Pharmaceutical Quality Management

CHAPTER 1

INTRODUCTION

By:

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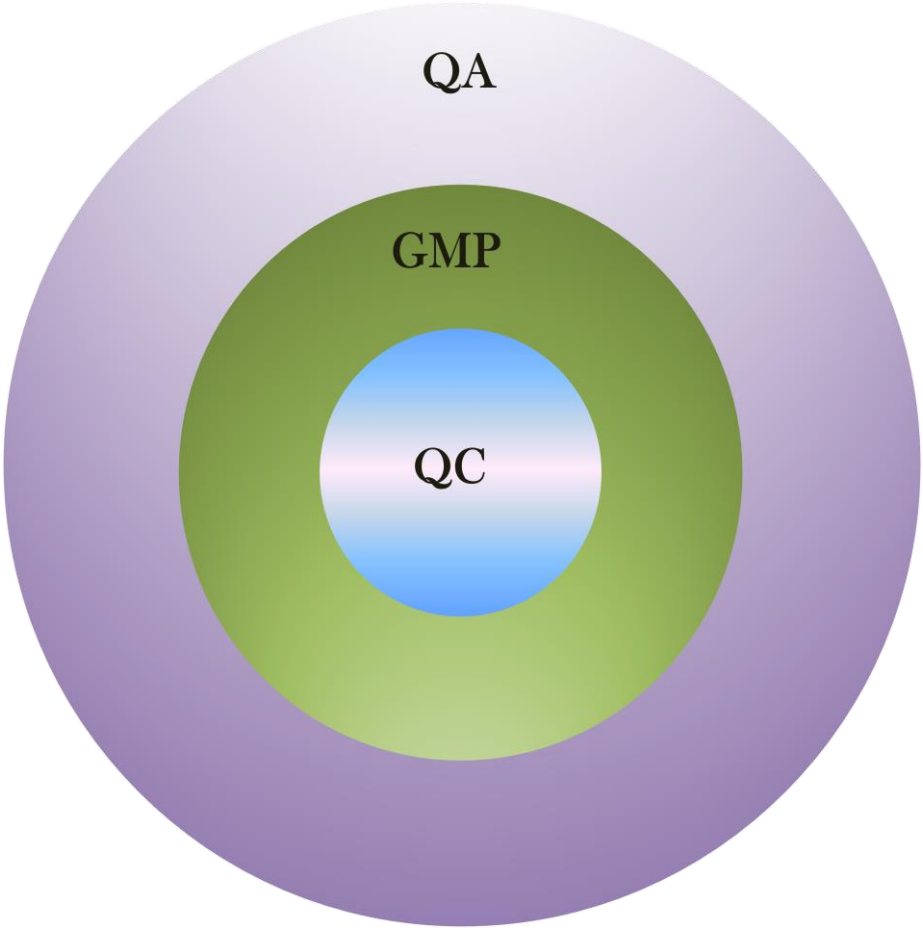
Quality:

- ☐ In manufacturing, a measure of excellence or a state of being free from defects, deficiencies and significant variations. It is brought about by strict and consistent commitment to certain standards that achieve uniformity of a product in order to satisfy specific customer or user requirements.
- ☐ ISO standard defines quality as "*the totality of features and characteristics of a product or service that bears its ability to satisfy stated or implied needs.”*

Structure for Ensuring Quality in Pharmaceutical Industry



Definitions

1) Quality Assurance

- ☐ Quality Assurance is a set of activities for ensuring quality in the processes by which products are developed
- ☐ ***Planned or systematic actions necessary to provide adequate confidence that a product will satisfy the requirements of quality***
- ☐ The maintenance of a desired level of quality in a service or product, especially by means of attention to every stage of the process of delivery or production.
- ☐ Quality Assurance is process oriented and focuses on defect prevention

2) Good Manufacturing Practices (GMPs)

- ☐ Is that part of Quality Assurance that aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use

☐ cGMP

- ☐ GMPs are enforced in the United States by the U.S. Food and Drug Administration (FDA), under Title 21 CFR. The regulations use the phrase "current good manufacturing practices" (cGMP) to describe these guidelines

3) Quality Control

- ☐ *Is that part of GMP concerned with sampling, specifications & 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*
- ☐ Quality Control aims to identify and correct defects in the finished product. It is a reactive process.

