



The Review Article on Quality Assurance

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ABSTRACT: -

Quality assurance (QA) in pharmaceuticals is a critical aspect of the healthcare industry, ensuring the safety, efficacy, and reliability of medicinal products. This project focuses on the key principles and practices involved in the quality assurance of pharmaceutical products, exploring the systems and procedures that govern quality throughout the drug development and manufacturing process. The study will examine various regulatory frameworks, such as Good Manufacturing Practices (GMP), and how they are implemented to maintain high-quality standards. Additionally, it will discuss the role of quality control, process validation, risk management, and continuous improvement in achieving consistent product quality.

The project aims to highlight the importance of QA in preventing defects, ensuring compliance with regulatory requirements, and safeguarding public health. Through case studies and industry examples, the research will analyze common challenges faced by pharmaceutical companies in implementing robust QA systems and propose solutions to overcome these hurdles. The findings will emphasize the role of modern technologies, such as automation and analytical tools, in enhancing quality assurance practices. By the end of the project, the importance of QA as an integral component of pharmaceutical production will be well understood, demonstrating its impact on global healthcare outcomes.

This project will provide an in-depth understanding of how QA ensures that every pharmaceutical product released to the market meets stringent quality criteria, protecting patient safety and fostering trust in the pharmaceutical industry.

KEYWORDS: -ISO, Quality assurance, Monitoring program, Quality, etc.

INTRODUCTION: -

Naturally, unless those standards are acknowledged by all as being adequate gauges of quality, there is no point in saying that a product fulfills them. So-called National Standards Organizations were founded and given the task of creating precisely these accepted national standards in response to the demand for internationally recognized indicators of performance and quality. These national organizations are numerous now, and there are literally hundreds of goods for which recognized standards have been established.

In reality, the British Standards Institution's well-known "Kite Mark" was first used to protect consumers by certifying that goods had been produced in accordance with the relevant British Standard. The Kite Mark is essentially a method of product certification.

Definitions: -

Quality Control: -

Quality control can be defined as "part of quality management focused on fulfilling quality requirements." While quality assurance relates to how a process is performed or how a product's made, quality control is more the inspection aspect of quality management. An alternate definition is "the operational techniques and activities used to fulfill requirements for quality."

Quality Assurance:

Quality assurance can be defined as "part of quality management focused on providing confidence that quality requirements will be fulfilled." The confidence provided by quality assurance is twofold internally to

management and externally to customers, government agencies, regulators, certifiers, and third parties. An alternate definition is "all the planned and systematic activities implemented within the quality system that can be demonstrated to provide confidence that a product or service will fulfill requirements for quality."

Concept of Quality control and Quality Assurance: -

What is the concept of Quality Control?

Quality control (QC) is a process through which a business seeks to ensure that product quality is maintained or improved. Quality control involves testing units and determining if they are within the specifications for the final product.

What are the concepts of quality assurance?

Quality assurance (QA) is a way of preventing mistakes and defects in manufactured products and avoiding problems when delivering products or services to customers; which ISO 9000 defines as part of quality management focused on providing confidence that quality requirements will be fulfilled.

SCOPES OF QUALITY ASSURANCE: -

- **Setting standards:** - Establishing quality standards and procedures.
- **Creating guidelines:** - Developing guidelines to follow throughout the development process.
- **Conducting measurements:** - Taking measurements as part of the process.

Reviewing and changing workflows: - Improving workflows to enhance the process.

- **Improving processes:** - Improving processes such as design, worker training, document control, management, and process audits.
- **Planning and analysing quality:** - All functional departments play a role in planning for and analysing quality.

Objectives of quality assurance: -

The objectives of QC department in a pharmaceutical industry are to ensure that:

- * There is a day-to-day control maintained over the quality aspects of drug products.
- * Incoming raw materials, in-process goods and finished products are all tested for compliance with predetermined quality specifications.
- * Environmental monitoring is performed to make sure products are manufactured, packed and stored under prescribed conditions.
- * Instruments are calibrated and working as expected.

