

Basic Concepts of Quality Assurance and Quality Control

By: Gargi Nanda
Nikita Macwan

Definitions

- Quality Assurance:

According to WHO, quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. With regard to pharmaceuticals, quality assurance can be divided into major areas: development, quality control, production, distribution, and inspections.

ISO 9000 defines as "part of quality management focused on providing confidence that quality requirements will be fulfilled"

Definitions

- Quality Control:

ISO 9000 defines quality control as "A part of quality management focused on fulfilling quality requirements".

It is that part of GMP concerned with sampling, specification & testing, documentation & release procedures which ensure that the necessary & relevant tests are performed & the product is released for use only after ascertaining it's quality.

Difference between QA and QC

Definition

- QA is a set of activities for ensuring quality in the processes by which products are developed.
- QA is a managerial tool
- QC is a set of activities for ensuring quality in products. The activities focus on identifying defects in the actual products produced.
- QC is a corrective tool

Difference between QA and QC (Contd.)

What are its goals and on what does it focus?

- QA aims to prevent defects with a focus on the process used to make the product. It is a proactive quality process.
- The goal of QA is to improve development and test processes so that defects do not arise when the product is being developed.
- QC aims to identify (and correct) defects in the finished product. Quality control, therefore, is a reactive process.
- The goal of QC is to identify defects after a product is developed and before it's released.

Difference between QA and QC (Contd.)

What and how does it work?

- Prevention of quality problems through planned and systematic activities including documentation.
- Establish a good quality management system and the assessment of its adequacy. Periodic conformance audits of the operations of the system.
- The activities or techniques used to achieve and maintain the product quality, process and service.
- Finding & eliminating sources of quality problems through tools & equipment so that customer's requirements are continually met.

Difference between QA and QC (Contd.)

Whose responsibility is it and what is the example of it?

- Everyone on the team involved in developing the product is responsible for quality assurance.
- Verification is an example of QA.
- Quality control is usually the responsibility of a specific team that tests the product for defects.
- Validation is an example of QC.

Responsibilities of QA

- The QA department is responsible for ensuring that the quality policies adopted by a company are followed.
- It helps to identify and prepare the necessary SOPs relative to the control of quality.
- It must determine that the product meets all the applicable specifications and that it was manufactured according to the internal standards of GMP.
- QA also holds responsible for quality monitoring or audit function.

Responsibilities of QA (Contd.)

- QA functions to assess operations continually and to advise and guide them towards full compliance with all applicable internal and external regulations.

Responsibilities of QC

- QC is responsible for the day-to-day control of quality within the company.
- This department is responsible for analytical testing of incoming raw materials and inspection of packaging components, including labelling.
- They conduct in-process testing when required, perform environmental monitoring, and inspect operations for compliance.
- They also conduct the required tests on finished dosage form.

Responsibilities of QC (Contd.)

- QC plays a major role in the selection of qualified vendors from whom raw materials are purchased. Testing of representative samples is required, and in many cases, an audit of vendor's operations is necessary to determine their suitability and degree of compliance with GMPs prior to their being approved.
- The environmental areas for manufacturing of various dosage forms are tested and inspected by QC department.

Sources of Quality Variation

Because of the increasing complexity of modern pharmaceutical manufacture arising from a variety of unique drugs and dosage forms, complex ethical, legal, and economic responsibilities have been placed on those concerned with the manufacture of modern pharmaceuticals. An awareness of these factors is the responsibility of all those involved in the development, manufacture, control, and marketing of quality products.

Sources of Quality Variation (Contd.)

Following variables may affect ultimate quality of product

- Raw material
- In process variations
- Packaging material
- Labeling
- Finish product
- Manual Error

Control of Quality Variation

1. Raw material control

- Good raw material specifications must be written in precise terminology, must be complete, must provide specific details of test methods, type of instruments, and manner of sampling must be properly identified.
- Each raw material is sampled according to standard sampling procedures and is sent to the quality control laboratory for testing according to written procedures. If acceptable, it is moved to the release storage area, after being properly stickered to indicate the item no., material name, lot no., release date, reassay date and sign of QA inspector.