4) Total Quality Management (TQM)/Total Product QUALITY(TPQ):

- ☐ The production of quality pharmaceutical products requires embracing the principles of Total Quality Management.
- ☐ ***Its basic principle is one of continually striving for process improvement that begins with product development and only concludes when feedback and follow up have been completed on customer complaints and suggestions.***
- ☐ TQM: will serve to improve productivity and customer satisfaction

5) Good Laboratory Practice

- ☐ Good Laboratory Practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

CONCEPTS

1) Difference between QC and QA

Credit: diffen.com	Quality Assurance	Quality Control
Definition	QA is a set of activities for ensuring **quality in the processes** by which products are developed.	QC is a set of activities for ensuring **quality in products,** focused on identifying defects in the products produced.
Focus	QA is a **proactive quality process** which aims to prevent defects in the process used to make the product.	QC is a **reactive process** to identify (and correct) defects in the finished product.
Goal	To **improve development and test processes** to reduce defects when the product is being developed.	To **identify defects** in a developed product before it's released.
How	QA establishes good quality management systems and the assessment of its adequacy and conformance audits of the system.	QC find & eliminates sources of quality problems through tools & equipment so that customer's requirements are continually met.
What	Prevention of quality problems through planned and systematic activities including documentation.	The activities or techniques used to achieve and maintain the product quality, process and service.
Responsibility	Everyone on the team involved in developing the product is responsible for quality assurance.	Quality control is usually the responsibility of a specific team that tests the product for defects.
Example	Verification is an example of QA	Validation/Software Testing is an example of QC
Techniques	Statistical Tools & Techniques can be applied in both QA & QC. When they are applied to processes (process inputs & operational parameters), they are called Statistical Process Control (SPC); & it becomes the part of QA.	When statistical tools & techniques are applied to finished products (process outputs), they are called as Statistical Quality Control (SQC) & comes under QC
As a Tool	QA is a managerial tool	QC is a corrective tool
Orientation	QA is process oriented	QC is product oriented

2) *QC FUNCTION AND RESPONSIBILITIES*

- ☐ QC is responsible for day to day control of quality within a company.
- ☐ This department s staffed with scientist and technicians responsible for the sampling and analytical testing of incoming raw materials and inspection of packaging components, including labeling.
- ☐ They conduct in process testing when required, perform environmental monitoring, and inspect operation for compliance finally the conduct the required test on final dosage form.
- ☐ QC is also responsible for monitoring product quality through distribution including testing of product complaint samples, evaluating product stability etc.
- ☐ Many companies have the heads of QC and production report to a common higher level of management, but with a QC being independent of production.
- ☐ The equipment and instrumentation in the laboratory must be suitable for performing the testing in an accurate and efficient manner.
- ☐ Detailed specification must be available, as well as validity test methods against which products and raw materials will be evaluated.
- ☐ The testing and acceptance of only high quality raw-materials is essential for the production of uniformly acceptable products.
- ☐ QC plays a major role in the selection and qualification of vendors from whom these materials are purchased.
- ☐ Testing of representative samples is required, and in many cases, an audit of vendor's operation is necessary to determine their stability and degree of compliance with GMPs and other relevant standards prior to being their approved. The vendor audit frequently is organized by QA with technical support from research QC, and manufacturing.

- ☐ QC is responsible, as a part of its testing and inspection functions, for monitoring the environmental conditions under which products are manufactured and/or held.
- ☐ Parenteral and ophthalmic products must be produced in a controlled environment that is designed to ensure their sterility.
- ☐ Major element for monitoring the non-sterile product manufacturing, such as, tablets, liquids, and capsules.
- ☐ Control of packaging components, those that come into direct contact with a product, is required. These materials must be inspected and tested against rigid specification to ensure that they meet predetermined functional standards.

3) Responsibilities of QA

- ☐ QA department with any organization because of its responsibilities normally will report to a relatively high level administrator within a company, depending on its size.
- ☐ QA will be independent of the economic issues associated with manufacturing and distribution.
- ☐ QA department is responsible for ensuring the quality policies adopted by a company are followed.
- ☐ QA serves as the primary contact with regulatory agencies and is the final authority for product acceptance or rejection.
- ☐ QA plays an important role in the identification and preparation of necessary policies and SOPs relative to the control of quality.
- ☐ A second major responsibility of QA department is the quality monitoring or audit function.
- ☐ QA functions not only determine that the procedures are current and correct and the properly trained operators are following them.

- ☐ Senior management of a company looks to the QA function to assess operation continually and to advise and guide them towards full compliance with all applicable internal and external regulations.
- ☐ QA department now tend to work as a team member with the other functional groups.

