An Overview of Established Practices and Parameters to Ensure Quality of a Pharmaceutical Product

A project submitted
by
Shimu Akter
ID: 12346007
Session: Summer 2012
to
The Department of Pharmacy
in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Dhaka, Bangladesh

October 2016

Certification Statement

This is to certify that this project titled “An Overview of Established Practices and Elements to Ensure Quality of a Pharmaceutical Product” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University is a review study and constitutes my own work under the supervision of Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, BRAC University. Appropriate credit has been given where I have used the language, ideas or writings of another and changes have been made as much as possible keeping in mind that the technical terms and requirements given in the guidelines cannot be entirely paraphrased.

Signed,

_____

Countersigned by the supervisor,

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Dedicated to my Parents

Acknowledgement

First of all, I would like to express my gratitude to Almighty, who has helped me to continue my study. This research could not also have been completed without the support of many people who are gratefully acknowledged here.

This project has been completed with the help of my supervisor Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, BRAC University. Her constant supervision and encouragement has made it possible to complete my work. Her linguistic and professional skills helped me to build up the capacity of expressing my thoughts in an ordered manner. She continually and persuasively conveyed a spirit of interest in regard to research and an excitement in regard to learning. I am obliged to her as she has given her valuable time to enrich my work.

I would also like to thank Tanisha Tabassum Sayka Khan for her continuous guidance throughout my work.

Finally, I would like to specially thank my parents for their constant invaluable support and prayers which have enabled me to dream big, and pursue something which can only be attained after passing hurdles.

Abstract

The quality of a pharmaceutical product is one of the most challenging considerations of the pharmaceutical industry because it is directly related to the patient health and safety. Every pharmaceutical product should be manufactured by a licensed pharmaceutical manufacturer according to the guidelines, which should be stringently monitored by the licensed pharmacist, in order to attain the target quality product. The guidelines that are followed in the pharmaceutical industry are several, such as the ICH guideline, WHO guideline, FDA guideline, etc.

A systematic approach needs to be designed and developed with the ‘end’ in mind, in order to ensure quality where the product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches. The impact of starting raw materials and process parameters on product quality must surely be well understood, with an emphasis on product and process understanding and process control. All processes involved must be continually monitored, evaluated, documented and updated in line with the ‘quality by design’ approach to allow for consistent quality throughout product life cycle.

The aim of the study was to highlight the various approaches and steps involved, and other relevant considerations that a pharmaceutical company must undertake, whether manufactured in-house or by outsourcing, in order to ensure product quality through ‘quality by design’ approach.

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Abbreviations

API- Active Pharmaceutical Ingredient

FPP- Finished Pharmaceutical Product

GMP- Good Manufacturing Practices

ICH- International Conference on Harmonization

MA- Marketing Authorization

DRA- Drug Regulatory Authority

IQ- Installation qualification

OQ- Operational qualification

PQ- Performance qualification

FDA- Food and Drug Administration

INN- International nonproprietary name

NMRA- National Medicines Regulatory Authorities

GHTF-Global Harmonization Task Force

CAPA- Corrective action and preventive action

QbD- Quality by design

CMA-Critical material attributes

CPP- Critical process attributes

CQA- Critical quality attributes

GCP- Good clinical practice

GLP- Good laboratory practice

Chapter 1

1.1 Introduction

According to FDA, ‘a pharmaceutical product is any substance or combination of substances designed for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or may be used to modify the structure or any function of the body’. It is also referred to as to as a medicine, pharmaceutical, pharmaceutical preparation, pharmaceutical product, medicinal product, medication, medicament, or simply a drug (FDA U.S. Food & Drug administration). The quality, safety, and efficacy of each and every pharmaceutical product is one of the most challenging considerations of the pharmaceutical industry since it is directly related to the patient health and safety. Every pharmaceutical product should be properly and effectively designed, developed and manufactured by a licensed pharmaceutical manufacturer according to the guidelines, which should be implemented and monitored by the licensed pharmacist, whether they are manufactured in-house or outsourced. The purity, identity, strength and all other quality characteristics of the specific pharmaceutical product must be established according to the design criteria to assure the essential levels of safety and effectiveness ("Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations," 2006).

The quality of a pharmaceutical product is an extremely important issue as this is directly related to health and this can only be attained by proper design, as well as effective implementation of administrative and technical efforts of the pharmaceutical industry in compliance to the guidelines ("Quality assurance of pharmaceuticals"). The use of poor-quality, ineffective, or even harmful medicines can result in therapeutic failure, resistance to drugs, exacerbation of disease, and even death ("Pharmaceutical legislation and regulation "). Product quality is determined by the design, development, and specifications applied to the product throughout its development and manufacture ("International conference on harmonization of technical requirements for registration of pharmaceuticals for human use ", 1999). However, if it fails to meet acceptable standards of quality, efficacy and safety, health service may be compromised. It is essential to recognize that the use of pharmaceutical products as health indicators is linked with the successful development of a country.

Quality is defined as the degree to which a set of inherent critical attributes (identity, strength, and purity) of a product and system or process parameters fulfills its requirements ("International

conference on harmonization of technical requirements for registration of pharmaceuticals for human use ", 1999). Since quality will vary from product to product, it needs to be defined in terms of its identification, physical and chemical attributes, assay, efficacy, dissolution and drug release, content uniformity, degradation products, toxicity, microbial limits, shelf life, etc. According to FDA, 'the pharmaceutical quality system assures that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded'.

'Quality assurance' is a concept that widely covers all parameters influencing the quality of the product. It is a complete aggregate of the arrangements designed with the objective of ensuring that pharmaceutical products have attained the required quality for their intended use. The eventual attainment of the proper quality of the product, appropriate for their intended use, is the responsibility of the pharmaceutical manufacturers (Quality assurance of pharmaceuticals : a compendium of guidelines and related materials, 2006). Quality assurance can thus be described as the integration of quality control (QC), Good Manufacturing Practice (GMP) and other factors, such as product design and development (Quality assurance of pharmaceuticals : a compendium of guidelines and related materials, 2006), that covers all parameters or variables individually and collectively affecting the quality of a product. These can be divided into four major areas: management, manufacturing, quality control, and documentation of the overall process (Assuring the quality of medicines, 2010).

According to the Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and related materials (2006), a well-defined system of quality assurance ensures that:

(a) Pharmaceutical products are designed and developed in a manner that considers the requirements of GMP, GLP, GCP, etc.

(b) Operations involving production and control are clearly documented and GMP requirements are adopted;

(c) Job descriptions are clearly written with the specified managerial responsibilities;

(d) The manufacture and supply of the product, including the use of the correct starting materials, packaging materials, etc., are correctly arranged and done;

(e) All essential controls on starting materials, intermediate products, and bulk products as well as on calibrations, in-process controls and validations are carried out;

(f) The finished product is accurately processed and checked, conforming to the specified procedures;

(g) The final products have to be certified by authorized persons that they have been produced and controlled according to the regulations before they can be marketed;

(h) Approved arrangements must be available to confirm that the pharmaceutical products are properly stored by the manufacturer, distributed, and subsequently handled to ensure that quality is maintained throughout their shelf-life;

(i) A system exists for self-inspection and quality audit that frequently evaluates the effectiveness and applicability of the quality assurance system;

(j) All deviations are reported, investigated and recorded exists;

(k) A process for approving any change that may have an impact on product quality; and

(l) Regular monitoring and assessment of the quality of pharmaceutical products must be done to confirm the consistency of the process as well to ensure its continuous improvement.

Pharmaceutical quality refers to the product being free of contamination and reproducibly delivers the therapeutic benefit that is promised in the label to the consumer. Evaluation of the quality of a pharmaceutical product can be done either by in vivo or in vitro performance tests. Quality by design (QbD), a relatively new and systematic approach, ensures that in vitro product performance will provide assurance of its in vivo product performance. In other words, QbD relates to product performance.

1.2 Rationale of the study

i. The countless guidelines and documents available by different regulatory authorities regarding how to manufacture a ‘quality’ pharmaceutical product can sometimes get very overwhelming for researchers as well as manufacturers.
ii. This plethora of information led to this study which will provide the interested researcher, in one document, a complete guide of all the factors and guidelines on how to achieve and maintain the ‘quality’ of a pharmaceutical product.

1.3 Methodology

A concerted effort was taken to collect information from different guidelines and relevant journals focusing on the topic. After collection, the documents were reviewed and information compiled for the benefit of everyone involved in the drug industry. The study has been divided

into chapters based on the main areas that are required to be stringently followed according to GMP and also monitored to ensure a quality pharmaceutical product

1.4 Study design

The figure below (Figure 1) is a flow chart showing the design of the study

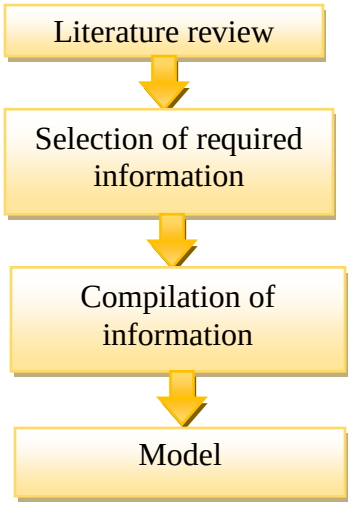


Figure 1: Flow chart of the study design

Chapter 2. Quality Management of Pharmaceutical Products

In a pharmaceutical industry, it is absolutely critical that management supports an independent group that makes final decisions on documents, quality, and product release. Quality management for a pharmaceutical industry is simply defined as the management of the functions of quality policy. The basic components of quality management can be outlined as:

i. A suitable framework of "quality system", including the organizational structure, procedures, processes and resources.
ii. Systematic actions necessary to ensure that the product (or service) will satisfy the postulated requirements for quality.

2.1 Pharmaceutical quality management system

In order to assist the pharmaceutical manufacturer with an effective quality management system, several guidelines were compiled. However, the ICH Q10 model was designed and made available as a useful and convenient guideline that can be implemented throughout the different stages of a product life cycle. The foundation of the ICH Q10 includes the regional GMP requirements, the ICH guidance "Q7 GOOD Manufacturing Practice for active pharmaceutical ingredients," and the ISO quality management system guidelines. The model is comprehensive and is based on international organization for standardization (ISO) quality concepts which includes the quality system elements and management responsibilities to ensure that a quality pharmaceutical product is achieved.

Most of the content of ICH Q10 is applicable for the manufacturing site which is specified by regional GMP requirements. This model strengthens all associations between pharmaceutical development and manufacturing activities, as it facilitates continuous improvement across the entire product life cycle (Guidance for Industry Q10 Pharmaceutical, 2009). However, for the successful implementation of such a model, several parameters or technical activities (section 2.2) need to be implemented and continuously improved. These parameters, mentioned below, are required to be implemented during the different stages of the product life cycle. Apart from these, there are also different elements (section 2.3) of a pharmaceutical quality system that need to be considered (Guidance for Industry Q10 Pharmaceutical, 2009).

2.2 Technical Activities

The following are four technical activities which are necessary to be implemented and controlled continuously through the product lifecycle, whether new or existing.

- Pharmaceutical development

The goal of the various activities of pharmaceutical development is to design and formulate a product, and develop its manufacturing process and analytical method in order to consistently deliver the intended performance and meet the needs of patients, and requirements of the healthcare professionals and regulatory authorities. The exploratory and clinical development studies are results of pharmaceutical development. This part of the lifecycle comprises of the following components:

  - Drug substance development
  - Formulation development (including container and closure system)
  - Manufacturing process development and scale- up
  - Analytical method development
  - Delivery system development
  - Manufacture of investigational products (if any)

- Technology transfer

Technology transfer of both product and process must be passed over between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge ultimately forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement. The components of this part of activity are the following:

  - Transfers within or between manufacturing and testing sites for marketed products
  - New product transfer during development through manufacturing

- Commercial manufacturing

The objectives of pharmaceutical manufacturing are to achieve product realization, establish and maintain control, and to allow continual improvement so that a target quality product reached the patient. The quality system should be effective in ensuring that the required product quality is routinely achieved, suitable process performance is attained, the set of controls are appropriate, improvement possibilities are identified and assessed, and information is regularly documented.