TABLE 27-1. Raw Material Quality Assurance Monograph

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- A. (Raw Material Name)
1. Structural formula, molecular weight
 2. Chemical name(s)
 3. Item number
 4. Date of issue
 5. Date of superseded, if any, or new material
 6. Signature of writer
 7. Signature of approval
- B. Samples
1. Safety requirement
 2. Sample plan and procedure
 3. Sample size and sample container to be used
 4. Preservation sample required
- C. Retest Program
1. Retesting schedule
 2. Reanalysis to be performed to assure identity, strength, quality, and purity
- D. Specifications (wherever applicable)
1. Description
 2. Solubility
 3. Identity
 - a. Specific chemical tests such as related alkaloids, organic nitrogen basis, acid moiety, or inorganic salt tests; sulfate, chloride, phosphate, sodium, and potassium tests; or other spot organic and inorganic chemical tests as needed.
 - b. Infrared absorption
 - c. Ultraviolet absorption
 - d. Melting range
 - e. Congealing point
 - f. Boiling point or range
 - g. Thin-layer, paper, liquid, or gas chromatography
 4. Purity and quality
 - a. General completeness of solutions, pH, specific rotation, nonvolatile residue, ash, acid-insoluble ash, residue on ignition, loss on drying, water content, heavy metals, arsenic, lead, mercury, selenium, sulfate, chloride, carbonates, acid value, iodine value, saponification value.
 - b. Special quality tests, particle size, crystallinity characteristics, and polymorphic forms
 - c. Special purity tests, ferric in ferrous salts, peroxides and aldehydes in ether and related degradation products
 5. Assay, calculated either on anhydrous or hydrous basis
 6. Microbial limits, especially for raw materials from natural sources
- E. Test Procedures
1. Compendial, USP, or NF references
 2. Noncompendial, detailed analytical procedure, weights; dilutions; extractions; normality; reagents; instrumentation used and procedure, if any; calculations
- F. Approved Suppliers
1. List of prime suppliers and other approved alternative suppliers, if any
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1. Raw Material Control (Contd.)

- QA personnel should keep preservation samples of active raw materials that consists of atleast twice the necessary quantity to perform all tests required, to determine whether the material meets the established specifications. These preservation samples should be retained for atleast 7 years. Approved material should be rotated so that the oldest stock is used first. Raw materials may be classified into 2 groups:
 - Active or therapeutic
 - Inactive or inert

2. In-process Items Control

- Conformance to compendial standards as the sole basis for judging the quality of a final dosage form can be grossly misleading. As the final dosage forms are produced in millions of units, the no. Of units assayed at the end is not likely to be representative of more than a small fraction of the actual production.
- The FDA-CGMP regulations emphasize environmental factors to minimize cross-contamination of products and errors, however, they do little to minimize within-batch and batch-to-batch variation. Therefore, it is important function of the IPQA program to ensure that the final products have uniform purity and quality.

2. In-Process Items Control (Contd.)

There are some critical steps to be followed in this:

- QA before start-up:
 - Environmental and microbiologic control and sanitation
 - Manufacturing Working Formula Procedures
 - Raw Materials
 - Manufacturing Equipment
- QA at start-up:
 - Raw Material Processing
 - Compounding
 - Packaging Materials Control
 - Labels Control
 - Finished Product Control

TABLE 27-5. Quality Assurance Operating Procedure

Page	No.
Date	Supersedes
	NEW
Written by	Checked by

Sanitation Control—Pest Control

*Certox: Insecticide**Type of action*

Kills on contact

*Formula**Approximate %*

Petroleum distillates	71.8%
Technical piperonyl butoxide*	12.0
Pyrethrine	1.2
Inert ingredients	15.0

Dilution

Dilute 1 gallon of concentrate with 4 gallons of water.

Time interval

To be used once weekly after working hours on Friday evenings.

Area designation

Floor and drains

Equipment

Spray unit for Certox
Certox concentrate
Safety equipment

Removal of waste materials

Removal of waste materials remaining in the spray units after exterminating shall be the responsibility of the exterminator.

Effectiveness inspection

It will be the responsibility of the quality assurance department to perform routine area checks to ascertain the effectiveness of the frequency of spraying.

It will be the responsibility of the area supervisor, however, to take necessary action immediately upon seeing any infestation.

Special restrictions and cautions

1. Foods should be removed or covered during treatment.
2. Do not store or use near heat or open flame.
3. Apply only as designated on area designation assignments.

Toxicity in humans

Severe allergic dermatitis and systemic allergic reactions are possible.

Toxic symptoms

Large amounts may cause nausea, vomiting, dizziness, headache, and other CNS disturbances.

Government status

EPA Registration Number: 1748-110

Since Certox presents no significant toxicity problem, no tolerance data are available.