Good laboratory practice: - (GLP)

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

GLP in quality assurance: -

GLP is the quality system applied to non-clinical safety and environmental studies during the development of new products such as medicines, industrial chemicals and pesticides. GLP gives assurance that study data submitted to government assessors is accurate, valid and of sound integrity.

GMP in quality assurance: -

Good manufacturing practice (GMP): - is a system for ensuring that products are consistently produced and controlled according to quality standards.

What are the 5 main components of GMP?

To simplify this, GMP helps to ensure the consistent quality and safety of products by focusing attention on five key elements, which are often referred to as the 5 P's of GMP—people, premises, processes, products and procedures (or paperwork).

Current Good Manufacturing Practice :(cGMP)

What is cGMP in QA?

"A term that is recognized worldwide for the control and management of manufacturing and quality control testing of foods, pharmaceutical products and medical devices." GMP is also referred to as "cGMP".

What is cGMP in quality assurance?

Quality assurance regulations that ensure the safety, quality, and consistency of products. The U.S. Food and Drug Administration (FDA) enforce cGMP regulations for pharmaceuticals, biotechnology, food, and beverages.

Overviews of ICH Guideline:

- Q1A(R2): stability testing of new drugs and product.
- Q1B: photo stability testing.
- Q1C: stability testing of new dosage form.
- Q1D: bracketing and matrixing designs and drugs product.
- Q1E: Evaluation of Stability Data.
- Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV.
- Q1/Q5C EWG: Targeted Revisions of the ICH Stability Guideline Series.

Good warehousing practice :(GWP)

In every organization, a warehouse is an important asset for the stock inventory storing. Therefore a good warehouse practices is necessary and important to be followed everyday in the daily operation.

Analysis of raw materials:

Raw materials analysis ensures your drug development process begins with high-quality substances that minimize impact on final product quality. Typical beneficiation processes include crushing, roasting, magnetic separation, flotation, and leaching.

Materials Selection Process:

- Identify product design requirements.
- Identify potential materials.
- Evaluate materials.
- Determine whether any of the materials meet the selection criteria.

Finished product:

Finished Product is defined as the medicinal product that has undergone all stages of Production, including packaging in its final container. The specifications for release of the Finished product must comply with the FDA regulations. The specifications of the finished product at manufacture may be different from those of the medicinal product at expiry.

Packaging product: -

Packaging means the wrapping or bottling of products to make them safe from damages during transportation and storage. It keeps a product safe and marketable and helps in identifying, describing, and promoting the product. "Packing is the preparation of product or commodity for proper storage and/or transportation".

Quality assurance test for tablets according to Indian, USA and British pharmacopoeias: -

General appearance: Size, Shape, Color, Odour, Taste, Surface texture, Physical flaws, and Consistency.

- ❖ **Hardness:** Ensures tablets can withstand manufacturing and shipping.
- ❖ **Friability:** Ensures tablets can withstand manufacturing and shipping.
- ❖ **Weight variation:** Maintains drug uniformity and distribution.
- ❖ **Content uniformity:** Evaluates the consistency of active ingredient amounts in a sample of tablets.
- ❖ **Disintegration:** Assesses how quickly the tablet breaks down.
- ❖ **Dissolution:** Assesses how quickly the tablet breaks down.

Regulatory Authorities:

food and drug administration: (FDA)

The scope of FDA's regulatory authority is very broad. FDA's responsibilities are closely related to those of several other government agencies. Often frustrating and confusing for consumers is determining the appropriate regulatory agency to contact. The following is a list of traditionally-recognized product categories that fall under FDA's regulatory jurisdiction; however, this is not an exhaustive list.

World Health Organization: (WHO)

A stringent regulatory authority (SRA) is a national drug regulation authority which is considered by the World Health Organization (WHO) to apply stringent standards for quality, safety, and efficacy in its

process of regulatory r Analytical method validation review of drugs and vaccines for marketing authorization.

- Analytical method validation.
- DQ, IQ, OQ, PQ of equipment.
- Water system validation.
- HVAC validation.
- Computer sys.

