



PHARMACEUTICAL QUALITY DURING PRODUCT LIFE CYCLE – A NEED OF HOLISTIC APPROACH

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ABSTRACT

The famous quote- “Quality is not inspected rather it is inbuilt”, suits perfectly in case of pharmaceutical business. Quality is the most vital aspect of medicines and hence pharmaceutical business. Once the pharmaceutical product is in market, there is no scope to rectify the defects at the users end; hence it becomes imperative to evaluate the quality of pharmaceutical product, during its life cycle. A pharmaceutical quality professional has to evaluate the product starting from its development stage up to delivered to patients. The pharmaceutical products are manufactured in batches (batch size ranging up to billion) and if defect is prevalent in one unit of product there is probability that it would affect the billions of consumers. Ideally, the pharmaceutical products should be designed properly, monitored during production process and care should be taken during distribution to protect the quality attributes to undergo any unforeseen deterioration. Quality by design (QbD) and further operation under aegis of Quality Risk Management (QRM) are the safest techniques in pharmaceutical world. Standard Operating Procedures (SOP) and adequate training to professions across the product life cycle is the key to deliver quality product. To ensure quality products consistently, the stake holders of pharmaceutical business should possess a holistic approach during all three stages of pharmaceutical business – Product Development, Good Manufacturing and Distribution in market.

KEYWORDS: Pharmaceutical Quality System, Product Quality Life Cycle, CGMP, ICH, USFDA, QbD.

INTRODUCTION

The most important aspects of pharmaceutical products are characterized by the elements: Safety, Identity, Strength, Quality and Purity. For a safe and secured medicinal product to arrive at the consumer and patient, distribution practice in addition to manufacturing process plays an important role in the quality system. Thus compliance to Good Manufacturing Practices (GMP) as well as to the Good Distribution Practice (GDP) guidelines shall strive to meet the need of all stakeholder of pharmaceutical business.

The pharmaceutical manufacturing involves quality at mainly following steps: raw material quality control, in-process quality assurance and product release by quality assurance department. The quality aspect during product distribution involves ensuring temperature controlled storage and shipment facilities. During manufacturing process the quality conformance of product is the main objective of manufacturing personnel. In order to reinforce the quality standards dedicated departments for quality control (QC) and quality assurance (QA) are operational. Each pharmaceutical manufacturing unit prepares standard operating procedures (SOPs) on the basis of principles laid down in current Good Manufacturing Practices (CGMP). The quality function evaluates and reviews the documentary evidences to

confirm the adherence of quality system within the organization. During inspections by regulatory body or customers, the quality function takes ownership to provide confidence to all stakeholders that pharmaceutical products manufactured bear the specified quality standards. Once the pharmaceutical products are released by Quality Assurance (QA), the ownership of distribution lies in hands of Supply Chain Managers. Unlike manufacturing units, the distribution centers have very few dedicated quality professional to take ownership of maintaining quality of products. The quantification of quality attributes during distribution is somewhat under less focus by manufacturers in Asian pacific countries.



Figure -1 Standard characteristics of pharmaceutical product.

The quality system, in addition to other traits, includes the requirement that the right product is delivered to the right customer well within assigned shelf life or expiry period of product. Bearing the vision and mission towards binding specification, as well as the responsibility towards patients, the pharmaceutical company must form a robust system to qualify - Internal resources and External Contractors.

STAKEHOLDERS OF PHARMACEUTICAL QUALITY

The patient's satisfaction data is an important indicator of quality in addition to observations of regulatory bodies and other interested parties. The cost of poor quality has got a gross impact on each stakeholder of pharmaceutical operation. The stakeholders and their impact can be summarized as under:

Stake Holders	Impact Element
Consumers or Patients	Lack of effect, Reduced efficacy Adverse drug reactions, Fetal course, Higher Cost
Corporate Investors	Loss of goodwill, Business Loss,
Manufacturers	Warning letters from regulatory body, Market complaints Product recalls, Challenges of investigations, Additional remedial and corrective-preventive actions Threat to employment of manufacturing personnel
Transport and Logistic Business	Business Loss, Credibility, Legal Action for quality defects caused during shipping
Wholesalers, Distributors & Retailers	Threat to employment Cost implications, Business loss
Government	Public pressure, Loss of credibility
Medical Practitioners	Difficulty in treatment, Clinical complaints, Credibility
Regulatory Bodies	Doubts created over sampling and auditing procedure, Charges of corruption, Multiple additional work burden.