The following components need to be looked into and monitored throughout the lifecycle of the product:

- Purchase and control of materials
- Provision of facilities, utilities and equipment
- Production (including packaging and labeling)
- Quality control and assurance
- Storage
- Release
- Distribution (excluding wholesaler activities)

- Product discontinuation

Product discontinuation occurs when the product either has not met the specifications or there is some reason for downsizing the product, e.g., negative sales, obsolete product, etc. This is an area where the handling of the terminal stage of the product lifecycle (once confirmed) must be done effectively. Whenever a product is discontinued, there must be a predefined approach to ensure the following activities are carried out in accordance to regulatory requirements:

- Retention of documentation
- Sample retention
- Continued product assessment and reporting

2.3 Systems throughout Product Lifecycle

There are several requirements that can be grouped into the following four systems, and which need to be implemented in a manner relevant to each stage of the product lifecycle while recognizing the differences among the stages as well as the different objectives of each stage:

- Process performance and product quality monitoring system (Table 1)
- Corrective action and preventive action (CAPA) system (Table 2)
- Change management system (Table 3)
- Management review of process performance and product quality System (Table 4)

The following requirements have been taken into account into the four above systems:

- The design, organization, and documentation of the pharmaceutical quality system should be well structured and explicit to be easily implemented.

- When developing a new pharmaceutical quality system or modifying an existing one, the size and complexity of the company's activities must be taken into consideration.
- The quality system should include appropriate processes, resources, and responsibilities to maintain assurance of the quality of outsourced activities and purchased materials.
- All management responsibilities must be explicitly described.
- The system should include process performance and product quality monitoring, corrective and preventive action, change management, and management review.
- Performance indicators must be identified and used to monitor the effectiveness of processes within pharmaceutical quality system.

According to the model, the companies are encouraged to evaluate opportunities for new approaches to improve product quality throughout its lifecycle.

Table 1: Process performance and product quality monitoring system throughout the product lifecycle

Development of the Pharmaceutical Product	Transfer of Technology	Commercial Manufacturing	Discontinuation of Product
Knowledge generated from process and product, and monitoring conducted for process and product during development can be used to develop a control strategy for manufacturing.	A preliminary indication of process performance and the successful integration into manufacturing is possible through monitoring of scale-up activities. Control strategy can be also developed from the knowledge collected during transfer and scale-up activities.	Assurance of the performance within a state of control and identification of improvement areas are possible through the development of a well-defined system for process performance and monitoring of product quality.	Stability testing of the product should be done at the end of manufacturing process. Post market analysis of the product parameters should continue to be carried out according to regional regulations.

Table 2: Corrective action and preventive action system throughout the product lifecycle

Development of the Pharmaceutical Product	Transfer of Technology	Commercial Manufacturing	Discontinuation of Product
Variability in product or process is explored. Corrective actions and preventive actions (CAPA) are inserted into the iterative design and development process.	Feedback and continual improvement can be achieved by use of CAPA.	Implementation of CAPA and evaluation of its effectiveness	CAPA should continue after the product is discontinued. Considerations on the impact on product remaining on the market should be taken, as well as other products that might be affected.

Table 3: Change management system throughout the product lifecycle

Development of the Pharmaceutical Product	Transfer of Technology	Commercial Manufacturing	Discontinuation of Product
Any change in the development process should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	Management and documentation of adjustments made to the process during technology transfer activities should be provided by the change management system.	A formal change management system should be in place for commercial manufacturing. The quality unit should be able to provide assurance of appropriate science and risk-based assessments.	An appropriate change management system should be undergone by any changes after product discontinuation.

Table 4: Management review of process performance and product quality throughout the product lifecycle

Development of the Pharmaceutical Product	Transfer of Technology	Commercial Manufacturing	Discontinuation of Product
Different features of management review can be performed to ensure adequacy of the product and process design.	To establish that the developed product and process can be manufactured on a commercial scale, aspects of management review should be performed.	Management review should be a structured system and be able to support continual improvement.	Product stability and product quality complaints should be reviewed by the management.

Chapter 3. Manufacturing of Pharmaceutical Products

The pharmaceutical products need to be manufactured accordingly to the approved guidelines, and continuously controlled to ensure that all standards of quality meet their intended use, according to the requirements of the marketing authorization. Each product must first go through the product (or pharmaceutical) development phase, also referred to as PD. This involves the following phases:

- Drug substance development. The active ingredient may be produced in the plant or may be purchased from an authentic supplier.
- Formulation development
- Manufacturing process development. This is done on a pilot- or small-scale. Once the process is developed as well as the analytical studies, this process is done on a large scale (commercial manufacturing) by means of technology transfer.
- Analytical study. All necessary analytical studies required for the quality assurance according to its label is developed at this stage.

Good Manufacturing Practice (GMP) is that part of quality assurance and arrangement that assures this requirement. GMP requirements are defined so that the following criteria are followed:

a) Manufacturing processes must be clearly defined and intermittently reviewed for any possible risks in the light of scientific knowledge and experience. They must be capable of manufacturing pharmaceutical products of the required quality that will consistently comply with their specifications;

b) Qualification and validation are routinely performed;

c) Instructions and methods are written in explicit language, specifically applicable to the facilities provided;

d) All necessary resources are provided, including:

- Sufficient and appropriately qualified, competent and trained personnel,
- Adequate layouts and space,
- Suitable equipment and services,
- Approved procedures and instructions,

- Appropriate materials, containers and labels,
- Suitable storage and transport,
- Adequate personnel, laboratories and equipment

e) Documentations are made available throughout the manufacture, showing all the steps required by the defined procedures have been taken to ensure the quality of the product. Any valid deviation, if observed, are fully recorded and further investigated with the aim of finding the cause. Corrective and preventive actions will then need to be appropriately taken.

f) Records covering the manufacture and distribution of the product are maintained, which will help to trace the complete history of a batch. These are retained in an explicit and accessible form.

g) The proper storage and distribution of the products must be done with the objective of minimizing any risk to their quality.

h) A system must be available to recall any batch of product from any part of the chain if required.

i) There must be a system where complaints about marketed products may be examined, causes of any reported defect investigated and appropriate measures then taken to prevent recurrence. (Quality assurance of pharmaceuticals : a compendium of guidelines and related materials, 2006).

The aim of GMP is primarily to diminish the inherent risks that may occur in any pharmaceutical production, these are generally of two types:

i. cross contamination
ii. mix-ups (Quality assurance of pharmaceuticals : a compendium of guidelines and related materials, 2006).

3.1 Guidelines for Manufacture of Pharmaceutical Products:

According to the current good manufacturing practice (cGMP), the guidelines for the manufacturing of the pharmaceutical products up to its storage in the warehouse include several factors, all of which are listed and described below:

i. Factors involved in the production of the product. These can be again subdivided as follows:
    - Personnel
    - Premises
    - Equipment
    - Sanitation and hygiene
    - Production:
        - Weighing and Dispensing
        - Dry Materials and Products
        - Mixing and Granulation
        - Compression
        - Coating
        - Hard Capsule filling
        - Liquids, Creams and Ointments
        - Process Validation
        - Batch and Lot Numbering System
        - Contamination

ii. Quality control. A detailed description of quality control will be covered in Chapter 2. Following is a list of what is generally required in a quality control strategy:
    - Control Parameters
        - Quality control test for raw materials
        - In process control
        - Quality control test for packaging materials
        - Quality control of finished products
        - Qualification and Validation
        - Environmental Control
        - Reprocessing
    - Analytical study
        - Stability study
        - Analytical method development and validation

iii. Packaging:
    - Coding of Components
    - Labeling
    - Line Clearance
    - In-Process Control
    - Operating Practices
    - Completion of the Packaging Operation

iv. Finished product quarantine and delivery to warehouse

v. Storage

vi. Documentation. A detailed description on documentation will be covered in Chapter 3. Every item needs to be documented in details and data integrity also needs to be maintained at all times, such as:
    - Raw Material Specifications
    - Production Documents
    - Test Method record
    - Quality Control Documents
    - Packaging Material Specifications
    - Batch Packaging Record
    - Warehouse and Distribution Documents
    - Documents for Maintenance, Cleaning and Monitoring of Manufacturing Areas and Equipment
    - Documents for Specific Equipment
    - Procedure and Record of Self Inspection ("WHO good practices for pharmaceutical quality control laboratories," 2009).

3.2 Factors Involved in the Manufacture of the Product

The following section gives a brief description of the different factors that are involved or required in the commercial manufacture of the pharmaceutical products.

3.2.1 Personnel

The development and continuous maintenance of an effective system of quality assurance to ensure the correct manufacture and control of pharmaceutical products completely depend upon people. Sufficient number of personnel having appropriate knowledge, competent skills and capabilities relevant to their assigned functions need to be present at all levels. It is extremely necessary that all personnel have a good mental and physical health to carry out their duties.

The organizational structure of the company need to be well defined, with the departments of production and quality assurance headed by individual manager. Each will need to be given full authority and facilities necessary to carry out their duties effectively. The quality assurance manager shall clearly define the method of delegating responsibilities in his/her absence. All employees engaged in the manufacturing activities will need to be trained in accordance with the principles of Current Good Manufacturing Practice ("Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001).

3.2.2 Premises

The premises, where the manufacturing pharmaceutical products will be carried out, need to be of suitable size, design, construction and location in order to execute proper operation, cleaning and maintenance of all equipment. To avoid contamination, cross contamination or confusion, adequate individual working area is an essential characteristic.

Some requirements of premises are given below:

- Protection against contamination from the environment.
- Protection against weather, flood, ground seepage and the access and harboring of any insects or animals. This is achieved by proper construction and maintenance.

The layout of every room, entrance, passage, and space need to provide for easy movement of materials and personnel with lowest possible traffic for operations to be carried out in the defined areas ("Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001).

3.2.3 Equipment

Equipment that are used for the manufacture of the pharmaceutical product need to be of adequate size, appropriate design and construction. They must also be suitably located in order to

effectively ensure product quality and process reproducibility, and to also facilitate its cleaning and maintenance. The design and construction of equipment must fulfill the following requirements:

- Equipment must have no leaking valves, lubricant drips, inappropriate repairs, etc. that could possibly adversely affect the product.
- Materials, such as lubricants or coolants, that are required for specific operations must not come in contact with any in-process materials that could possibly change the strength, safety, identity, quality, or purity of raw material, intermediate, bulk or the finished product beyond the established limits.
- Equipment must be easily and regularly cleanable.
- All equipment designated for use with flammable substances or chemicals must be explosion proof.
- Equipment must be installed suitably and located to eliminate cross contamination.

Regular maintenance checks of the equipment must be done at appropriate intervals to prevent malfunctions or contaminations that can alter the strength, safety, identity, quality, or purity of the product beyond established limits ("Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001).

3.2.4 Sanitation and Hygiene

High level of sanitation must be practiced at every level during the manufacturing of the products. The sanitation and hygiene program must include anything that may be a source of contamination to the product, such as all personnel, premises, equipment and apparatus, production materials and containers, etc. The possible sources of contamination should be identified and eliminated through a well-defined comprehensive schedule of sanitation and hygiene. All the sanitation and the hygiene procedures need to be validated and assessed at regular intervals to ensure that the program has effectively met all the requirements. The following need to be maintained and monitored at all times:

- All personnel, before and during employment, need to undergo health examinations. Operators who are engaged in visual inspections of the product need to have regular eye examination.

- Personal hygiene need to be maintained by those involved with manufacturing ("Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001).

3.2.5 Production Process

The first few manufacturing process for a new drug is done by the PD personnel. Once the method is reproducible, this is handed over to the production or commercial manufacturing personnel. The drug products need to be of consistent quality, conferring to their specifications. This can only be achieved if their production is done according to well-defined procedure, mentioned below.

- As mentioned earlier, equipment must be well sited (so as not to interfere with other operations), technically suitable, easy to maintain and clean. The design, position and operation of equipment must ensure that there is no contamination from any type of foreign materials such as lubricants, rust, abraded particles or foreign ingredients.
- Manufacturing facilities must be designed in such a manner that will ensure there will be no cross-contamination.
- The organization must use manufacturing processes that are validated. All established processes, materials or products, procedures, activities, systems, equipment or mechanism used in the manufacture or control procedures must be validated employing a retrospective approach. Validation of all production procedures shall be conducted in accordance with previously defined procedures and a record of the results also maintained.
- Documentation must be available showing the suitability of all materials, as well as the performance and reliability of equipment and systems and the competency of personnel.
- Any form of contamination in a drug product will not be accepted. The air, water, personnel and all surfaces that come in contact with the product during the manufacturing process are all known potential sources of contamination. Regular monitoring of the manufacturing environments must be stringently done to ensure the detection of any risk of contamination and corrective actions also need to be taken.