4) Good Manufacturing Practices (GMPs)

- ☐ The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world.
- ☐ The European Union's GMP (EU-GMP) enforces similar requirements to WHO GMP, as does the FDA's version in the US.
- ☐ Similar GMPs are used in other countries, with Australia, Canada, Japan, Saudi Arabia, Singapore, Philippines, Vietnam and others having highly developed/sophisticated GMP requirements.
- ☐ In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in what is commonly referred to as "The Orange Guide", which is named so because of the color of its cover; it is officially known as *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*
- ☐ Since the 1999 publication of *GMPs for Active Pharmaceutical Ingredients*, by the International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation (ICH), GMPs now apply in those countries and trade groupings that are signatories to ICH (the EU, Japan and the U.S.), and applies in other countries (e.g., Australia, Canada, Singapore) which adopt ICH guidelines for the manufacture and testing of active raw materials.

5) Total Quality Management (TQM)

- ☐ The production of quality pharmaceutical products requires embracing the principles of Total Quality Management.

- ☐ Its basic principle is one of continually striving for process improvement that begins with product development and only concludes when feedback and follow up have been completed on customer complaints and suggestions.
- ☐ TQM: will serve to improve productivity and customer satisfaction
- ☐ The concept of TQM requires total commitment of senior level management and supervision of all departments, operators, suppliers and customers.
- ☐ The quality function is a part of team composed of:
- ☐ Research, production, marketing sales, and customer service
- ☐ In many firm QA DEPARTMENT has the responsibility to organize and implement programs with these objectives in mind.

Good Laboratory Practice (GLP)

OECD

- The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 29 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to co-ordinate and harmonize policies, discuss issues of mutual concern, and work together to respond to international problems.

- The GLP regulations for non-clinical laboratory studies published by the US Food and Drug Administration in 1976 provided the basis for the work of the Expert Group, which was led by the United States and comprised experts from the following countries and organisations: Australia, Austria, Belgium, Canada, Denmark, France, the Federal Republic of Germany, Greece, Italy, Japan, the Netherlands, New Zealand, Norway, Sweden, Switzerland, the United Kingdom, the United States, the Commission of the European Communities, the World Health Organisation and the International Organisation for Standardisation.

Definitions of Terms

- **1. Good Laboratory Practice (GLP)** is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.
- **2. Standard Operating Procedures (SOPs)** means documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines.

GOOD LABORATORY PRACTICES PRINCIPLES

- 1. Test Facility Organisation and Personnel.
- 2. Quality Assurance Programme(QAP).
- 3. Facilities.
- 4. Apparatus, Material and Reagents.
- 5. Test systems.
- 6. Test and Reference Substances.

- 7. Standard Operating Procedures(SOP).
- 8. Performance of The Study.
- 9. Reporting of Study Results.
- 10. Storage and Retention of Records and materials.

1. Test Facility Organization and Personnel

Study Personnel Responsibilities

• Should have the Knowledge of the GLP principles.

• Access to the study plan and appropriate SOP's.

• Comply with the instructions of the SOP's.

• Record raw data.

• Study personnel are responsible for the quality of their data.

• Exercise health precautions to minimize risk.

• Ensure the integrity of the study.

2. Quality Assurance Program

Responsibilities of the QA Personnel

• Access to the updated study plans and SOP's.

• Documented verification of the compliance of study plan to the GLP principles.

• Inspections to determine compliance of the study with GLP principles.

• Three types of inspection. – Study-based inspections. – Facility-based inspections. – Process-based inspections.

• Inspection of the final reports for accurate and full description.

• Report the inspection results to the management.

• Statements

3. Facilities

• Suitable size, construction and location.

• Adequate degree of separation of the different activities.

• Isolation of test systems and individual projects to protect from biological hazards.

• Suitable rooms for the diagnosis, treatment and control of diseases.

• Storage rooms.

4. Apparatus, Materials and Reagents

• Apparatus of appropriate design and adequate capacity.

• Documented Inspection, cleaning, maintenance and calibration of apparatus.

• Apparatus and materials not to interfere with the test systems.

• Chemicals, reagent and solutions should be labeled to indicate identity, expiry and specific storage instructions.

5. Test Systems

• Physical and chemical test systems.

• Biological test systems.

• Records of source, date of arrival, and arrival conditions of test systems.

• Proper identification of test systems in their container or when removed.

• Cleaning and sanitization of containers.

• Pest control agents to be documented.

6. Test and Reference Items

• Receipt, handling, sampling and storage

• Characterization.

• Known stability of test and reference items.

• Stability of the test item in its vehicle (container).

• Experiments to determine stability in tank mixers used in the field studies.

• Samples for analytical purposes for each batch.

7. Standard Operating Procedures (SOP)

• Written procedures for a laboratories program.

• They define how to carry out protocol- specified activities.

• Most often written in a chronological listing of action steps.

• They are written to explain how the procedures are suppose to work.