3. Manufacturing Variation Control

- Monitoring environmental conditions under which products are manufactured/stored
- Monitoring of air and water systems to prevent contamination– Air Handling Units
- Monitoring of personnel
- Feedback and follow-up

Quality Assurance Management Procedure

1. How to write Standard Operating Procedure?

- SOP describes standard SOP format that you can use immediately for your quality procedure.
- SOP has instructions on how to write a formal operating procedure for your systems which your people can follow everyday.

2. All Document-Classifications, Definitions and Approval Matrix

- In this SOP you will find all type of quality and Technical/Master file documents to build up a good quality management system for your manufacturing sites, definition of documents, their classification, approval requirements and retention requirements.
- This procedure has schematic diagrams for your understanding of how different types of documents are prepared and stored in a typical documentation.

3. Quality Documentation Management and Change Control

- This SOP describes how to generate new quality documents or change control of existing documents, review of quality documents, satellite file management, role of document author, approver, document control officer and satellite file administrator.
- In this SOP you will also find numbering systems of different quality documents like audit files, SOP's, forms, manuals, training files, QA agreements, project files etc and their effective archiving system.

4. Documentation Rule for GMP Documents

- This SOP describes the principles to be followed in GMP documents, entry of data and information, signature requirements and correction technique of incorrectly entered data or information.

5. Quality Documentation- Tracking, Control and Distribution

- In this SOP you will find mainly the role of document control officer during the initiation, creation, circulation and approval of new quality related documents.
- It also describes the procedure of modification and review of existing document using a documentation database.
- Management of existing and superseded documents is also a part of this procedure.
- You will see all the forms referred during the instruction are attached at the end of the procedure.

6. Preparation, Maintenance and Change Control of Master Documents

- This SOP particularly focused on the management of master file documents like specifications, control methods, raw materials, finished goods and packaging specification and test reports, formulation, stability files etc required to generate during the product registration in the market.
- This SOP gives instruction on their creation, change control, numbering system, approval requirements and maintenance in a simple master file database.
- You will see all the forms referred during the instruction are attached at the end of the procedure.

7. Deviation Report System

- It is a regulatory requirement to capture all sorts of deviations evolves in your systems in order to maintain the continuous improvement to your processes and systems.
- This SOP describes how to categorize the deviations between production, audit, quality improvements, technical deviations, customer complaints and environmental, health and safety deviations.
- It describes the management responsibilities of initiating deviation, capture data, analysis, investigation, determination of assignable causes, generation of management report and initiatives to be taken on corrective and preventative actions.

8. Example- Checklist for Batch Documentation

- This SOP describes the identification of all documentation relevant to a production process in the form of "Batch Documentation Checklists" and to ensure their collection by completion of the checklists by Authorized Persons.
- This procedure is based on an example of tablet packaging process described in the 'Manufacturing' category.

9. Evaluation of Batch Documentation and Release of Sale

- This procedure describes the process of collection, evaluation and record of batch related document generated during the production of a batch before an authorized person can release the batch for sale.
- This procedure is based on an example of tablet packaging process described in the 'Manufacturing' category.

10. Raw Materials- Laboratory Testing and Documentation

- This SOP describes the procedure for sampling, location, pre-testing, testing and documentation of all raw materials and components subject to test, out of specification results, microbiological tests and release procedure for passed raw materials and components.

11. Finished Goods- Laboratory Testing and Documentation

- This SOP describes the procedure for sampling, location, pre-testing, testing and documentation of all finished products subject to test, reagents and standards to be used for analysis, management of out of specification results, microbiological tests and release procedure for passed finished goods.

Relationship Between QA, QC and GMP



Total Quality Control

- The concept of total quality control refers to the process of striving to produce a perfect product by a series of measures requiring an organised effort at every stage in production.
- Although the responsibility for assuring product quality belongs principally to QA personnel, it involves many departments and disciplines within a company. To be effective, it must be supported by team effort.
- Quality must be built into a drug product during product and process, and it is influenced by the physical plant design, space, ventilation, cleanliness and sanitation during routine production.

Total Quality Control (Contd.)

- In products and process designing, it considers many parameters like:
 - Materials
 - In-process and product control
 - Specification and tests for active ingredients, excipients
 - Specific stability procedures of the product
 - Freedom from microbial contamination and proper storage
 - Containers, packaging and labelling
 - Product protection from moisture, light, volatility, and drug/package interaction

Total Quality Management

- According to ISO, TQM is defined as:
"A management approach of an organisation centred on quality, based on the participation of all its members and aiming at long term success through customer satisfaction and benefits to all members of the organisation and society."