- Each batch of intermediate, finished or bulk product must be given a specific batch number for identification.
- Approved materials may be allowed into the dispensary area.
- The design, maintenance as well as use of equipment and the premises require special attention in order to overcome problems of cross contamination and dust control.
- An effective dust control system must be installed in every equipment.
- Filtered air of suitable quality must be supplied to the coating pans for drying purpose.
- Empty capsule shells that are used for production purpose must be stored under suitable condition to prevent drying and brittleness or other effects of moisture ("Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001).

3.2.6 Packaging

The essential function of this step of the operation is to manage the bulk product by subdividing them. Packaging must be stringently performed, designed to protect the identity, quality and integrity of the final package. The following three parameters must be considered.

- The packaging operations must be done according to the SOP (standard operating procedure). Details must be recorded on the batch packaging record.
- Before the start of the packaging operations, it is essential to ensure that the work area and equipment are clean and free from any product or product residues that are not required for the operation.
- Finished bulk product and packaging components must also be checked and verified against the master packaging procedure or a specific packaging order to avoid any mistake (Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

3.2.7 Finished Product Quarantine and Transfer to Warehouse

Strict isolation of the finished product is the last point of control before the product enters the warehouse and is available for market distribution. The product and its packaging records must meet all specified requirements before the products are released to the warehouse

- All written procedures must explicitly mention the transfer of the finished product into the quarantined area, storage while waiting approval, requirements that must be met for approval and subsequent transfer to the finished goods warehouse.
- If the finished product is held for any reason by the quality control unit, whether it be the entire packaged batch or a lot, they must be held in the finished goods quarantine (Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

3.2.8 Storage

- All materials need to be stored in a manner to ensure there is no risk of mix-up or contamination. Regular inspection is required and accordingly materials should be stored in that manner.
- The materials need to be stored under suitable and designated environmental condition. In case of any special storage conditions, monitoring must be strictly maintained.
- Outdoor storage is done only for materials kept in secured containers such as metal drums and where the condition of the materials will not be affected (WHO good practices for pharmaceutical quality control laboratories, 2009).

3.3 Contract Manufacturing

The manufacture of pharmaceutical product involves different intricate processes of operation that are generally carried out in the pharmaceutical plant. However, the pharmaceutical owner may also engage an outside party/parties to complete the entire manufacturing process, or one or more several operations, under contract. The outside entities performing manufacturing operations for the product owner are called contracted facilities. Following are some of the manufacturing operations that the contracted facilities perform for a pharmaceutical company:

(1) Formulation

(2) Filling and sealing

(3) Chemical synthesis

(4) Cell culture and fermentation, including biological products

(5) Analytical testing and other laboratory services

(6) Packaging and labeling

There are several benefits in using contract facilities in many ways, as mentioned below:

- enhanced speed and efficiency in specific processes
- expanded capacity
- expertise in a specific technology

However, all contracted facilities must be compliant with the Current Good Manufacturing Practices for all manufacturing, testing or other support operations performed and this is the responsibility of the owner using this facility to ensure that they are all implemented.

3.3.1 Contract Manufacturing and Quality Management

It is essential that the manufacturers evaluate the contractors for cGMP compliance both by establishing a formal agreement that describes cGMP responsibilities, including quality measures, and also by regularly auditing the contractor's facilities. The product owners may hire another party to perform the operational processes that are part of a manufacturer's inherent responsibilities and the Quality systems.

3.3.2 Quality Agreement

A Quality Agreement is a comprehensive written agreement that defines and establishes the obligations and responsibilities of the quality units of each of the parties involved in the contract manufacturing of drugs subject to CGMP.

3.3.2.1 Elements of a Quality Agreement

A written quality agreement, describing the roles and responsibilities of the owner and the contracted facility, should track the basic components of the cGMP regulations (or, ICH Q7 guidance for APIs) to ensure coverage of all applicable cGMP responsibilities. The quality agreement must be well-drafted, with explicit language to define key quality roles and responsibilities; establish communication expectations; provide key points of contact for both parties; specify what products and/or services the contracted facility will provide to or for the owner; and establish who has final approval for various activities (Quality Units and other stakeholders). Most quality agreements contain the following basic sections:

- Purpose/Scope
- Terms (including effective date and termination clause)

- Dispute Resolution
- Responsibilities, including communication mechanisms & contacts
- Change control and revision

(Guidance for Industry-Contract Manufacturing Arrangements for Drugs: Quality Agreements , 2013)

Problems with a contract manufacturer or testing lab can emerge in several unexpected places. From changes in personnel or equipment to faulty SOPs and training, the list may seem impossible to manage. However, it needs to be scrupulously managed, because regulators have put this on the responsibility of the owners and not the contract manufacturers.

Creating a contract manufacturer management system that covers all possibilities is a huge undertaking. Fortunately, the experts behind the internationally recognized GMP Manual have laid out all the details in this comprehensive, step-by-step guide. Managing contract manufacturers and testing laboratories cover all aspects of selecting and managing contract manufacturers and testing labs in a well-documented report, including:

- Scope of the contract
- Responsibilities of both parties
- Selecting a project team
- Creating a project plan
- Change control
- Procurement
- Sampling
- Stability testing
- Transportation
- Documentation
- Communication
- And more

These reports serve as a guideline to ensure that the contracted manufacturers and testing facilities are operating in compliance with the FDA and EU GMP principles, and most of all, a particular pharmaceutical manufacturer’s own high standards.

Chapter 4. Quality Control

Quality is a characteristic that cannot be tested into a batch of product but must be built into each batch of product during all stages of the manufacturing process. The objective of the industry today is to adopt ways to meet regulatory standards, which are obviously minimal expectations, versus adopting a commitment to high quality medicines. Therefore, the word “quality” in quality control can be said to be indicative of both the qualitative and quantitative characteristics of the pharmaceutical product, as well as of the process by which it is manufactured ("Quality control procedure in pharmaceutical industry," 2009). Quality of a pharmaceutical product will only be ensured if all the procedure according to the guidelines are stringently executed. Licensed pharmaceutical products should be manufactured by licensed manufacturers, according to proper guidelines (Quality assurance of pharmaceuticals : a compendium of guidelines and related materials, 2006). The pharmaceutical industry is responsible to design and produce products that provide quality, purity, stability, safety, uniformity of contents and desired physiological availability to the consumer (Quality control procedure in pharmaceutical industry, 2009). Quality control can only be ensured if all steps involved from the beginning to the end of the production of the pharmaceutical product is done stringently according to the guidelines, followed by validated quality control tests at all necessary stages. It involves all decisions concerning the quality of the product and must not be confined to laboratory operations.

The quality control testing of pharmaceutical product generally require repetitive testing of the samples of the product, as well as the active ingredient, using numerous test methods. The quality control laboratories also need to be addressed according to the guidelines (WHO good practices for pharmaceutical quality control laboratories, 2009).

All marketed drugs must be safe and therapeutically active, with their performance consistent and predictable at all times. Sophisticated analytical methods for any new or improved drug products being produced are required to be developed for their evaluation to ensure continuous quality control. Quality control is a crucial operation in the manufacture of drug products by the pharmaceutical industry. This area requires a systematic approach that will predefine the objectives in order to develop the appropriate control strategy and quality risk management. Therefore, it is mandatory for the manufacturer to submit relevant data for the following areas:

- Predefined objectives

- Quality control test for the raw materials
- Quality control test for the packaging materials
- In process control
- Qualification and Validation
- Analytical study
    - Stability study
    - Analytical method development and validation (WHO good practices for pharmaceutical quality control laboratories, 2009).
- Environmental Control
- Change control
- Quality control of finished products
- Rejection and re-use of materials
- Complaints and recalls
- Documentation and Records

4.1 Predefined objectives

The manufacturer needs to first define the quality profile of the specific products and identify each and every CQA.

4.2 Quality Control for Raw Materials

The next step of the manufacturer is to identify the CMAs (appendix) and CPPs (appendix), followed by determining the functional relationships linking CMA and CPP to CQA (appendix). An important criteria of the quality control department of the pharmaceutical company is to also ensure that the raw material (APIs and excipients) are regularly tested. These raw material must be released for the production only after all the tests have been done with satisfactory results (Quality Control of Raw Materials (APIs and Excipients), 2007) Ensuring the quality of excipient is very important, as excipients have well-defined functions in a drug product. As part of regulatory assessments, the manufacturer needs to identify the possibility of presence of any residue. Selection of the excipients must be carefully reviewed and assessed for safety to be included in the product (Qualification of Excipients for Use in Pharmaceuticals, 2008).

There are a number of test parameters that are available for raw materials of a pharmaceutical product. Each raw material must go through the following tests for confirmation with specification for identity, strength, purity and quality parameters:

- Appearance
- Solubility
- Identity
- pH
- Moisture content
- Particle size detection
- Viscosity
- Absorbance
- Refractive index
- Assay
- Potency
- Melting point ("Guide to inspections of pharmaceutical quality control laboratories,").

It is the responsibility of every drug manufacturer to make sure that these is no risk at any point of the supply chain. These can only be done if the quality controls are stringently carried out. Moreover, every manufacturer need to ensure that the excipient maker has taken into account the following considerations:

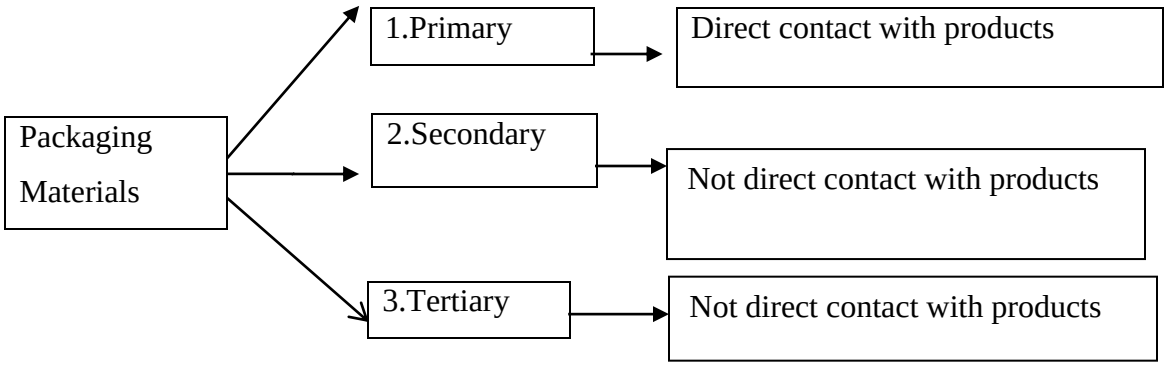
i. Defining the steps in the process to which GMPs apply
ii. Understanding the process and its critical control points
iii. Assessing points of highest risk of cross-contamination

Similarly every pharmaceutical manufacturer needs to take into account the following considerations:

i. Determine whether the excipient maker has completed an assessment against the standard
ii. Determine whether there were gaps identified in the assessment - and the excipient maker’s proposed time frame for closure of those gaps
iii. Determine whether the excipient maker’s management team has committed to the management responsibilities described in the standard (The New Excipient GMP Standard: A Guide for Drugmakers, 2014).

4.3 Quality Control for Packaging Materials

The different packaging materials used in the pharmaceutical industry can be classified as follows (Guidelines on packaging for pharmaceutical products, 2002):



i. Primary Packaging: This is in direct contact with the dosage form or equipment and must have no interaction with the drug.
   Example: blister packages, strip packages, etc.

ii. Secondary Packaging: This is the consecutive covering that stores the primary pharmaceuticals packages in it.
   Example: cartons, boxes, etc.

iii. Tertiary packaging: This is the final outer covering that provides bulk handling and shipping of pharmaceuticals from one place to another
   Example: containers, barrels, etc. (Pareek & Khunteta, 2014).

Quality control tests of packaging material need to be implemented in order to establish that the components and container closure system will maintain the characteristics established in the suitability studies. The specifications for packaging materials and containers must always be documented and include the nature, extent and frequency of routine tests. Such tests usually include the following (Guidelines on packaging for pharmaceutical products):

- Tests to identify the material
- Visual inspection (cleanliness, defects)
- Physical tests
- Chemical tests
- Dimensional tests

- Microbiological tests

Following are some specific tests that are done on specific packaging materials.