Medicines and healthcare products regulatory agency: (MHRA)

The Medicines and Healthcare products Regulatory Agency (MHRA) is an executive agency of the department of health and social worker in the United Kingdom which is responsible for ensuring that medicines and medical device work and are acceptably safe.

Therapeutic Goods Administration :(TGA)

The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods, including medicines, medical devices, and diagnostic tests. The TGA is part of the Australian Government Department of Health and Ageing.

Documentation in pharmaceutical industry: -

Document is any written statement or proof of any activity in pharmaceuticals. Good documentation is a systematic procedure of preparation, checking, verifying, issuing, storing and reviewing of any documents.

Documentation in pharmaceutical industry:

Master Batch Record: (MBR)

Master Batch Record means the document that defines the manufacturing methods, materials, and other procedures, directions and controls associated with the manufacture and testing of the Product, which may be amended in writing from time to time by mutual agreement of the parties.

Batch Manufacturing Record: (BMR)

Master Manufacturing Record means the compilation of records containing the procedures and Specifications for manufacturing a Finished Product A Master Manufacturing Record may be prepared as a single document or file or may be prepared using an index system that specifies the location and identity of individual files.

Quality audit plan:(QAP)

Quality audits and compliance are essential pillars of organizational integrity and success. While quality auditing involves a systematic review of processes to ensure alignment with standards and drive improvement, compliance ensures adherence to legal regulations and industry standards.

Submission documents for regulators: (DMFs)

DMFs should be submitted in the electronic Common Technical Document (eCTD) format. The format of the DMF is important for regulatory authorities to accept it. DMFs are confidential documents that provide details about the processes, materials, and quality standards used in drug manufacturing, processing, packaging, and storing. There are several types of DMFs, each with a different purpose.

Common Technical Document:(CTD)

A Common Technical Document (CTD) is a set of specifications for a dossier that is used to register medicines and biological products. The CTD was developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It is used to assemble information about the safety, quality, and efficacy of a product.

Electronic Common Technical Documentation:(eCTD)

eCTD stands for Electronic Common Technical Document, which is a standard format for submitting regulatory information to health authorities. It's used in the pharmaceutical industry to transfer information from agencies to companies.

Concept of regulated and non-regulated markets:

The main difference between a regulated and an unregulated market is that regulated markets are licensed and authorized, while unregulated markets are not:

Regulated markets:

These markets are licensed and authorized, and go through a vetting process before instruments are admitted to trading. They are often referred to as public markets, and are controlled by a regulatory body that protects the public interest. Regulated markets are subject to strict regulatory requirements, and consumers can approach the regulator for redress if they are not satisfied with the services of a service provider.

Unregulated markets:

These markets are governed by the prevailing contracts between the participating parties, and are not regulated by a specific regulator. They are also loosely referred to as private products or private offers. In unregulated markets, consumers may not have recourse if they are not satisfied with the services of a service provider.

Some examples of regulated markets include stock exchanges, while over-the-counter markets are usually not regulated or only moderately regulated.

Principles of Drug discovery and development:

Basic Principles of Drug Discovery and Development presents the multifaceted process of identifying a new drug in the modern era, providing comprehensive explanations of enabling technologies such as high throughput screening, structure-based drug design, molecular modelling pharmaceutical profiling, and translational

