INTERNATIONAL JOURNAL OF ADVANCE RESEARCH, IDEAS AND INNOVATIONS IN TECHNOLOGY

ISSN: 2454-132X

Impact Factor: 6.078

(Volume 7, Issue 3 - V7I3-2186)

Available online at: https://www.ijariit.com

Quality Life Cycle of the Pharmaceutical Products

Prateek Goyal
prateekgoyal1@gmx.com
Mansarovar Global University, Bhopal, Madhya Pradesh

Dr. Vishal Gupta
pharmacy@mguindia.com
Mansarovar Global University, Bhopal, Madhya Pradesh

ABSTRACT

Quality in the pharmaceutical industry is a very important. Quality cannot be tested into the products. But building-in quality from the development phase and throughout a product's life cycle will deliver a perfect quality product. Quality is the most vital aspect of medicines and any short fall may generate risks to the patient. It is anticipated that adequate training of pharma professional and practicing the validated controls will deliver quality product. However, this should not be the one-time event but an activity that continues throughout a product's life. The consistency in quality parameters shall be evaluated considering all three manufacturing stages simultaneously, including the Key Starting Material (KSM), Active Pharmaceutical Ingredient (API) and Pharmaceutical Finished Pharmaceutical Product (FPP).

Keywords: *Product life cycle, Quality evaluation, cGMP, EU, USFDA, Pharmaceutical quality system, Quality Target product profile, Critical material attributes, Critical quality attributes, Critical process parameters, Quality Risk Management, Design space, Control Strategy, Life cycle Management and Continuous improvement.*

1. INTRODUCTION

All Pharmaceutical Products have three essential stages in their manufacturing life cycle. They are Key Starting Material (KSM), Active Pharmaceutical Ingredient (API) and Drug Product (DP). KSMs are the starting material used for the manufacturing of APIs. An 'API KSM' is a raw material that is used in the production of an API and is incorporated as a significant structural fragment into the structure of the API. APIs are further used as a starting material for the manufacturing of Drug Products.

Quality is very important in each of these three stages. Quality cannot be tested into the respective stage. But building-in quality from the development phase and throughout a product's life cycle will deliver a perfect quality product. Quality is the most vital aspect of medicines and any short fall may generate risks to the patient. It is anticipated that adequate training of pharma professional and practicing the validated controls will deliver quality product. However, this should not be the one-time event but an activity that continues throughout a product's life. Also, the evaluation shall be performed considering all three manufacturing stages simultaneously.

Quality in the pharmaceutical industry is the most important attribute. Many Regulatory agencies like USFDA, ICH, WHO, EU, MHRA, TGA, CDSCO etc. anticipate the best quality in pharmaceutical products. These Regulatory bodies have issued numerous guidelines which provide outline on the requirements pharmaceutical quality. Regulatory bodies require Quality Assurance (QA) to cover all aspects that could have an impact on the quality of pharmaceutical products. The objectives shall be to ensure that the medicine competently provides the desired effect to the person taking it; to protect patients from accidentally being administered an incorrect or contaminated medication; and to ensure medicines comply with the regulations.

Pharmaceutical Quality Systems (PQS) consist of six key factors, which are designed to provide high quality finished pharmaceutical products. They are quality, production, facilities and equipment, laboratory controls, materials, and packaging and labelling. Pharmaceutical companies strive to provide high quality products to enable them to enhance their reputation, maximize profit and to provide high quality drugs to humans and animals. To meet these targets, they rely on well-designed PQS, which involve the coordination of quality through processes, with the aim of producing finished products of the highest quality.

The Product quality review is a GMP requirement and should be conducted periodically, or on another routine basis, as justified, to evaluate process consistency through reviews of (not limited to):

- critical in-process control and critical test results.
- all batches that failed to meet established specification.
- all critical deviations or non-conformities and related investigations.
- any changes made to the processes or analytical methods.
- results of the stability monitoring program.
- all quality-related returns, complaints and recalls.

- adequacy of corrective actions.
- the current impurity profile versus the established impurity profile.

The cumulative effects of changes to systems and processes should also be reviewed periodically to determine if there is a need to revalidate. The Product Review may be used to evaluate process performance with respect to validation.

Review of Product Quality is limited to the review of trends available at three different manufacturing stages, individually. For building the quality in entire life cycle of the products, it is required to evaluated at all three stages simultaneously and the possible impacts of variations in one stage shall be evaluated at subsequent stages of manufacturing.

1.1 Current practices

Available methodologies discuss about the development of quality product and to evaluate quality of product during product life cycle. This approach is confined to periodic evaluation of product and process and is based on Quality by design (QbD) concept.