STAGES OF PHARMACEUTICAL PRODUCT QUALITY LIFE CYCLE

The global pharmaceutical manufacturers faced worrisome situations recently, when United States Food and Drug Administration (US-FDA) issued warning letters to numerous companies and imposed ban of business. The detailed investigations of each case against such manufacturing plants were carried out to uncover

the root cause of their quality issues. Never the less the pharmaceutical giants who faced the undesired situations of warning letter or import ban were trapped in mid way and they had limited scope to benchmark their process with holistic approach involving the product life cycle. Through this research study there is an attempt made to provide an overview of components involved in product life cycle for maintaining the quality benchmark.

The pharmaceutical products have different facets during product life cycle eg basic evaluation, design and development, manufacturing and distribution of products into the market.



Figure -2, Pharmaceutical products quality development and improvement cycle

The cyclic process may be assumed to start from overall evaluation. A pharmaceutical manufacturer is expected to have ongoing program to collect and analyze product and process data that relate to product quality must be established. The data throughout product life cycle should include critical process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and evaluated by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

The quality aspects of pharmaceutical products during various phases of product life cycle are as under:

1. Pharmacological evaluation of molecular action

Scientist and innovators are continuously engaged to discover the correct molecule for most effective treatment of any disease. The quality of a drug product largely depends up on the correctness of innovation of molecule. If the molecule discovered has major side effects, the product life span shall be small and within few years the product with such molecules shall be out pharmaceutical market.

2. Product design development

The pharmaceutical scientists and pharmaceuticals specialists design the product dosage forms namely as: tablet, capsules, dry syrups, suspensions, injectable, transdermal products, ointment, inhaler etc. The product design depends up on the studies of drug actions on target patients.

3. Bioequivalence studies, projected actions and vivo/vitro evaluation

The bioequivalence studies provide the evidences of efficacy of product by creating a benchmark of dissolution pattern during drug administration by patients.

4. Stability Studies and shelf life fixation

A comprehensive Stability Study is carried out with small scale batches and the data helps to develop the shelf life fixation of pharmaceutical product. First chapter of Quality section of guidance paper Q1: ICH issued by International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (known as ICH). There is provision to carry out long term and accelerated condition stability studies. Based on studies the inference is drawn to assign the product storage condition on product labels.

5. Analytical method development

In order to define and determine the quality attributes the analytical method validations are carried out to exactly ascertain the amount of drugs and impurities in line with quality segment of guidance of International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

6. Compatibility studies of container closure system

Compatibility studies between product containers and closure systems are evaluated by various experiments followed by charging the samples in test containers for long term and accelerated condition of stability studies. Container permeability, photo and/or thermal resistant requirements of containers are finalized on the basis of drug design and characteristics.

7. Technology transfer to manufacturing sites

The formulation, research and development department transfers the technology package comprising of all technical aspects. The gap of perception between technology donor and acceptors shall lead to serious quality issues throughout product life cycle, hence organizations tend to follow a well structured technology transfer programme.

8. Production planning

Appropriate equipment train are planned to carry out production process and automated packaging line are arranged in parallel to other resource planning.

9. Procurement of starting material (Raw Material and Packaging Components)

The starting materials for production consists of active pharmaceutical ingredients (API), excipients and packaging materials.