Total Quality Management (Contd.)

- The pharmaceutical industry is a vital segment of health care system which is regulated heavily because; any mistake in product design or production can be severe, even fatal. The poor qualities of drug are not only a health hazard but also a waste of money for both government and individual consumers. So, the maintenance of the quality with continuous improvement is very important for pharmaceutical industries. From this concept Total Quality Management (TQM) was established. The aim of TQM is prevention of defects rather than detection of defects. So TQM is very important for pharmaceutical industries to produce the better product and ensure the maximum safety of healthcare system and also protect waste of money for both government & individual consumers.

Total Quality Management (Contd.)

- Total Quality Management consists of organization-wide efforts to install and make permanent a climate in which an organization continuously improves its ability to deliver high-quality products and services to customers. While there is no widely agreed-upon approach, TQM efforts typically draw heavily on the previously developed tools and techniques of quality control.
- The production of quality pharmaceutical products requires embracing the principles of TQM.

Total Quality Management (Contd.)

- Additionally, TQM will serve to improve productivity and customer satisfaction.
- The concept of TQM requires the total commitment of senior level management and supervision of all departments, operators, suppliers, and costumers.
- It continually strives for process improvement that begins with product development and only concludes when feedback and follow-up have been completed.

Activities in TQM

TQM is the foundation for activities, which include:

- Commitment by senior management and all employees
- Meeting customer requirements
- Reducing development cycle times
- Just in time/demand flow manufacturing
- Improvement teams
- Reducing product and service costs
- Systems to facilitate improvement
- Line management ownership
- Employee involvement and empowerment
- Recognition and celebration
- Challenging quantified goals and benchmarking
- Focus on processes / improvement plans
- Specific incorporation in strategic planning

Functions of TQM

- Product quality criteria are established, and detailed specifications are written. Meticulous, written procedures must be prepared for production and control. Raw material must be characterised and then purchased from reputable, approved suppliers.
- Facilities must be designed, constructed, and controlled to provide the proper stable environment for protecting the integrity of products. Equipments must be selected that is efficient and can be cleaned readily and sanitised.

Functions of TQM (Contd.)

- Personnel must be trained properly. The directions they use must be in writing, approved by responsible individuals.
- Distribution departments are responsible for controlling the shipping and handling of products, using inventory-control systems.
- The marketing department must be sensitive to the costumers' needs and be responsive to complaints.

Functions of TQM (Contd.)

- QA is ever present and gives approval only after assessing and being assured that the entire production process has been completed satisfactorily and that all the aspects of the GMPs have been satisfied.

Advantages of TQM

- Improves reputation- faults and problems are spotted and sorted quicker.
- Higher employee morale- workers motivated by extra responsibility, team work and involvement in decisions of TQM
- Lower cost- decrease waste as fewer defective products and no need for separate.
- Quality control inspector

Disadvantages of TQM

- Initial introduction cost.
- Benefits may not be seen for several years.
- Workers may be resistant to change

Major Keywords of Quality Assurance



Calibration

Validation

Qualification

Calibration

- Calibration is defined as operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties (of the calibrated instrument or secondary standard) and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication.

Validation

- Validation is a process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages. In Pharma Industry it is very important apart from final testing and compliance of product with standard that the process adapted to produce itself must assure that process will consistently produce the expected results.

Validation (Contd.)

Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

- Equipment validation
- Facilities validation
- HVAC system validation
- Cleaning validation
- Process Validation
- Analytical method validation
- Computer system validation
- Packaging validation
- Cold chain validation