Test for Primary Packaging Material:

- For vial, ampoule, amber bottle and glass following tests must be performed:
    - Visual testing, Hydrolytic resistance, Alkalinity test
- For the Printed Aluminum Foils tests are done to check for the following:
    - Missing letters
    - Color variation
    - Rubbing
    - Blank (miss-feeds absence of second color)
    - Clarity and legibility
    - Pin hole
    - Mix-up
    - Contamination
    - Shipping Damage
- For the aluminum tubes test are done to check the followings**:**
    - Missing letters
    - Color variation
    - Rubbing
    - Blank (miss-feeds absence of second color)
    - Variation in length
    - Contamination
    - Shipping Damage
- Test for Secondary Packaging Material:
    - Visual testing, GSM Determination (Guidelines on packaging for pharmaceutical products).

4.4 In Process Quality Control (IPQC)

This area requires the development of an appropriate control, including justifications. The function of IPQC is to monitor and adapt the manufacturing process so that the pharmaceutical product meets the required specification. It can also include control of equipment and

environment in some cases. The identification, quality, strength and purity of the in-process materials need to be tested and according to the specifications, approved or rejected by the QC unit during the manufacturing process. The in-process materials that are rejected should be identified and controlled under a well-defined quarantine system designed to prevent their use in manufacturing (Pranshu Tangri, 2014). This section will identify the critical material attributes (CMA), critical process parameters (CPA), and the functional relationships that link CMA/CPP to critical quality attribute (CPA).

A written procedure should be established and stringently followed. Following are examples of the different features that in process quality controls measure (Gausepohl & Mukherji, 2007):

i. Physical parameters

- Time
- Temperature
- Pressure
- Weight
- Particle size
- Hardness
- pH
- Loss on drying
- Disintegration time
- Viscosity

ii. Attributive features

- Color
- Visible impurity
- Integrity
- Fractional part
- Completeness

There are different IPQC tests that need to be carried out for the various dosage forms Below is a list of the different IPQC tests that are generally done on the different dosage forms (Pranshu Tangri, 2014):

Tablets:

- Assay of active ingredients
- Drug contents determination
- Moisture contents of granules
- Weight variation of uncoated tablets
- Hardness test
- Disintegration test

Syrups and Suspension:

- Particle size
- Weight per ml
- pH
- Assay of active ingredients
- Drug contents determination

Semi-solids:

- Assay of active ingredients
- Drug contents determination
- Uniformity and homogeneity test
- Viscosity and specific gravity test
- Filling test

Injectables:

- Pyrogen test
- pH
- Clarity test
- Stability test
- Leakage test
- Checkup of particulate matters Drug contents determination

In-process control provides a controlling production, as well as performs a quality assurance function. The in-process control methods, that are part of the manufacturing formula, are compiled and validated under the supervision of quality control (Gausepohl & Mukherji, 2007).

4.5 Qualification and Validation of Quality Control

There are four stages of qualification (appendix) that need to be done as a process of quality control:

- Design qualification (DQ)
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ) (Analytical instrument qualification)

- Design qualification (QD). This is the first element of the validation of facilities, systems or equipment. The compliance of the design with GMP should be demonstrated and documented. (Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001)
- Installation qualification (IQ). The important factors that need to be considered for this type of qualification are:
  - Equipment design features (materials of construction, etc.)
  - Installation conditions (wiring, utilities, functionality, etc.)
  - Preventative maintenance
  - Calibration
  - Safety features
  - Cleaning schedules
  - Spare parts list
  - Supplier documentation and manuals
  - Software documentation
  - Environmental conditions (such as clean room requirements, temperature, and humidity)
- Operational qualification (OQ). Operational Qualification is usually required to be performed before a system or process can be approved and released for use. OQ considerations include:
  - Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
  - Raw material specifications
  - Software parameters
  - Material handling requirements

  - Process operating procedures
  - Process change control
  - Short term stability and capability of the process, (latitude studies or control charts)
  - Training
  - Potential failure modes, action levels and worst-case conditions (Failure Mode and Effects Analysis, Fault Tree Analysis)
  - The use of statistically valid techniques such as screening experiments to establish key process parameters and statistically designed experiments to optimize the process.

- Performance qualification (PQ). The key objective of this phase is to demonstrate whether the quality process will consistently produce a product acceptable under the specified operating conditions. The following are the PQ parameters that need to be approved:
  - Actual product and process parameters and procedures documented in OQ
  - Acceptability of the product
  - Assurance of process capability as established in OQ
  - Process repeatability
  - Long term process stability

  OQ and PQ lead to the development of parameters for continuous monitoring and maintenance. Process data and product data need to be also analyzed to identify any deviation that can be controlled. Depending on the nature of the process and its sensitivity, following are the causes of variation that can be controlled:
  - Humidity
  - Temperature
  - Light
  - Environmental contaminants
  - Human factors (training, ergonomic factors, stress, etc.)
  - Variability of materials
  - Variations in electrical supply
  - Vibration
  - Wear and tear of equipment

  Validation (appendix), on the other hand, is achieved by measuring any factor or variable that

can be quantified (Agnihotri, Kaur, Kumar, & Chahal, 2013). In order to validate the equipment or process, generally a plan is outlined that answer the following points:

- What is being validated
- Place of validation
- Reason of validation
- The validation stages that are required
- Validation time frames

The plan should also identify the validation team of people performing the validation and define responsibilities for:

- Overall management of the validation
- Development of protocols
- Performing the validation and recording the outcome
- Reviewing and approving the protocols and validation records
- Reviewing the validation outcomes and signing off the validation as acceptable

Effective qualification and validation can be achieved when the following procedures are carried out according to GMP regulations.

4.5.1 Validation Master Plan

This is developed and continuously revised in response to the organizational and operational changes based on the validation policy. It should clarify the following issues:

- Under what circumstances the validation should be performed?
- Who is responsible for the process?
- How will the validation be performed and documented?
- How will the validated state be maintained through regular servicing, calibration and requalification?

Apart from the process itself and the master plan, the company needs to identify the different types of validation that need to be done.

4.5.2 Process Validation

Process validation assures that a specific process will consistently produce a product, meeting its predetermined specifications and quality attributes (Robert A.Nash, 2003). The assurance of

product quality is derived from careful attention to a number of factors, such as selection of quality (components) and materials adequate product and process design and (statistical) control of the process through in-process and end-product testing (FDA). A high degree of confidence can be established by the careful design and validation of both the process and its control systems, resulting in all individual manufactured units of a given batch or succession of batches meeting acceptable specifications (Herbert A.Lieberman).

Process qualification and process validation need to be designed and documented in a manner that that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.(L. Nandhakumar, 2011)

Process validation involves the accumulation of data from the stages designed to perform production and appraisal of those data in order to confirm that the process being followed can reliably deliver a product of predetermined standard in a reproducible manner.

This form of validation is a requirement of current Good Manufacturing Practices (GMPs) and is implemented during the manufacture of both drug products and medical devices. The U.S. Food and Drug Administration (FDA) also defines process validation as a method that establishes documented evidence to assure that a specific process consistently produces a product meeting its predetermined specifications and quality attributes.

During process validation, two factors are quite important to be taken into consideration people who must perform the validation and faults that can occur during validation. The steps involved in production significantly influence the quality of the finished product and thus, it is necessary to take stringent actions to avoid any anomalies that could hamper the specified attributes of the product.

The different approaches to ensuring process validation can be listed as follows:

Determination of the Validation Batches

Process Description

Product Specifications and Quality Attributes

Quality of Raw Materials Used

Facilities and Equipment Used

Risk Analysis

Critical Processing Steps and Process Parameters

Test Plans

Acceptance Criteria

Sampling Plan

Techniques for Interpretation of the Test Results

Reference Documents

Equipment Qualification and Method Validation

Changes to the Validation Protocol

Departments Involved in the Validation and Time Schedule

Authorization of the Validation Protocol

Validation plan

The preparation and employment of a validation plan should not be considered as the test of a single individual working apart from the application development team. An evaluation team representing all the various interests – test sites, main applications and area of assessment should be hired. The draft from of the validation plan, although a general requirement in its early stages, should be a living document, and be revised at each stage of planning. The draft plan may not be expected to be contain detailed questionnaire design. However, the final version of the plan produced before validation should be very specific and have detailed information on validation practice

Stages of Process Validation:

Process validation can be divided into three stages:

Stage 1- Process Design: In this stage, data based on knowledge gained through development and scale-up activities are gathered and analyzed to define the commercial manufacturing process.

Stage 2 – Process Qualification: In this stage, it is confirmed whether a process design is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: In this stage, routine validation is performed to assure that the process remains in a state of control.

Types of Process Validation:

The implementation of process validation involves four type of approaches:

A) Prospective validation (or premarket validation)

B) Retrospective validation

C) Concurrent validation

D) Revalidation

A. Prospective validation

Prospective validation involves the collection and analysis of the documented evidence prior to the commencement of production. At this stage, some critical situations are identified, risk-benefit ratio of the process is evaluated, and trials are performed on the basis of which an overall assessment is made on the feasibility of the process. This approach to validation is normally undertaken when a new formula is introduced or an alteration is made to a manufacturing process which may affect the product's characteristics.

B. Retrospective Validation

Retrospective validation is designed for an already operating process and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment. Validation of these facilities, processes, and process controls are usually based on historical data to provide the necessary documentary evidence that the process being followed is performing in a consistent manner. Therefore, this type of validation is only acceptable for well-established processes and is conducted during the audit of a validated process (Nandhakumar, Dharmamoorthy, Rameshkumar, & Chandrasekaran, 2011).

C. Concurrent Validation

Concurrent validation involves the documentation of evidence that a facility and processes work in the same way as they have been purported, based on the information generated during actual imputation of the process. This approach takes into consideration the monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

D. Revalidation

Revalidation involves periodic validation of the process and also includes investigative review of existing performance data. This approach is essential to maintain the quality of the product and validated status of the plant, equipment, manufacturing processes and computer systems. The possible reasons for performing the revalidation process include:

- The transfer of a product from one plant to another.
- Change to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality.
- The necessity of periodic checking of the validation results.
- Significant (usually order of magnitude) increase or decrease in batch size.
- Sequential batches that fail to meet product and process specifications.
- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.

Outsourcing validation: Outsourcing validation studies can help a company to meet deadlines by supplementing existing staff and supporting specific projects. Securing the maximum benefit from a validation contractor requires a systematic approach and clear communications. A long-term outsourcing relationship begins with a proposal, which describes your requirements accurately and in sufficient detail.

Matrixing: Validation of the packaging of the finished dosages form is equally important to ensure the quality and safety of a product. Matrixing is a process done across different products to evaluate the packaging of different products in a common packaging presentation.

4.5.3 Cleaning Validation

Validation of the cleaning process is essential since it warrants the level of cleanliness. All cleaning procedure that come in direct manufacturing contact must be validated in order to avoid any level of cross contamination affecting the quality of the product. Generally, this type of validation is directed to process steps or situations where there is any risk of contamination or carryover of materials and cleaning agent residues from the previous cleaning process or manufactured product affecting the API quality. The method of validation of cleaning procedures is clearly mentioned in guidelines and selection must be based on several parameters such as

calculation of residual limits based on potency, toxicity, stability etc. ("Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001).

4.5.4 Validation and Thermal Performance Qualification for Transport Systems

This system validates the temperature, pressure, insulation, humidity and all other critical environmental and storage parameters of the drug product transport system. The transport systems need to be monitored by approved monitoring systems, also known as continuous verification.

4.5.5 Computer System Validation

The term ‘computer system validation’ covers a broad range of systems, such as automated laboratory systems connected with computers, manufacturing database system and SAP (Systems Applications and Products). Commercially available software that has been qualified will not always require the same level of testing. If the existing system has not been validated at the time of installation, a retrospective validation will need to be conducted if appropriate documentation is available. Sufficient controls must be present in the computerized systems to prevent unauthorized access or changes to data. There should also be controls that will prevent omissions in data (e.g., data not captured when system is turned off). The system should include a record of the previous entry, any data change made, as well as who made the change and when the change was made (Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

4.5.6 Periodic Review of Validated Systems

Finally, all systems as well as processes must be periodically evaluated to confirm that they are operating as required and expected. If there are no significant changes made to the system or process, and a quality review confirms that the system or process is consistently producing material according to all the specifications, revalidation is generally not required.