10. Qualification and Validation of manufacturing facility, equipment and process

The consistency of product quality largely depends upon the execution of facility and equipment qualification governed by approved protocol, which contains critical process parameters and corresponding product quality attributes. The qualified facility is used for manufacturing of pharmaceutical products, through a validated process. The process validation consists of challenging the critical process parameters against pre-determined acceptance criteria. Qualification & Validation reports shall contain the history of all deviations and their remedial actions, with a risk mitigation recommendations.

11. Batch processing records (BPR)

The sequence of validated manufacturing process is laid down in batch records with a provision of online entries of evidences of critical processes. The batches are manufactured with help of instructions laid down in batch processing records (BPR) and Standard Operating Procedures (SOP). The evidence of each activities performed are archived for future references and investigations of market complaints and batch failures reported after release of batch from manufacturing unit.

12. Handling of product through effective training of manufacturing personnel

There is a famous quote – “Quality is not inspected, it is inbuilt”. Thus there should be appropriate focus building quality products by capable professionals, which can be only through effective training. The pharmaceutical professionals do develop and build up the quality resource and system for delivering quality products. The qualification and training or good combination of the two shall ensure the flawless manufacturing of product and quality control.

13. Product Storage and distribution facility

The quality system (QS) of pharmaceutical distributors and wholesalers should be capable to ensure that

- only medicinal products with appropriate regulatory approval are distributed,
- medicinal products storage conditions are under constant supervision,
- the possibility of medicinal products contamination or cross contamination is minimized during transportation
- all medicinal products are kept in a proper, safe place.

14. Retail outlet facility and sales network

The retailers should be qualified pharmacist who shall know the technical requirement of product handling and

how the medicinal products are adequately handled in the store. The retailers and pharmacy personnel should be knowledgeable enough to describe the quality instructions and medicinal guidelines.

FACTORS AFFECTING THE QUALITY OF PRODUCT

Each pharmaceutical regulator has started significant emphasis on quality risk management (QRM). The risk to product quality may be due to inherent as well as external. In order to achieve and maintain quality throughout the pharmaceutical product life cycle, there are internal as well as external factors:

The internal factors include:

- Manufacturing Facility infrastructure
- Laboratory infrastructure
- Manufacturing Instructions
- Standard Operating Procedure
- Skilled workforce

The external factors include:

- Climatic conditions like temperature and humidity
- Investors aspiration and vision
- Availability of Latest Technology
- Suppliers of Starting Material (Raw Materials and Packing Materials)
- Availability of competent contractors
- Regulatory approvals

The QRM exercise is the exhaustive listing of elements which has potential to hazard the quality of products. QRM summarily consists of (a) Risk identification (b) Risk evaluation and (c) Risk mitigation. The risk management is described in details in guidance Q9: ICH. More is the attention on risk management during product life cycle, lesser is the potential of impact on product quality during.

CONCLUSION

To deliver a quality product to consumers, there is a requirement of a high level of association between the partners and collaborating agencies. In addition, the pharmaceutical company should have a manageable number of outsourced contractors with whom strategic association has been established and their performances should be periodically evaluated.

- ✓ The qualification of facility, equipment, utilities and validation of manufacturing cum analytical processes shall help to accomplish the quality goal on consistent basis. The qualification of the potential external collaborating agencies like starting material supplier, manpower suppliers, technology suppliers, logistics and transporters shall help to avoid external quality risk.
- ✓ Each manufacturer should evaluate whether it has gained sufficient understanding about product life cycle to provide a high degree of assurance in its manufacturing process to justify distribution of the product. Responsive Product Lifecycle approach

provides the capability to both manage and centralize product information, helping pharmaceutical companies by addressing some of the most essential needs including fast-moving market, lowering overall operating and production costs and appreciating quality standards such as Quality by Design (QbD).

- ✓ There is need to follow the quality system during product development, manufacturing and distribution as major contributors to product quality during its life cycle. Patient complaints data should be considered as a key performance indicator (KPI) to assess the overall quality of product and system throughout its life cycle.

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