Types of Validation

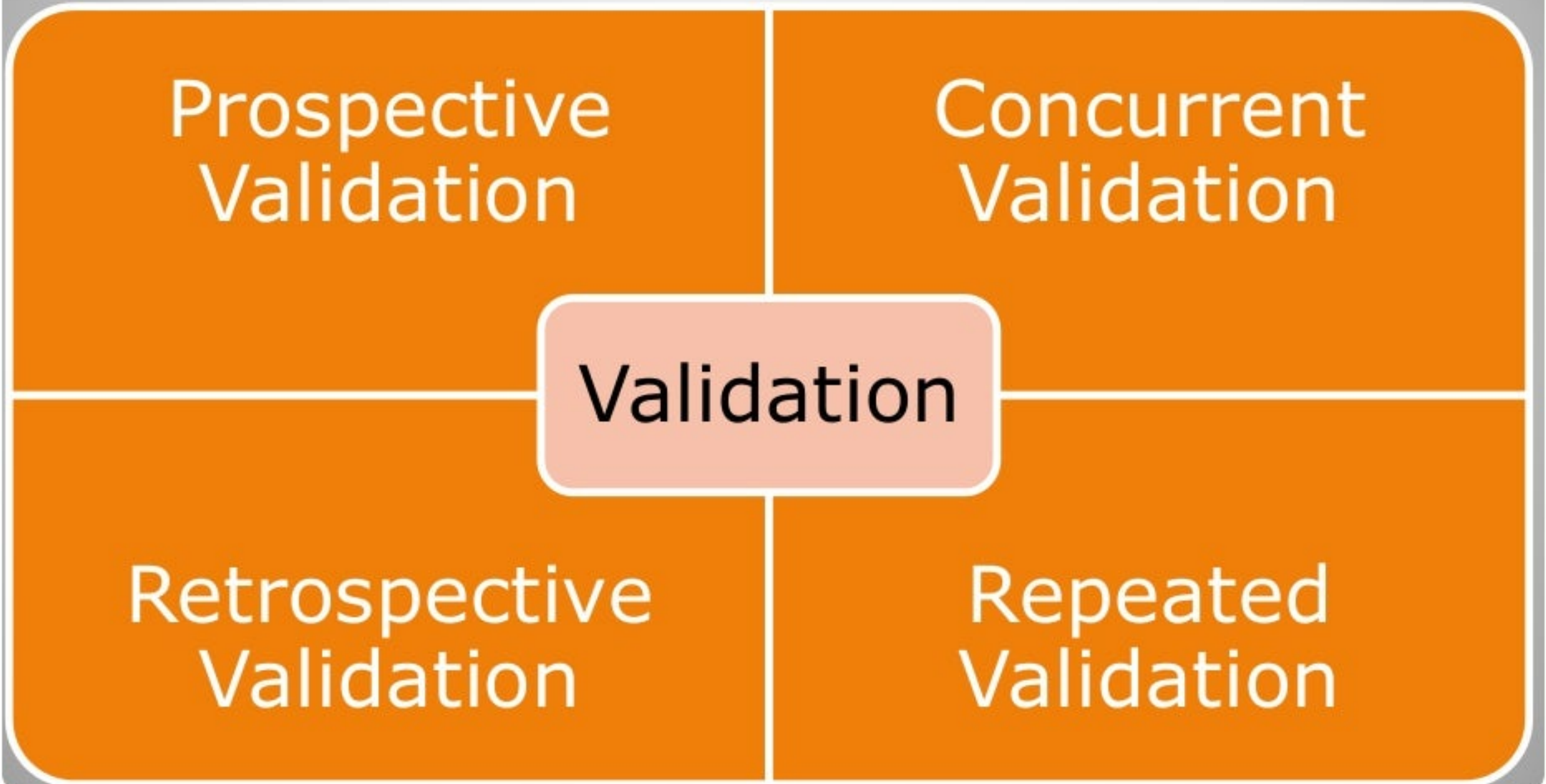
Prospective
Validation

Concurrent
Validation

Validation

Retrospective
Validation

Repeated
Validation



1. Prospective Validation

- Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps: these are then evaluated on the basis of past experience to determine whether they might lead to critical situations.
- Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the production scale, e.g. in the preparation of injectable products.

2. Concurrent Validation

- Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process.
- Concurrent validation together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

3. Retrospective Validation

- Retrospective validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analysed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.
- Retrospective validation is obviously not a quality assurance measure in itself, and should never be applied to new processes or products.

4. Revalidation or Repeated Validation

- Revalidation is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality.

Qualification

- Qualification is defined as action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Qualification (Contd.)

Qualification includes the following steps:

- Design qualification (DQ)- Demonstrates that the proposed design (or the existing design for an off-the-shelf item) will satisfy all the requirements that are defined and detailed in the User Requirements Specification (URS). Satisfactory execution of the DQ is a mandatory requirement before construction (or procurement) of the new design can be authorised.
- Installation qualification (IQ) – Demonstrates that the process or equipment meets all specifications, is installed correctly, and all required components and documentation needed for continued operation are installed and in place.

Qualification (Contd.)

- Operational qualification (OQ) – Demonstrates that all facets of the process or equipment are operating correctly.
- Performance qualification (PQ) – Demonstrates that the process or equipment performs as intended in a consistent manner over time.