A checklist of activities is required to continuously review the validation activity. These activities can be listed as follows:

- Form a multi-functional team for validation
- Plan the approach and define all the requirements
- Identify and outline the processes

- Mention the process parameters and desired output
- Choose verification and/or validation
- Develop a master validation plan
- Decide on methods and tools for validation
- Design the validation protocols
- Perform IQ, OQ, PQ and documentation results
- Determine and implement continuous process controls

4.6 Analytical Study

The common analytical study performed in the pharmaceutical to manage the quality of the product can be divided into two broad categories:

- Stability study
- Analytical method development and validation

4.6.1 Stability study

Stability of a pharmaceutical product may be defined as 'the capability of a particular formulation in a specific container system to maintain its physical, chemical, protective, toxicological, microbiological and informational specifications for the scientific and commercial success of it' (Kommanaboyina, 1999). Stability testing studies are performed to provide evidence on how the quality of an active pharmaceutical ingredient or medicinal product may change with time under the influence of normal environmental factors such as temperature, humidity, and light. These tests are used to establish a shelf life for the medicinal product as well as recommended storage conditions. It is 'a complex set of procedures involving substantial cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation' (M. S. Charde, 2013). Accordingly, labels are given to the drug products with an expiration date, that is, the time after which the drug can no longer be considered within the legal potency requirement. These tests are to be carried out on the different pharmaceuticals product in their finished marketed forms in order to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products.

The four main type of degradation by which a drug product can degrade are heat, hydrolytic, oxidative, and photolytic degradation. Choosing suitable reagents such as the concentration of acid, base, or oxidizing agent and varying the conditions like temperature and length of exposure

can attain the preferred level of degradation. However, it is necessary to control the degradation to a desired level. The generally recommended degradation varies between 5-20%. This range covers the generally permissible 10% degradation for the small molecule of a pharmaceutical drug product, for which the stability limits 90%-110% of the label claim (Trivikram Rawat, 2015). Stability testing procedures have been divided into 4 types:

- **Accelerated stability testing**

In accelerated stability testing the samples are subjected to stress, refrigerated after stressing, and then assayed. The likelihood of instability in the measurement system is reduced in comparison to the real-time stability testing, since the duration of the analysis is short. In accelerated stability testing, comparison of the unstressed product with stressed material is also done within the same assay and the stressed sample recovery is expressed as a percent of unstressed sample recovery. For statistical reasons, the treatment in accelerated stability projections is recommended to be performed at four different stress temperatures. However, for thermolabile and proteinaceous components, relatively accurate stability projections are obtained when denaturing stress temperatures are avoided.

- **Real-Time stability testing**

Real-time stability testing is normally performed for a longer duration of the test period in order to allow considerable product degradation under the given storage conditions. The duration of the test depends upon the stability of the product which should be long enough to indicate clearly that no measurable degradation occurs. The test must be able to distinguish degradation from inter-assay variation of the products. During testing, data is collected at an appropriate interval such that a trend analysis is able to distinguish instability from day-to-day ambiguity.

- **Stress testing or forced degradation**

This type of study is done so as to mimic likely conditions in market place storage. Forced degradation, also known as stress testing, stress studies, stress decomposition studies, forced decomposition studies, is a method that involves degradation of the pharmaceutical products at conditions more severe than the accelerated conditions. According to the ICH guideline, forced degradation is deliberated to identify the likely degradation products which further helps in determination of the intrinsic stability of the drug molecule and establishing degradation pathways (Trivikram Rawat, 2015). Knowledge of the stability of molecule helps in selecting the correct formulation and package as well as providing proper storage conditions and shelf life,

which is also essential for regulatory documentation (R. D. P. Blessy M, Prajesh N. Prajapati, Y.K. Agrawal, 2013).

- **Retained sample stability testing**

In this study, stability samples are selected to be retained or stored for at least one batch a year. If the number of batches marketed in a year exceeds 50, stability samples from two batches are recommended to be taken. At the time of first introduction of the product in the market, the stability samples of every batch may be taken, which may be decreased to only 2% to 5% of marketed batches at a later stage. According to this study, the stability samples are tested at predetermined intervals. Generally, if a product has a shelf life of 5 years, it is established to test samples at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months (Sanjay Bajaj, 2012).

4.6.1.1 Parameters for Stability Testing

There are several parameters for each dosage form that can be used as a guide for the type of tests to be included in a stability study. These are as follows:

- Physicochemical properties, such as appearance, water content, disintegration, and dissolution, are the parameters considered for the stability testing of drug substance formulated as tablets and capsules. For topical, ophthalmic, parenteral and suppositories, the parameters considered for stability testing include pH, clarity of solution, sterility and particle size distribution.
- Chemical properties such as assay and degradation product are the parameters taken for performing the stability testing of drug substance in capsule, tablet, suppository dosage forms.
- Microbial properties like microbial purity, etc. are the parameters considered for the stability testing of drug substance in capsules, tablets and suppositories (M. S. Charde, 2013).

4.6.1.2 Importance of stability testing

Stability testing is essentially done as a concern for the well-being of the patient suffering from the disease for which the products have been designed. Apart from the unstable product degrading into toxic decomposition products, loss of activity up to a level of 85% of that declared on the label may lead to failure of the therapy resulting sometimes even in death e.g. nitroglycerine tablets for angina and cardiac arrest. It has thus become a legal requirement to

provide data for certain types of stability tests to the regulatory agencies before acquiring approval of a new product. Other benefits of stability studies of the marketed products are to provide information that may be useful in the selection of adequate formulations, excipients and container closure systems for development of a new product (Sanjay Bajaj, 2012).

4.6.1.3 Protocol for stability testing

The protocol for stability testing is a written document that describes the key components of a well-controlled stability study. A well designed stability protocol should contain the following information (Maninderjit Kaur, 2013).

- Batches
- Containers and closures
- Orientation of storage of containers
- Sampling time points
- Sampling Plan

4.6.2 Analytical method development and validation

The analytical method, an important part of stability study, is developed according to BP and USP. If the product is not including in pharmacopeia, the industry need to validate the method according to the SOP of the industry. The most common types of analytical methods are:

- Identification tests. These are intended to ensure the identity of an analyte by comparing the sample with standard. This is achieved by comparing a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.
- Quantitative tests for impurities content
- Limit tests for the control of impurities
- Quantitative tests

The reason for developing the validation of an analytical procedure is to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Method validation is an integral part for the quality control of INN drug. Typical validation characteristics are listed below:

- Accuracy
- Precision (repeatability and reproducibility)

- Range
- Linearity
- Limit of detection (LOD)
- Limit of quantitation (LOQ)
- Selectivity/ specificity
- Robustness/ ruggedness
- Stability and system suitability studies (Ravichandran V, 2010).

4.6.3 Bioanalytical Method Validation

The pharmaceutical industry has developed tremendously in the last few decades and is now manufacturing and marketing biologics or biological products that have shown outstanding results in the treatment of rare diseases such as non-Hodgkin's lymphoma, melanoma asthma, leukemia etc. In case of the quantitative determination of such drugs or/and its metabolites in biological materials such as blood, plasma, serum or urine, tissue, skin samples etc. different methods, such as bioanalytical methods, are used. These methods are quite sensitive and requires to be performed carefully. In order to ensure success in implementation of the methods each step need to be validated critically. Validation of the bioanalytical methods also requires performing all of the procedures in a manner that the results are reliable and reproducible for the intended use. Chromatographic Method and Ligand Binding Assays are the two commonly used types of bioanalytical methods ("Guidance for Industry -Bioanalytical Method Validation ", 2013).

There are different ways in which the validation of the method can be performed. Following are the different type of validation of the analytical method.

- Full Validation. This type of bioanalytical method validation is performed for the following conditions:
  - During development and implementation of a new bioanalytical method
  - For analysis of a drug entity that is new
  - For an existing method where a metabolite quantification is added
- Partial Validation. This method is performed when additional validation is needed to an already established and validated method. The method is modified to ensure the performance of the method. Partial validation may be as little as only one accuracy and precision determination to a nearly full validation. Modifications or changes of a typical bioanalytical method that fall into this category include but are not limited to:

  - Bioanalytical method transfers between laboratories or analysts
  - Change in analytical methodology (e.g., change in detection systems)
  - Change in anticoagulant in harvesting biological fluid (e.g., heparin to EDTA)
  - Change in matrix within species (e.g., human plasma to human urine)
  - Change in sample processing procedures
  - Change in species within matrix (e.g., rat plasma to mouse plasma)
  - Change in relevant concentration range
  - Changes in instruments and/or software platforms
  - Modifications to accommodate limited sample volume (e.g., pediatric study)
  - Rare matrices
  - Selectivity demonstration of an analyte in the presence of concomitant medications
- Cross Validation. This type of validation is when two or more methods are used for data generation with the same study or different studies comparison of these data ("Guidance for Industry -Bioanalytical Method Validation," 2001).

It is necessary to first establish a specific, detailed, written description of the method in the form of a protocol, study plan, report, and/or SOP. This will be followed by investigation of each step mentioned on the method. The extent to which each variable such as procedural, environmental etc. could affect the measurement of the analyte in the method must be clearly defined and confirmed. The validation of the measurements for each analyte in the method is also necessary.

The SOP must include:

- All aspects of analysis from the time the sample is collected and reaches laboratory until the results of the analysis are reported.
- Record keeping, security and chain of sample custody (accountability systems that ensure integrity of test articles).
- Sample preparation and analytical tools such as methods, reagents, equipment, instrumentation, and procedures for quality control and verification of results.

Method development and validation for a bioanalytical method should include

- Selectivity
- Accuracy, precision, and recovery
- The calibration curve

- Sensitivity
- Reproducibility
- Stability of analyte in spiked samples.

4.6.3 Routine Analysis

For the routine analysis of drugs in a validated analytical method the following are generally undertaken:

- System suitability
- Calibration curves ("Guidance for Industry -Bioanalytical Method Validation ", 2013).

4.7 Environmental Control

Written procedures must be available for environmental monitoring, as well as for gowning, cleaning and disinfection within manufacturing areas. These procedures must mention “target”, “alert” and “action” limits for the environmental contaminants. It must also include the action(s) to be taken if and when the limit is exceeded or particular indicator organisms are detected. The test method, along with the sample size employed, must be capable of detecting the presence of low levels of indicator organisms, such as Pseudomonas.

There are different sampling techniques that are available for the monitoring of microbial contamination. Each technique has its own interpretation and it is generally necessary to use a combination of techniques utilizing a formal sampling program to identify trends or highlight exceptional results within the manufacturing environment. The commonly used techniques are:

- Air sampling
- Settle plates
- Particle counting
- Contact plates
- Hand plates
- Water sampling (Current good manufacturing practice guidelines for drugs, 1999).

4.8 Change Control

An effective change control system should be developed and established to evaluate any change that could possibly affect the production and control of the intermediate or the active ingredient being used. Written procedures must include the identification, documentation, appropriate

review, and approval of changes in any raw material, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units as well as reviewed and approved by the quality unit(s). Any potential change on the quality of the intermediate or API must be immediately evaluated. A well-defined procedure in determining the level of testing, validation, and documentation is required to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may have on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process ('Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,' 2001).

4.9 Quality Control of Finished Products

The final testing of the finished product is done in the quality control laboratories. The final product is released once the tests for compliance with predetermined standards is met. Following is a list of the test parameters generally performed on finished products:

- average weight
- disintegration
- dissolution
- hardness
- friability
- identification
- appearance
- odor
- solubility
- presence of heavy metal
- assay
- uniformity of weight
- percentage of stated dose

4.10 Rejection and Reuse of Materials

The active ingredients and intermediate products that fail to meet established specifications must be identified and quarantined, and later evaluated to determine whether they are to be rejected or can be reused (or reprocessed). If rejected, the final disposition of those materials must be recorded. On the other hand, an intermediate or API that does not meet the standards or specifications to be used can, however, be introduced back into the process after repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, etc.) that are part of the established manufacturing process. However, if such a reprocessing is used for a larger number of batches, the reprocessing must be included in the standard manufacturing process. The person in charge must not get confused with reprocessing. If the continuation of a manufacturing step after an in-process control test step is considered to be part of the normal process, it must not be considered as reprocessing. However, introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be done after careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and over-reacted materials.

