameter to be prepared for all the stages of process and standard deviation to be calculated. Then UTL (Upper Trend Limit) and LTL (Lower Trend Limit) to be defined for those parameters. If any parameter is out of UTL, that should be denoted with blue colour and if any parameter is out of LTL, that should be donated with red colour followed by what are the actions taken by end user to be mentioned in the APQR. Every attachment prepared pertaining to APQR should be signed off by all cross functional team leads. APQR should reviewed by respective cross functional team leads and should be approved by QA head only, not by designee.

Ideal format of APQR

Name of the product:

Generic Name:

Code of the product:

Financial year:

Manufacturing address:

Objective:

Scope:

Responsibility:

Number and critical parameters identified by manufacturing sciences:

Prepared by Quality Assurance/ In-Process Quality Assurance:

Review by Production

Review by Manufacturing sciences:

Review by Quality Control Analytical:

Review by Quality Control Microbiology:

Review by Quality Control Raw material:

Review by Engineering and Maintenance:

Review by Instrumentation:

Review by Warehouse:

Review by National Regulatory Affairs (If required):

Review by International Regulatory Affairs (If required):

Actions required/ CAPA for non-compliances:

Attachments, if any:

Review by QA:

Conclusion:

Evaluation:

Approved by QA Head:

CONCLUSION

Annual product quality review is the document which is useful to analyse the overall status of the product in view of GMP during regulatory inspections. All regulatory inspectors will verify APQR mandatorily, hence APQR details to be verified accordingly before documenting in APQR. It should be product specific respective of locations. Use additional appendix or attachments, if required when and where. APQR should be duly approved by QA head and not by any other in effective quality management systems. If any information forgets to capture in APQR, that should be routed through addendum. Sometimes regulatory inspectors will ask for addition of some parameters as per their national guidelines, at that time addendum will be useful.

CONFLICT OF INTEREST

All authors are from different university except Divya Jyothi G (DJ G) and cumulatively carryout this work. All authors declaring that there is no conflict of interest regarding this publication.

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