• Routine inspection, cleaning, maintenance, testing and calibration.

• Actions to be taken in response to equipment failure.

• Keeping records, reporting, storage, mixing, and retrieval of data.

• Definition of raw data.

• Analytical methods.

8. Performance of the Study

• Prepare the Study plan.

• Content of the study plan. › Identification of the study. › Records. › Dates. › Reference to test methods. › Information concerning the sponsor and facility.

• Conduct of the study.

9. Reporting of Study Results

• Information on sponsor and test facility.

• Experimental starting and completion dates.

• A Quality Assurance Program Statement.

• Description of materials and test methods.

• Results.

• Storage (samples, reference items, raw data, final reports) etc.

10. Storage and Retention of Records and Materials

The study plan, raw data, samples.

– Inspection data and master schedules.

– SOPs.

– Maintenance and calibration data.

– If any study material is disposed of before expiry the reason to be justified and documented.

– Index of materials retained.

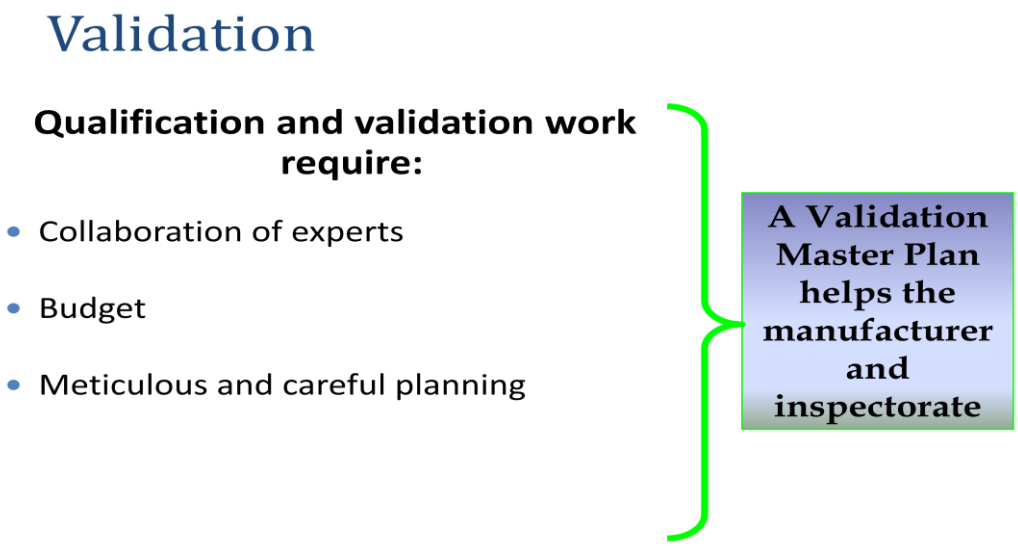
Validation

WHO validation definition

- The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.
- **VALIDATION**: Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics

Qualification or Validation?

- A system must be *qualified* to operate in a *validated* process
- Qualify a system and/or equipment
- Validate a process
- Qualification versus validation, e.g. *qualify* an autoclave, whereas you *validate* a sterilization process



Types/Options of Validation

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Revalidation
5. Change control

1. **Prospective validation:** This is carried out during the development stage. It involves establishing documented evidence that a process, procedure, system, equipment or mechanism used in manufacture does what it purports to do, based on a pre-planned validation protocol.

2. **Concurrent validation:** This is carried out during normal production of products intended for sale. It requires a full understanding of the process, based on prospective work. It involves very close and intensive monitoring of the steps and critical points in at least the first three production-scale batches.

3. **Retrospective validation:** This is the analysis of accumulated results from past production to assess the consistency of a process. It includes trend analysis on test results and a close examination of all recorded process deviations. It is important to analyse 10-25 batches manufactured over a period of 12 months, to provide a statistically significant picture. It is not the preferred method of validation and should be used in exceptional cases only.

4. **4. Revalidation**: This involves a repeat of the process validation, to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

5. **5. Change control**: This is a formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

The Validation Master Plan (VMP)

- A Validation Master Plan (VMP) is a document that summarizes the manufacturer's overall philosophy, intentions and approach to be used for establishing performance adequacy.

- The VMP should present an overview of the entire validation operation, its organizational structure, its content and planning, the core of the VMP being the list/inventory of the items to be validated and the planning schedule.

The Validation Master Plan (VMP) is

- Philosophy
- Content
- Strategy
- Recommendation only
- Cover manufacturer’s validation policy and needs
- Provides information on validation organization
- It should describe:
    - why?
    - what?
    - where?