4.10.1 Reworking

Batches that will be need to be reworked should be subjected to appropriate evaluation, testing, stability testing if required, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. A concurrent validation to define a protocol defining the rework procedure, how it will be carried out, and the expected results will be the appropriate validation approach for rework procedures. If there is only one batch to be reworked, a report can be written and the batch released once it is found to be acceptable.

There must be procedures that will provide protocols for comparing the impurity profile of each reworked batch against batches manufactured by the established process. If the routine analytical methods are inadequate to characterize the reworked batch, additional methods must be used (Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

4.10.2 Recovery of Materials and Solvents

Recovery from mother liquor or filtrates of reactants, intermediates, or the active ingredient is acceptable, provided the approved procedures for the recovery and the recovered materials meet specifications suitable for their intended use.

Solvents can be recovered and again used in the same process or in different processes, provided that the procedures of recovery are controlled and monitored to confirm that the solvents meet appropriate and established standards (Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

Fresh and recovered solvents and reagents can be combined after adequate testing has shown their suitability for all manufacturing processes in which they may be used. The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented (Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

4.10.3 Return of Active Ingredients or Intermediates

Intermediates or active ingredients that will be returned must be identified and quarantined. If there is any doubt in the quality of the returned intermediates or APIs due to the conditions under which they have been stored or shipped before or during their return or the condition of their containers, they must be reprocessed, reworked, or destroyed. Records of returned intermediates or APIs must be maintained. For each return, the documentation prepared must include:

- Name and address of the receiver
- Intermediate or API, along with batch number, and the quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

(Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

4.11 Complaints and Recalls

All complaints, related to quality, whether received orally or in writing, should be recorded and investigated according to a well-defined procedure. The complaint records must include the following:

- Name and address of complainant
- Name (and, where appropriate, title) and phone number of the person submitting the complaint
- Nature of the complaint (including name and batch number of the API)
- Date of complaint received
- Action initially taken (including dates and identity of person taking the action)
- Follow-up action taken
- Response provided to the originator of complaint (including date of response sent)
- Final decision on intermediate/API/batch

(Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, 2001).

Recalls are generally classified into three classes according to the following system:

- Class I recalls occur when the products are potentially life threatening or could cause a serious risk to health. Some examples of Class I Defects are:
    - Wrong Product (label and contents are different products)
    - Correct product but wrong strength, with serous medical consequences
    - Microbial contamination of sterile injection or ophthalmic product
    - Chemical contamination with serious medical consequences
    - Mix up of some products with more than one container involved
- Class II recalls occur when the product defects could cause illness or mistreatment, but are not of Class I. Some examples of Class II recalls are:
    - Mislabeling e.g. wrong or missing text or figures.
    - Missing or incorrect information leaflets or inserts
    - Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
    - Chemical/ physical contamination (significant impurities, cross contamination,

  - particulates)
  - Mix up of products in containers
  - Noncompliance with specification (e.g. assay, stability, fill/ weight or dissolution)
  - Insecure closure with serious medical consequences (e.g. child resistant containers, cytotoxic products, potent products)
- Class III recalls occur when product defects will not pose a significant hazard to health, but withdraw may be initiated for other reasons. Examples of Class III recalls are:
  - Faulty packaging e.g. wrong or missing batch number or expiry date
  - Faulty closure
  - Contamination microbial spoilage, dirt or detritus, particulate matter

According to Pharmaceuticals Product Recall Guidelines, 2016, Class I or Class II recalls are considered to be urgent safety-related recalls.

4.12 Documentation

All steps and processes starting from the very first point in the supply chain up to the product reaching the patient or customer need to be clearly documented. This has been discussed in details in the following chapter.

Chapter 5. Documentation

Documentation is an essential part of the quality management system and it must be related to all aspects of GMP and quality assurance. Its objective is to define and clearly outline the specifications for all materials as well as the method of manufacture and control, to ensure that all personnel involved with manufacture have the information necessary to decide whether or not to release a batch of a drug to be marketed, and to provide an audit trail that will permit investigation of the history of any suspected or defective batch. The specifications should also describe, in details, the requirements with which the products or materials used or obtained during manufacture have to conform in order to serve as a basis for quality evaluation (K. Patel & Chotai, 2011). Following is a list of what needs to be documented:

- All concerned personnel dealing with manufacture need to know what to do and when to do it.
- Authorized personnel need to have all information necessary to decide whether or not to release a batch of a drug for sale.
- Existence of documented evidence, traceability, records and an audit trail that will permit investigation must be available.
- The availability of data required for validation, review and statistical analysis must be ensured.
- Documents regarding "labels" that need to be applied to containers, equipment or premises must be in the company's designated format. They should also be clear and unambiguous. The use of colors on the labels to indicate status (e.g. quarantined, accepted, rejected, and clean) is also helpful. All finished drug products must be labeled having the following information for easy identification:
    - Name of the drug product
    - A list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, and volume)
    - The batch number assigned by the manufacturer
    - The expiry date in an encoded form
    - Any special storage conditions or handling precautions that may be necessary
    - Directions for use, and warnings and precautions that may be necessary

- The name and address of every supplier of every single item required in the manufacture of the product
- The name and address of the manufacturer or the company or the person responsible for placing the product on the market

(Quality assurance of pharmaceuticals : a compendium of guidelines and related materials, 2006).

5.1 Documentation System and Specifications

- All related documentation in the manufacture of intermediates or APIs should be carefully prepared, meticulously reviewed, approved, and finally distributed (whenever required) according to approved procedures. These documents can be either in paper or in electronic form, should be meticulously controlled and revision histories should be maintained.
- All necessary documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records) should be done according to an established procedure and retained. The retention periods for all these documents should also be clearly specified.
- Generally, all production, control, and distribution records must be retained for at least 1 year after the expiry date of the batch. Records of APIs should be retained for at least 3 years after the batch has been completely distributed.
- When entries are made, these should be done clearly in spaces provided for such entries, immediately after performing the activities, and should also identify the person making the entry. Corrections to entries should be dated and signed, leaving the original entry still legible.
- Original or copies of records should be readily available during the retention period. Records that can be promptly retrieved from another location by electronic or other means are acceptable.
- Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records

- Specifications must be established and documented for everything starting from raw materials, intermediates where necessary, APIs, to labeling and packaging materials. In addition, specifications may be required for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically affect quality.
- If electronic signatures are used on documents, they need to be authenticated and secured.

5.2 Equipment Cleaning and Use Record

Records of major equipment use, cleaning, sanitation, and/or sterilization and maintenance should be maintained, showing the date, time, product, and batch number of each batch processed in the equipment as well as the person who performed the cleaning and maintenance.

5.3 Records of Raw Materials, Intermediates, API Labeling and Packaging Materials

Records of raw material, intermediate products, API labels and packaging materials should be maintained at all times. These include the following:

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
- The results of any test or examination performed and the conclusions derived from this
- Records tracing the use of materials
- Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications
- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials

5.4 Master Production Instructions (Master Production and Control Records)

An instruction list of the master product for each intermediate and API should be prepared with the date and signature of one person and independently checked, dated, and signed by another person of the quality department.

Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable;
- A complete list of raw materials and intermediates;
- An accurate quantity of each raw material or intermediate, including the unit of measure;
- The production location and major production equipment to be used;
- The instructions for storage of the intermediate or API to ensure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

5.5 Batch Production Records (Batch Production and Control Records)

Record of batch production records must be prepared and documented for each intermediate and API and must include complete information relating to the production and control of each batch. The batch production record must be checked before issuance to make sure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction must be done. These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

Documentation for batch production records includes the followings:

- Dates and appropriate times
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used

- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed
- Signatures of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label for intermediate or API
- Representative label of API or intermediate if made commercially available
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
- Results of release testing

5.6 Laboratory Control Records

Laboratory control records must contain complete data from all tests conducted to guarantee compliance with established specifications and standards. It contains the following information:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing
- A statement of or reference to each test method used
- A record of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions
- A record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested
- A complete record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors

- A statement of the test results and how they compare with established acceptance criteria
- The signature of the person who performed each test and the date(s) the tests were performed
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards

Complete records should also be maintained for:

- Any modifications to an established analytical method
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices
- All stability testing performed on APIs
- Out-of-specification (OOS) investigations

5.7 Batch Production Record Review

Written procedures should be developed and established for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released for distribution.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released for distribution. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s). All discrepancies, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company ("Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," 2001).

5.8 Data integrity problems

Data integrity is the maintenance, assurance or accuracy of, data over its entire life-cycle. It is a critical aspect to the design, implementation and usage of any system that stores, processes, or retrieves data. This must be stringently maintained and ensured through the entire lifecycle of each and every product manufactured. Data integrity problems are most common issue in GMP, and the three main areas of concern include:

- Lack of adequate controls
- Lack of staff competence
- Lack of adequate root cause analysis

These issues are often the result of insufficiently controlled processes, poor documentation practices, lack of quality oversight or professional ignorance. With the increased scrutiny on data integrity, establishing internal competency and assessment programs is essential and thus requires the following:

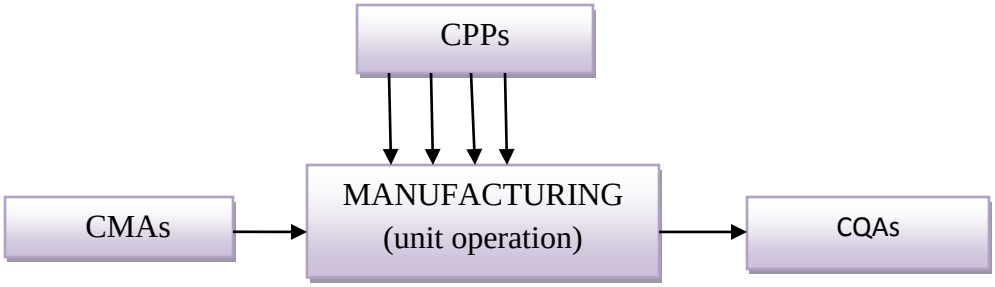
- Identify likely risks and select the most appropriate controls
- Review case study validation tests to see if data integrity is actually being verified
- Draft a memo to be sent out by your senior team to all company employees about good data integrity
- Draft your own personal business case and plan for implementing a data integrity control framework at your company (FDA news Announces: Data Integrity: The Key to FDA and GMP Compliance, July 14-15, 2016, Arlington, VA, 2016).

Staying off the regulatory radar and securing organizational data integrity and good documentation practices requires: a quality approach to manufacturing that encompasses preventing instances of contamination, mix-ups, deviations, failures, and errors in production processes and facilities. According to the FDA's Current Good Manufacturing Practice, this is accomplished by "establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories." For even the most organized

and systemized organizations, there are a lot of controls and regulations with which they must comply. Following these criteria will set the formation for a data integrity program that meets FDA expectations ‘that data be reliable and accurate’. But, as previously noted, document and records validation is just one aspect of ensuring data integrity, and as such, organizations should be prepared to implement meaningful and effective strategies to manage their data integrity risks across the entire spectrum of their operation. This includes isolating database servers and web servers on separate networks; disabling and securing unnecessary network services; instilling and enforcing access controls; recognizing and eliminating known vulnerabilities and exploitations; implementing real-time security warnings; continually monitoring, updating, and auditing systems regularly.

Chapter 6. Pharmaceutical Quality by Design

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding as well as process control, taking into account sound science and quality risk management. Quality by Design (QbD) is being incorporated by the manufacturers in the entire manufacturing process to significantly improve the quality of the entire manufacturing process. Figure 2 represent the relationship between CMAs, CPPs, and CQAs. During the QbD process, product design and understanding include the identification of CMAs, which are different from CQAs. CQAs are for output materials while CMAs are for input materials including drug substance, excipients, and in-process materials. The CQA of an intermediate may become a CMA of the same intermediate for a downstream manufacturing step. Process design includes the identification of CPPs and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs, that is of significant importance. From the viewpoint of QbD, CMAs and CPPs can be varied within the established design space, without significant influence on CQAs, and as a result, the quality of the final product will meet the QTPP.



$CQAs = f (CPP_1, CPP_2, CPP_3...CMA_1, CMA_2, CMA_3...)$

Figure 2: Critical Quality Attributes and Critical Process Parameters: Quality by Design Approach.