QbD involves a thorough understanding of the relationship of product performance with product attribute and process. Traditionally, formulations are manufactured to meet quality control tests outlined in product specifications. If the product is deemed fit for commercial purpose, then it should meet quality control tests. In case of a batch failing to comply with these tests, it is reprocessed or rejected which opens doors for regulatory questions and obvious cost burden. Following are the key elements of QbD:

- Identifying quality target product profile (QTPP)
- Identifying critical quality attributes (CQAs)
- Identifying critical material attributes (CMAs)
- Design product and defining product design space
- Process design and defining process design space
- Defining control strategy
- Process validation
- Regulatory filings
- Process monitoring, life cycle management and continuous improvement.

The application of QbD in pharmaceutical product development is systematic, involving multivariate experiments utilizing process analytical technology (PAT) and other tests to identify critical quality attributes based on risk assessments.

The PAT process involves the identification of scientific and engineering principles and variables that affect product quality. PAT is useful in the reduction of cycle times, prevention of reject product and waste, real-time product release, greater use of automation and facilitation of continuous processing. This will generate processes which consistently produce quality products. The understanding of the characteristics of the drug and other components of the drug product is required to design such a process. Undetected variability of raw materials may be manifested in the final product if certain critical attributes of pharmaceutical ingredients are not well-understood or taken into consideration during a manufacturing process. Therefore, a thorough identification and understanding of these attributes should be carried out. However, there are some difficulties that exist for this, such as collecting representative samples from powder samples, which is very much prone to errors. Time defined end points such as blending for a particular time period may not be useful for assuring the product quality as the differences in the critical attributes of the raw materials will not be considered.

1.2 Proposed system and methodology

To build quality in entire life cycle of the product (Key Starting Materials, Active Pharmaceutical Ingredients and Finished Pharmaceutical Products) considering the unidentified changes, drifts, trend shifts occurring in due to variability in the input raw materials, manufacturing processes and process capabilities etc. This shall be done by using the QbD elements like QTPP, CQA, CMA and CPP to enhance the product quality. Finally, product and process capability of all three stages shall be continually reviewed and improved during product lifecycle management.

The Product Life Cycle means the series of phases that every product continues through until it reaches the stage where it is finally discontinued from the market. Product lifecycle should consider all steps of manufacturing i.e., KSM, API and FPP.

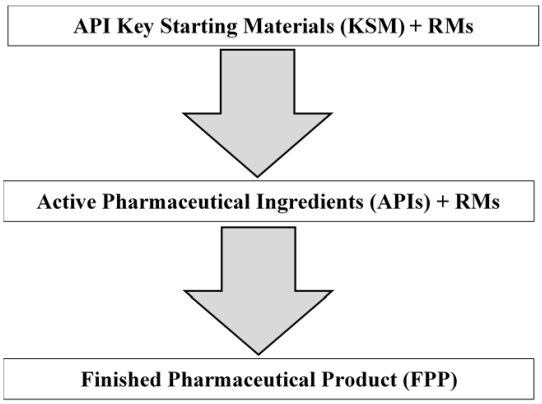

Chart-1 Stages of Pharmaceutical Product manufacturing

Product and process knowledge will be managed and updated from development through the commercial life of the product up to product discontinuation. Knowledge management will be done with a systematic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge will include, prior knowledge, pharmaceutical development studies, technology transfer, process validation studies over the product lifecycle, manufacturing experience, innovation, continual improvement, and change management activities. This will be executed by using tools like Quality Target product profile (QTPP), Critical material attributes (CMA), Critical quality attributes (CQA), Critical process parameters (CPP), Quality Risk Management (QRM), Design space, Control Strategy and Life cycle Management and Continuous improvement. Application of evaluation tools is listed below:

QTPP will relate to the quality of a Key starting material, drug substance and the drugs products that is necessary to deliver a desired therapeutic effect. QTPP is a predetermined summary of the characteristics of the drug product that will ideally be essential to ensure the desired quality with respect to safety and efficacy of the product. These predetermined QTPP evolve over time during drug development and may be modified to incorporate new knowledge, as is warranted by ongoing clinical studies such a dose effect and toxicology data.

Critical quality attributes considering physical, chemical, biological or microbiological properties or characteristics will be evaluated, that need to be controlled to ensure product quality. CQAs will be ensured within appropriate limits, range, and distribution to ensure the desired product quality. Physical, chemical, biological or microbiological properties and

characteristics of all input materials will be ensured within an appropriate limit, range, or distribution to ensure the desired quality of output material. All CPPs whose variability will have an impact on a critical quality attribute will be monitored or controlled to ensure the process produces the desired quality.

Quality risk management is a systematic process for the identification, assessment and control of risks to the quality of pharmaceutical products across the product lifecycle. Key objective of QRM in pharmaceutical development and manufacturing is to identify which material attributes and process parameters affect the drug product CQAs, that is, to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the CQAs are within the desired requirements. This will cover the evaluation of risk to the final consumer of product i.e., patient.

Design-space verification at the commercial scale manufacturing will be ensured to be within acceptable ranges for individual CPPs and CMAs at optimized during development scales. After the development of quality pharmaceutical product, ongoing assurance will be gained during routine manufacturing that the process remains in a state of control. A continual evaluation program depending upon the information and knowledge gained from the product and process development will be used. This information and interpretation will be the base for forming a method to control of the manufacturing process that results in product with the anticipated quality attributes.