The VMP helps:

- A VMP helps management: to know what the validation programme involves with respect to time, people and money, and to understand the necessity for the programme.
- A VMP helps leaders and members of the validation team: to know their tasks and responsibilities.
- A VMP helps GMP inspectors to understand the manufacturer's approach to validation and how the validation activities are organized and managed.

Features of VMP

- The VMP identifies which items (products, processes, systems) are subject to validation. It defines the nature and extent of the testing expected and it outlines the test procedures and protocols to be followed to accomplish validation.
- The VMP should be a summary document. It should be brief, concise and clear. It should not repeat information documented elsewhere but refer to existing documents such as policy documents, SOP's and validation protocols/reports. It should include validation of analytical techniques which are to be used in determining the validation status of other processes or systems. All validation activities included in the VMP should be summarized and compiled in a matrix format. Such a matrix should provide an overview and contain all items covered by the VMP that are subject to validation describing the extent of validation required [i.e. IQ, OQ and/or PQ].
- The contents of the VMP should be agreed by top management. Management should thus be aware of the nature and extent of the work required and the resources that may be needed.

Validation Activities in VMP

- The VMP should include every validation activity, e.g. validation of analytical techniques which are to be used in determining the validation status of other processes or systems.
- Revalidation provides the evidence that changes in a process and/or the process environment that have been introduced either intentionally or unintentionally, do not adversely affect process characteristics and product quality.

- There are two basic categories of revalidation : (a) Revalidation in cases of known change (including transfer of processes from one pharmaceutical manufacturer to another or from one site to another), (b) Periodic revalidation carried out at scheduled intervals. The VMP should include the revalidation intervals.
- The VMP should define how new process cycles will be validated.
- Large validation projects, such as water systems, HVAC systems, should have separate VMPs.
- Reasonable unexpected events (worse case) are required to be covered in the VMP e.g:

- power failure
- computer crash and recovery
- filter integrity test failure

Content of Validation

The "Introduction" to the VMP

- Validation policy
- Project scope
- Location and timing (including priorities)
- Validation procedures
- Standards

VMP should state who is responsible for:

- Preparing the VMP
- The protocols and SOPs
- Validation work
- Report and document preparation and control
- Approval/authorisation of validation protocols and reports in all stages of validation process

- Tracking system
- Training needs in support of validation

VMP should contain:

- Cross references to documents
- Specific process considerations
- Specific characteristics briefly outlined
- Validation list (What to validate)
    - premises, systems and equipment
    - processes
    - products
- Descriptions of
    - plant (where to validate)
    - processes
    - products
- Personnel attributes
    - expertise and training
- Key acceptance criteria
- Format for protocols and other documentation
- List of relevant SOPs (How)
- Planning and scheduling (When)
- Location (Where)
- Estimate of staffing requirements (Who)
- A time plan of the project (When)

- Annexes

VMP should contain change control

- Policy and procedure
- Risk assessment
- Authorization
- Failure to properly document changes to the system means invalidation of the process

Changes that require revalidation

- Software changes; Controllers
- Site changes; Operational changes
- Change of source of material
- Change in the process
- Significant equipment change
- Production area changes
- Support system changes

In summary, a VMP should contain at least:

- Validation policy
- Organizational structure
- Summary of facilities, systems, equipment, processes to be validated
- Documentation format for protocols and reports
- Planning and scheduling
- Change control
- Training requirements

Qualification

- Qualification is pre-requisite of validation.
- Pre-requisites of Validation (Facilities, Systems and Equipment)

Design qualification [DQ]:

- Design qualification [DQ]: In this qualification, compliance of design with GMP should be demonstrated. The principles of design should such as to achieve the objectives of GMP with regards to equipment.

Installation qualification [IQ]:

- Installation qualification should be carried out on new or modified facilities, systems and equipment. The following points should be included in the installation qualification. Checking of installation of equipment, piping, service and instrumentation
- Collecting of supplier's operating working instructions and maintenance and their calibration requirement. Verification of material(s) of construction Source of spares and maintenance

Operational qualification [OQ]:

- OQ should follow IQ. OQ should include the following Test(s) developed from the knowledge of the process(s), system(s) and equipment. Defining lower and upper operating limits.
- Completion of OQ will result in finalization of Calibration Operating and cleaning procedure Operator's training Maintance requirements Formal release of the facilities, systems and equipment.

Performance Qualification [PQ]:

- After IQ and OQ have been completed, the next qualification that should be completed is PQ. PQ should include the following Test using production materials, substitutes or simulated products. These can be developed from the knowledge of the process and facilities, system or equipment
- Tests to include conditions(s) with upper and lower limits. It will be useful to discuss briefly process capability design and testing and process qualification.