6.1 Development Process using Quality by Design Approach

The process is a systematic approach (Figure 3) that begins with a target product profile, describing the use, safety and efficacy of the product, followed by defining a target product quality profile. This profile will be used by the formulators and process engineers as a

quantitative alternate for aspects of clinical safety and efficacy during product development. The steps will lead to necessary prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Risk assessment must be used to prioritize knowledge gaps for further investigation.

The formulation is then designed and the critical material (quality) attributes of the final product identified. The formulator must remember at all times that the product formulation must be controlled to meet the target product quality profile. This is followed by design of the manufacturing process that will produce a final product having the critical material attributes identified earlier.

The critical process parameters and input (raw) material attributes must be then identified and controlled in order to achieve these critical material attributes of the final product. The risk assessment is used to prioritize process parameters and material attributes for experimental verification. Prior knowledge with experiments are combined to establish a design space or other representation of process understanding. Establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected. Changes in scale and can be guided by a risk assessment. Continually monitor and update the process to assure consistent quality.

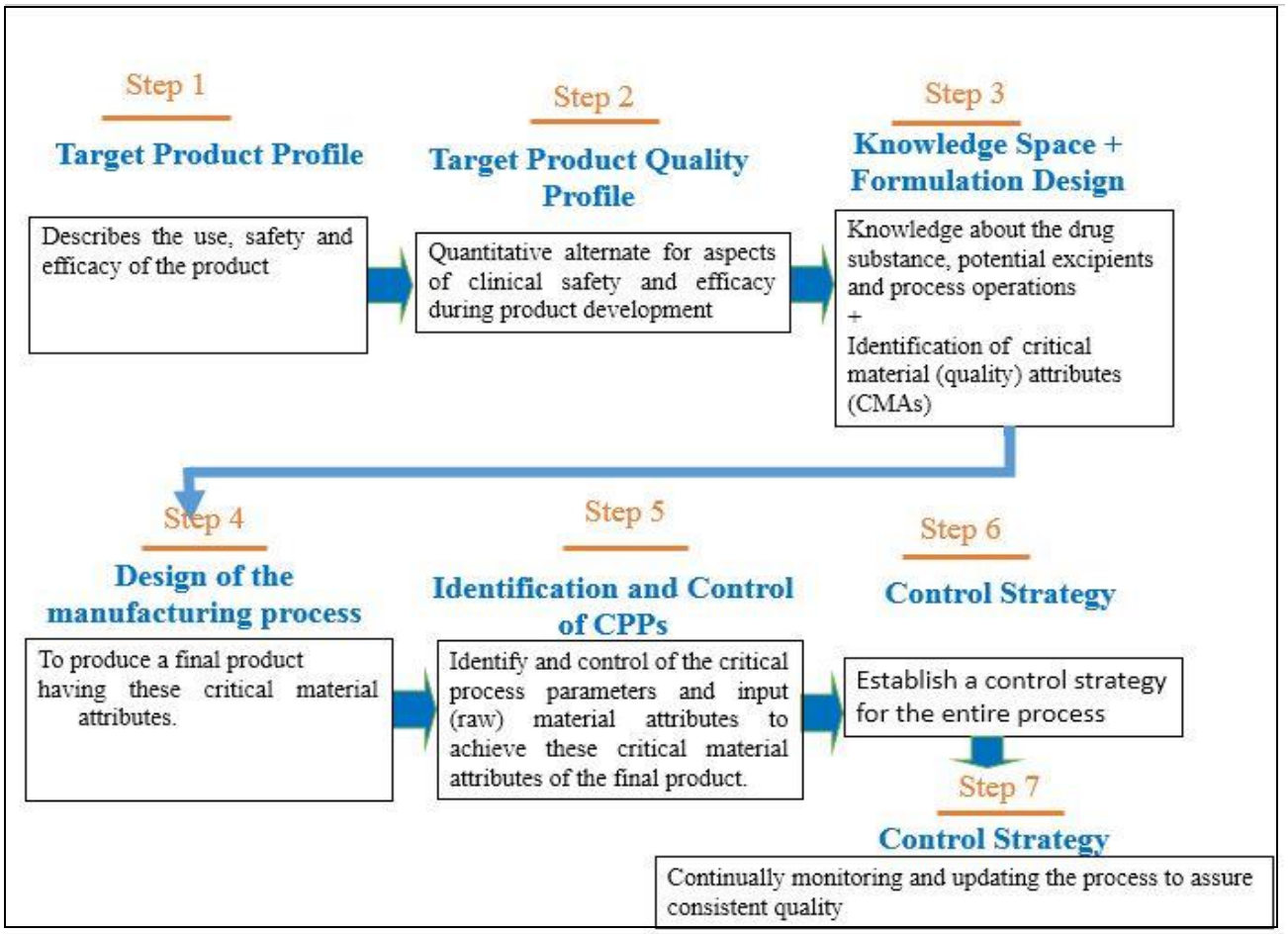


Figure 3: Steps of Quality by Design

6.2 Traditional *vs* Quality by Design (QbD) Approach to Pharmaceutical Development

According to the Qbd approach to pharmaceutical development, the product quality is built in by design and not test in. There are very distinct differences between the traditional approach and the QbD approach which has been shown below in Table 5 and Figure 4.

Aspects	Current	QbD
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT (process analytical technologies) utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Control Strategy	By testing and inspection	Risked-based control strategy, real time release possible

Table 5: Comparison between Current approach & QbD approach

Quality by End Product Testing Vs QbD approach

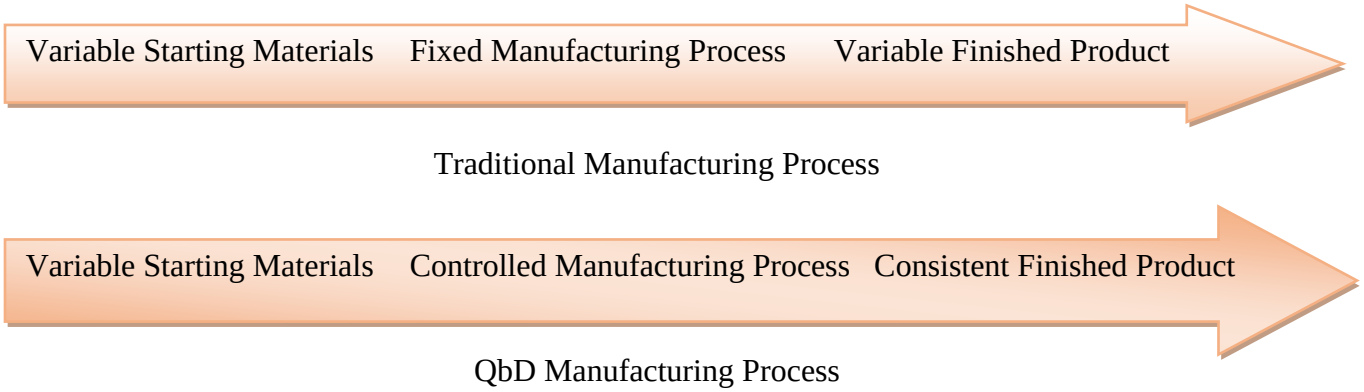


Figure 4: Traditional Manufacturing Process *vs* QbD Manufacturing Process

6.3 Advantages of QbD

Apart from the QbD approach to pharmaceutical development providing opportunities for more flexible regulatory approaches, there are additional benefits for the pharmaceutical industry adopting the QbD approach. These can be listed below:

- More efficient and effective control of change.
- Return on investment / cost savings.
- Ensures robust commercial manufacturing methods for consistent production of quality drugs.
- Ensures the consumers that therapeutic equivalent generics are manufactured every single time.
- Offers the agency that quality applications are submitted to improve the review efficiency and to reduce the application approval times.
- QbD methodology helps in identifying and justifying target product profiles, product and process understanding.
- Helps in continuous improvement.
- Better understanding of the process.

Chapter 7. Conclusion

It is absolutely critical to every drug manufacturer's operation to ensure that their quality controls or quality control management system will keep their products from being at risk, no matter where it is in the supply chain. The central goal of a quality system is the consistent production of safe and effective products.

The study developed a comprehensive quality systems model (Figure 5), highlighting consistency with the regulators' requirements for manufacturing, such as cGMP, ICH, etc. The model also depicts the steps that the manufacturers are required to implement to ensure such quality systems. When the guidelines are fully developed, and effectively managed, a quality system will surely lead to consistent, predictable processes that ensure that pharmaceuticals are safe, effective, and available for the consumer. A quality approach to manufacturing that encompasses preventing any instances of contamination, mix-ups, deviations, failures, and errors in production processes and facilities must surely be ensured. Properly recorded, reported, and traceable information is also absolutely essential to be developed and maintained throughout the development, formulation and manufacture of 'quality' pharmaceutical products in line with established protocols, and in ensuring products' identity, quality, strength, purity and safety before it is distributed in the market. According to FDA's Current Good Manufacturing Practice, proper quality can be accomplished by "establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories."

Specifications should be based on mechanistic understanding of how formulation and process factors interact and impact on the Critical Product Attributes (CQAs) of a product. This understanding should be derived from

- Prior knowledge, both from the literature and personal experience
- Preliminary data from development activities

All CQAs based on safety and efficacy, and science- and risk-based approach to identify material attributes and/or process parameters that could possibly impact the CQAs must be well addressed and documented. Finally, an appropriate control strategy and proper documentation must be in place. This enhanced approach, known as quality by design, is a systematic approach that begins with predefined objectives.

According to the approach, product development would additionally include:

1. A systematic evaluation, understanding and refining of the formulation and manufacturing process, including:

    •Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs

    •Determining the functional relationships that link material attributes and process parameters to product CQAs

2. An enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for a design space and/or real-time release testing (ICH Q8).

It can, thus, be concluded that a systematic approach needs to be designed and developed with the 'end' in mind, in order to ensure quality where the product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches. The impact of starting raw materials and process parameters on product quality must surely be well understood, with an emphasis on product and process understanding and process control. All processes involved must be continually monitored, evaluated, documented and updated in line with the 'quality by design' approach to allow for consistent quality throughout product life cycle. The parameters affecting the quality of the final pharmaceutical product were taken and a model developed which depicts the entire process. Each step in the model shown will ultimately lead to a 'quality' product, which is possible each time if the 'quality by design approach' is implemented.

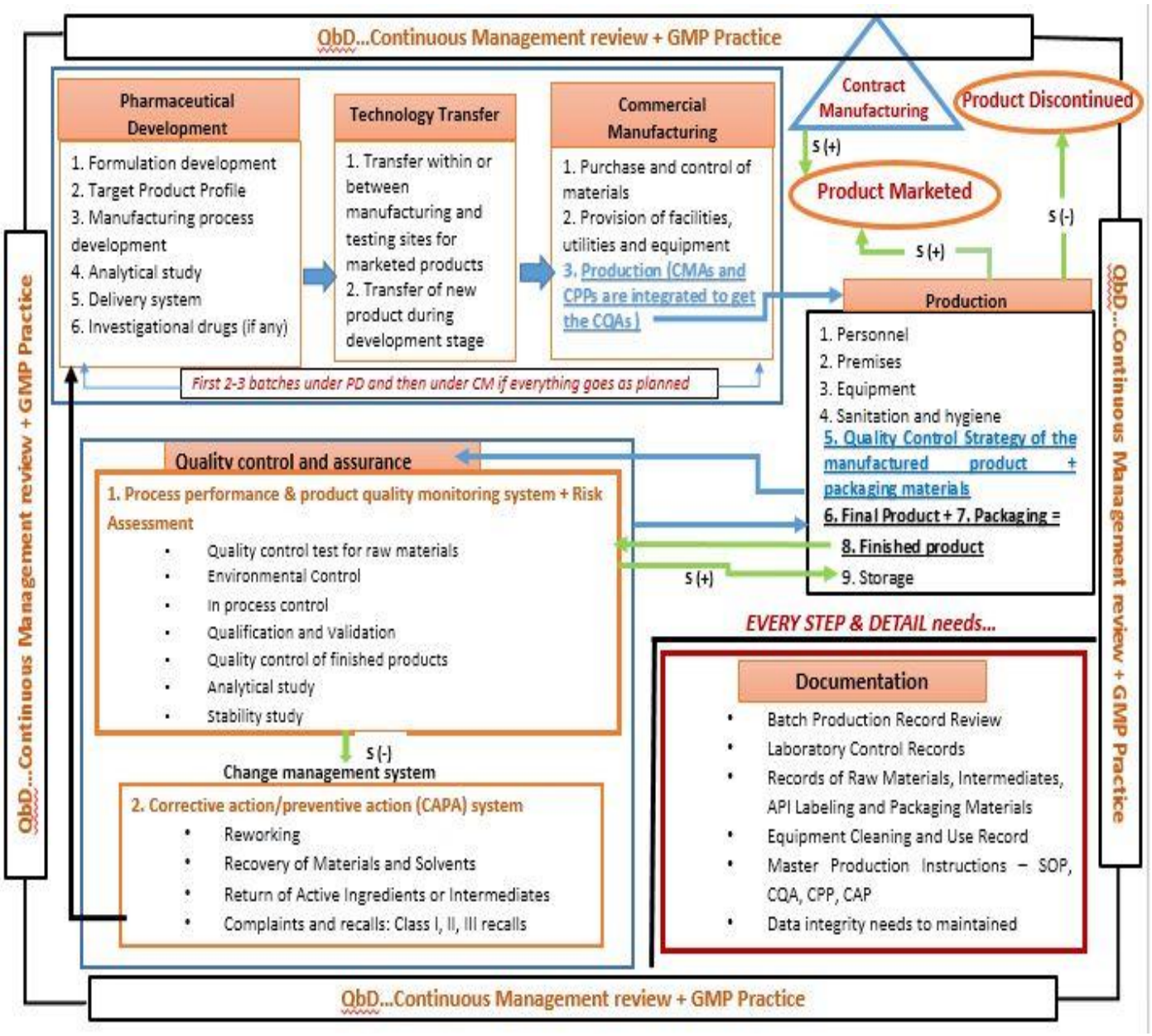


Figure 5: A Schematic Model showing the Manufacturing of a Pharmaceutical Product