Set of controls, derived from current product and process understanding that ensures process performance and product quality will be evaluated. This will include:

- Input material attributes (e.g., drug substance, excipients, container closure).
- Equipment operating conditions (process parameters).
- In-process controls.
- Finished product specifications.
- Controls for each unit operations.
- Methods and frequency of monitoring and control.

Regular periodic or rolling quality reviews of selected product, shall be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for starting materials, API and finished product to highlight any trends and to identify product and process improvements. Such reviews shall normally be conducted and documented, considering previous reviews, and shall include at least:

- Quality built in by design, development, and manufacture; and confirmed by testing.
- Risk-based approach to maximize economy of time, effort, and resources.
- Preservation of the best practices of current review system and organization.
- Best available science and wide consultation to ensure high quality reviews.
- Review of Starting materials, Solvents, Recovered Solvents, Raw materials, Packaging materials used for the product, including those from new sources.
- Review of critical in-process controls and finished product results and comparison with Process Validation.
- Review of all batches that failed to meet established specification and their investigation.
- Review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
- Review of all changes carried out to the processes or analytical methods.
- Review of the results of the stability monitoring programme and any adverse trends.
- Review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- Review of adequacy of any other previous product process or equipment corrective actions.
- Review of compliance with Regulatory GMP requirements.
- Qualification and calibration status of relevant equipment, instruments, computer systems and utilities including HVAC, water, compressed gases, etc.
- Qualification of facility, unidirectional flow and other add-ons to avoid chances of contamination and cross contamination.

The results of this review shall be statistically evaluated for process capabilities, and an assessment shall be made whether corrective and preventative action or any revalidation shall be undertaken. Reasons for such corrective actions shall be documented. Corrective and preventative actions shall be completed in a timely and effective manner.

Quality reviews shall be grouped by product manufacturing stage like Key Starting Material, Active Pharmaceutical Ingredient and Drug Product.

There shall be a technical agreement in place between the Quality Unit including Quality Assurance and Quality Control, which will define their respective responsibilities in producing the quality review. The final batch certification shall be reviewed. Regular quality reviews shall be conducted with the objective of verifying the consistency of the process. Such reviews will be conducted and documented and will include at least:

- Review of critical in-process controls and critical test results.
- Summary of all batches of starting and packaging materials received in a year and their approval status.
- Summary of the suppliers/manufacturers of the materials.
- 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, Assay, Microbial monitoring, and bioburden etc.
- Compilation of the Certificate of analysis (COA) results obtained from supplier/ manufacturer, if the batch is released based on supplier's COA.
- Summary of details related to any significant deviations observed such as rejection of vendor lots.
- Review of all batches that failed to meet established specifications.
- Review of all critical deviations or non-conformances and related investigations.
- Validation status of Reprocessing, Reworking and use of recovered solvents and mother liquor.
- Potential impurities (e.g., related substances, degradants, inorganic impurities, residual solvents, elemental impurities) in the drug substance.
- Impurities that can be potentially genotoxic (like nitrosamine impurities).
- Review of any changes carried out to the processes or analytical methods.

- Change in sampling techniques and Pharmacopoeial status of Reference Standards.
- Review of results of the stability monitoring program.
- Review of all quality-related returns, quarantine, complaints and recalls.
- Review of adequacy of corrective actions.
- The results of this review shall be evaluated, and an assessment made of whether corrective action or any revalidation shall be undertaken. Reasons for such corrective action shall be documented. It will be ensured that corrective actions are completed in a timely and effective manner.

This will provide rationale for:

- Risk and knowledge-based decision
- Systematic approaches process development
- Continuous Improvement
- Capable processes

2. CONCLUSION

Appropriate elements of manufacturing process controls for the manufacture of human and animal drug products, including Key Starting Material, Active Pharmaceutical Ingredients will be ensured.

This research will provide approaches, all manufacturers can use to manufacture quality product perpetually. Application of outcome of proposed research work will not only ensure the pharmaceutical manufacturing organizations to deliver a quality product throughout the life cycle of the product, but also ensure the patient or the consumer safety.

3. ACKNOWLEDGEMENT

We gratefully acknowledge the support of M/s Matwel Pharma Pvt Ltd., which facilitated this evaluation.

4. REFERENCES

[1]21CFR (2019). Part 210-211; Current Good Manufacturing Practice for Finished Pharmaceuticals, Title 21--Food And Drugs, Chapter I--Food And Drug Administration, Department Of Health And Human Services Subchapter C--Drugs: General, [Code of Federal Regulations, Title 21, Volume 4, Revised as of April 1, 2019].

[2]EU EudraLex (2018). EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines, Dec 2018.

[3] CDSCO Schedule M, Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products.

[4]WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fifty-fourth report, WHO Technical Report Series, no. 1025 (April 2020).

[5] TGA Australia, GMP guidance (Mar. 2019).