Role of QA in Pharma Industries

1. To establish Quality Audit

- Establish the quality management system to describe how the firm complies CGMPs and operates to maintain a state of control
- Keep current with good industry practices, and applicable to the mission of your operation.

2. To audit compliance to the Quality System

- Audit for compliance to policies and procedures: on paper vs. practice
- Report on the performance of the quality system, including trends, that help decision making for targeted actions

3. To establish procedures and specifications

- Ensure that procedures and specifications are appropriate and followed.
- Ensure that the procedures and specifications of firms under contract are also appropriate and followed, i.e., maintain control and take responsibility for third-party services providers (contract manufacturers, contract laboratories, etc.)

4. To establish manufacturing controls

- Ensure that appropriate manufacturing in-process controls are implemented.
- Ensure in-process controls are performed during manufacturing operations and results are satisfactory

5. To perform laboratory tests

- Perform laboratory testing of components, containers, in-process materials, packaging materials and drug product using validated methods against scientifically-derived, fit-for-purpose specifications
- Approve or reject drug products manufactured, processed, packed, or held under contract by another company, i.e., final product release is not delegated to a contractor
- Perform retests or reexamine approved components, drug product containers and closures after long storage or exposure to adverse conditions.

6. To review and approve or reject

- Review and approve/reject any document that gives work instructions and set requirements such as procedures, protocols, test methods, and specifications—including changes to these documents
- Review and approve/reject reprocessing and rework procedures
- Review and approve/reject production batch records and make the final decision to release a product lot into commerce.

7. To ensure investigation of nonconformance

- Ensure investigation is conducted and root cause is eliminated for production and control record errors, discrepancies, and failure to meet specification, including quality attributes
- Review complaints to determine if it relates to a failure to meet specification, if so investigate and report to FDA if it is serious and unexpected

8. To keep management informed

- Report on product, process and system risks
- Report on outcome of regulatory inspections and ensure responses are complete and managed to verifiable closure

9. To describe responsibilities in writing

- Have a complete and compliant procedure that describes responsibilities
- Follow the procedure

10. To remain independent

- Ensure there is no conflict of interest between regulatory responsibilities and actual daily activities
- Be independent reviewer and approver with respect to manufacturing and process/ product development units

Control and Assurance of Manufacturing Practices

1. Personnel

Important parts for a successful personnel are:

- Proper selection
- Training
- Motivation of Production
- Packaging
- Control

It is essential that the qualified personnel be employed to supervise the formulation, Processing, Sampling, testing, packaging and labelling of the drug product, and that competent staff be placed in charge of the maintenance of machinery, equipment and sanitation.

2. Equipments and Buildings

- The building should provide adequate space for the orderly placement of materials and equipment to minimize any risks of mix-ups or cross-contamination between the drugs, excipients, packaging and labelling from the time the materials are received to the time the products are released.
- The desired characteristics of equipments for producing quality products are numerous, however, the equipment should be of suitable size, accuracy and reproducibility.

3. Control of records

- The records, such as Master Formula and Batch production records, should be prepared and maintained in accordance with established procedures.

4. Control of Production Procedures

- To ensure that products have the intended characteristics of identity, strength, quality, and purity, production and the related in-process quality control procedures should be rigidly followed as required by the master formula record or batch production record.

5. Packaging Control

- A packaging record bearing an identification number is issued to the packaging section. This record specifies the packaging materials to be used, operations to be performed, and the quantity to be packaged.

6. Validation

- Validation of a process is the demonstration that controlling the critical steps of a process results in products of repeatable attributes or causes a reproducible event.

Control and Assurance of Finished Products

- Unless the testing procedures by which the product quality is finally measured are established on an equally sound basis, the entire system may be deficient.
- Product failures causing rejections or recalls after market introduction are serious and can be easily detected and minimized by an effectively administered quality testing program.
- Therefore, the testing of the finished products for compliance with the established standards prior to release of the material for distribution is a critical factor for quality control and assurance.

Summary

- The professional, social and legal responsibilities that rest with the pharmaceutical manufacturers for the assurance of product quality are tremendous. It is only through well-organized, adequately staffed, and accurately performed process and dosage form control that adequate quality assurance can be achieved.
- The manufacturer is in a position to
 - Control the sources of product quality variation
 - Ensure the correct and most appropriate manufacturing and packaging practices
 - Assure that the testing results are in compliance with the standards or specifications
 - Assure product stability

Thank You!!!