Chapter 8. Recommendations for Future Work

Although the holistic and systematic approach of QbD was relatively new to the pharmaceutical industry at the beginning of the 21st century, elements of QbD have already been found to be incorporated across the industry globally long before then. Whether one is manufacturing the products or managing outsourced services, this comprehensive report will help make sure that all facilities are operating in compliance with the regulatory principles, and most of all, your own high standards.

However, the three main areas of concern include:

- Adequate controls
- Staff competence
- Adequate root cause analysis

These issues are often the result of insufficiently controlled processes, poor documentation practices, lack of quality oversight or professional ignorance leading to a failure in quality product.

Future work can be recommended to explore whether the different pharmaceutical companies in Bangladesh have incorporated QbD across the industry.

Appendix

Glossary

Accuracy: The accuracy of an analytical procedure expresses the closeness between the expected value and the value found. This is sometimes entitled trueness.

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Authorized person: The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with results produced by a reference or traceable standard over an appropriate range of measurements.

Capability of a Process: Ability of a process to realize a product that will fulfill the requirements of that product. The concept of process capability can also be defined in statistical terms.

The Validation Master Plan (VMP): It is a quality management system document, a controlled document, approved by senior laboratory management and regularly reviewed.

Change Management: A systematic approach to proposing, evaluating, approving, implementing, and reviewing changes.

Cleaning Validation Master Plan: A cleaning validation master plan is a document containing all the strategies, testing and groupings employed at a manufacturing site to demonstrate new and continued verification of a firm's assurance that critical process cleaning is conducted, verified and documented. This document should also contain rationale for testing acceptance criteria as well as required development and documentation.

Cleaning Validation Protocol: A cleaning validation protocol contains all the justification and instructions to demonstrate how a delineated piece or set of equipment will be shown to meet a client's acceptance criteria for cleanliness in critical process equipment. This cleaning validation protocol will help drive a manufacturing firm to gather the necessary data to

demonstrate a cleaning process in control without the possibility of cross contaminating the next manufacturing run in that same equipment.

Computer System: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Computerized System: A process or operation integrated with a computer system.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

Continual Improvement: Recurring activity to increase the ability to fulfill requirements.

Control Strategy: A planned set of controls, derived from current product and process understanding that assures process performance and product quality.

Corrective Action: Action to eliminate the cause of a detected nonconformity or other undesirable situation.

Critical Quality Attributes (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8).

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8).

Critical Material Attribute (CMA): A physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material.

Cross-contamination: Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Dispensing area: The dispensary area is an area that permits a transition from "dirt" bulk storage containers to clean containers for the dispensed materials intended for manufacture.

Excipients: Excipients are defined as the substance present in the finished product other than the active ingredient.

Formal stability studies: Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of an API or the shelf life of a FPP.

GSM: GSM means 'Gram per square meter' that is the weight of materials in gram per one square meter. By this we can compare the materials in unit area which is heavier and which is lighter.

Innovation: The introduction of new technologies or methodologies.

In-process control: Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in process control.

Installation qualification (IQ): establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered.

Intermediate precision: Intermediate precision expresses within-laboratories variations. For example different days, different analysts, different equipment, etc.

Knowledge Management: Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components.

Limit of detection (LOD): LOD is the analytical procedure that calculates the minimum level at which a compound can be detected, using analyte solutions of decreasing concentration. LOD is generally defined as 3 times the noise level.

Limit of quantitation (LOQ): it is the analytical procedure that estimates the minimum level at which a compound can be quantitated, using analyte solutions of decreasing concentration. LOQ is generally defined as 10 times the noise level.

Linearity: The linearity of an analytical procedure is its ability to obtain test result which is directly proportional to the concentration of analyte in sample.

Manufacture: All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

Manufacturer: A company that carries out operations such as production, packaging, repackaging, labeling and relabeling of pharmaceuticals.

Marketing authorization (product license, registration certificate): A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeia or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.

Operational qualification (OQ): establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements.

Packaging material: Packaging material is any material employed in the packaging of medicinal products, excluding any outer packaging used for transportation or shipment.

Performance Indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process, or system, also known as performance metrics in some regions.

Performance qualification (PQ): establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

Pharmaceutical product: Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality.

Precision: The precision of an analytical method is the closeness of agreement among individuals test result of the same homogeneous sample under prescribed conditions where the method is applied repeatedly. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

Preventive Action: Action to eliminate the cause of a potential nonconformity or other undesirable potential situation.

Process validation protocol: a document stating how validation will be conducted, including test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.

Process validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.

Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabeling, to completion of the finished product.

Product Realization: Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorization) and internal customers' requirements.

Qualification: Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification. Qualification is the process of assurance that the specific system, premises, equipment and other facilities are able to reach the predetermined criteria to confirm its function that meets it purpose.

Quality Manual: Document specifying the quality management system of an organization.

Quality Objectives: A means to translate the quality policy and strategies into measurable activities.

Quality Planning: Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfill the quality objectives.

Quality Policy: Overall intentions and direction of an organization related to quality as formally expressed by senior management.

Quality Risk Management: A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality: The degree to which a set of inherent properties of a product, system, or process fulfils requirements.

Quarantine: The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

Range: It is the interval between the upper and lower concentration of analyte in the sample.

Repeatability: Repeatability expresses the precision under the same operating conditions over a short interval of time.

Recovery: The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.

Reprocessing: Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/ lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications.

Reproducibility: Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Reworking: Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Specification: A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Specificity: Specificity is the analytical procedure that ability to assess the analyte in presence of component which may expected to present.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. **Stress testing – forced degradation (FPP):** Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photo stability testing and compatibility testing on APIs with each other in FDCs and API(s) with excipients during formulation development.

Stress testing– forced degradation (API): Studies undertaken to elucidate the intrinsic stability of the API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Verification: confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

Validation: Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification). It may be defined as a means to prove that an equipment or process actually performs as per design or requirement.

References

USP.(2007). Retrieved from http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/chapter3.pdf

(FDA U.S. Food & Drug administration).Retrieved from http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm

Agnihotri, A., Kaur, S., Kumar, J., & Chahal, R. (2013). Performance qualification: Critical to validation. Asian J Transfus Sci, 7(1), 4-5. doi:10.4103/0973-6247.106711

Analytical instrument qualification. Retrieved from https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c1058.pdf

Assuring the quality of medicines. (2010). Retrieved from http://apps.who.int/medicinedocs/documents/s19964en/s19964en.pdf

Blessy M, R. D. P., Prajesh N. Prajapati, Y.K. Agrawal. (2013). Development of forced degradation and stability indicating studies of drugs—A review. Journal of Pharmaceutical Analysis.

BRÜMMER, D. H. (2011). How to approach a forced degradation study. LIFE SCIENCE(31).

Current good manufacturing practice guidelines for drugs. (1999).

Dr. Christian Gausepohl, P. M. In-process control.

Guidance for Industry -Bioanalytical Method Validation. (2001). Retrieved from http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf

Guidance for Industry -Bioanalytical Method Validation (2013). Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf

Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. (2001).

Guidance for IndustryQuality Systems Approach to Pharmaceutical CGMP Regulations. (2006). Retrieved from http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf

Guide to inspections of pharmaceutical quality control laboratories. (26 September 2016). Retrieved from http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074918.htm

Guidelines on packaging for pharmaceutical products. Retrieved from http://apps.who.int/medicinedocs/documents/s19638en/s19638en.pdf

Herbert A.Lieberman, L. L., Josep B.Schwartz. Pharmaceutical dosage forms (2 ed. Vol. 3): MARCEL DEKKER, INC.

International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (1999). Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf

Kishore Kumar Hotha, S. P. K. R., V. Kishore Raju , L. K. Ravindranath. (2013). Forced degradation studies: Practical approache-overview of regulatory guidance and literature for the drug product and drug substances.

Kommanaboyina, B. (1999). University of Rhode Islan. Retrieved from http://digitalcommons.uri.edu/cgi/viewcontent.cgi?article=1261&context=theses

L. Nandhakumar, G. D., S. Rameshkumar andS. Chandrasekaran. (2011). An overview of pharmaceutical validation: Quality assurance view point. International journal of research in pharmacy and chemistry.

Leolevi, G. C. W., L.I.Pugsley,. (1964). Quality Control of Pharmaceuticals. 91.

M. S. Charde, M. M. S., A. S. Welankiwar and Jitendra K. (2013). Development of analytical and stability Testing method for Vitamin-A palmitate formulation. International Journal of Pharmaceutical Chemistry. doi:10.7439/ijpc

Maninderjit Kaur, G. K., Harpreet Kaur and Saurav Sharma. (2013). Overview on stability studies. International journal of pharmaceutical, chemical and biological sciences.

pharmaceutical legislation and regulation

pharmaceutical product recall guidlines. (2016). Retrieved from https://www.drugoffice.gov.hk/eps/do/en/doc/guidelines_forms/Pharmaceutical_Products_Recall_Guidelines.pdf

pharmaceuticals product recall guidlines (2016).

Pranshu Tangri, P. M., Shaffi, Abhay ML Verma, Lakshmayya. (2014). In process quality control: A review. International Journal of Industrial Pharmacy and Bio Sciences.

Qualification of Excipients for Use in Pharmaceuticals. (2008). Retrieved from http://ipecamericas.org/sites/default/files/ExcipientQualificationGuide.pdf

Quality assurance of pharmaceuticals 2.

Quality assurance of pharmaceuticals : a compendium of guidelines and related materials. (2006). (Vol. 2).

Quality Control of Raw Materials (APIs and Excipients). Retrieved from http://www.gmp-compliance.org/daten/seminarpdf/ECA-Quality-Control-Raw-Materials.pdf

Quality control procedure in pharmaceutical industry. (2009). Retrieved from http://thepharmacistpharma.blogspot.com/2009/03/quality-control-procedure-in.html

Ravichandran V, S. S., Sundram K. M. AND Harish Rajak. (2010). Validation of analytical methods – strategies & importance. International Journal of Pharmacy and Pharmaceutical Sciences, 2(0975-1491).

Robert A.Nash, A. H. W. (2003). Pharmaceutical process validation (Vol. 129): Marcel Dekka, INK.

Sanjay Bajaj, D. S. a. N. S. (2012). Stability Testing of Pharmaceutical Products. Journal of Applied Pharmaceutical Science.

Trivikram Rawat, I. P. P. (2015). Forced degradation studies for Drug Substances and Drug Products- Scientific and Regulatory. journal Of pharmaceutical science and research.

WHO good practices for pharmaceutical quality control laboratories. (2009). Retrieved from http://pharmalytik.com/images/stories/PDF/GPCL-rev_QAS09_296_01052009.pdf

Y, H. (2010). Pharmaceutical product quality control and good manufacturing practices. 1-16.