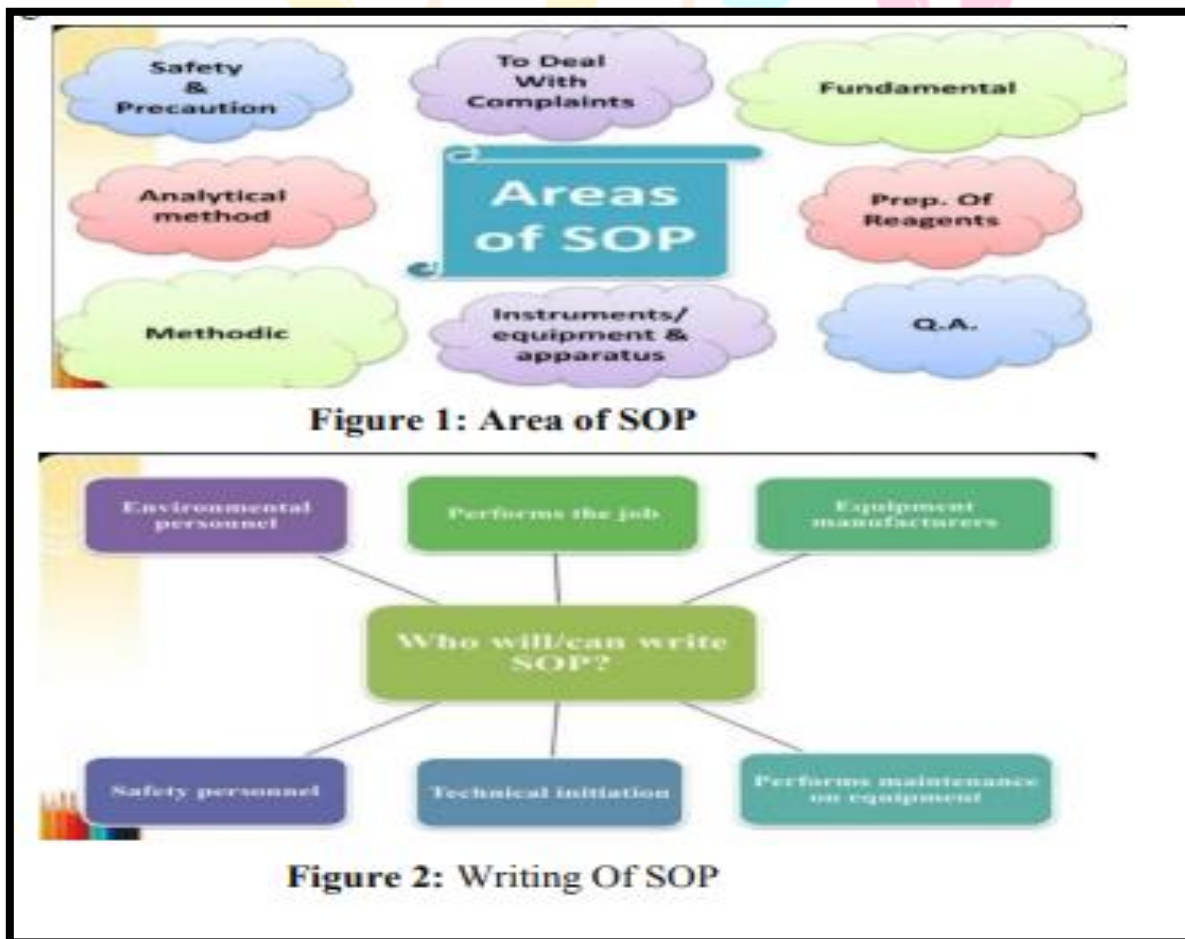
Clinical research process:

a broad-topic review of clinical research that is usually written by an expert in the field. Here are some tips for writing a review article and some things to consider when reviewing a clinical research paper.

Preparation of Standard Operating Procedure: (sop)

SOP
the

is



written step by step instrument that how to Perform the activities to complete the task. All concern persons required to follow these steps. SOP are the application in all type of industries, Rules & Regulation, Government laws & Organization to running the own business.

OTHER NAMES OF SOP:

- SOP: WI (Work Instruction)
- SSOP: Safe Standard Operating Procedure.
- PCS: Process Work Sheet.
- SWS: Standard Work Sheet.

Objective: Specify the goal of the action or activity.

Scope: Indicate the purposes for using the process or method, any organizational or legal requirements, and any restrictions on its use.

Responsibilities: Indicates the level of personal response.

reliability and the required experience the user should be required to use the tools correctly.

References: References were consulted to create these SOPs and to provide further in-depth details.

Definitions: This section defines any acronyms, abbreviations, or technical terminology that is used.

Precautions: Indicate the activities that can harm equipment, degrade samples, or perhaps affect important phases in the method and the validation of results.

Procedure

The supplies needed to achieve that aim are listed together with all relevant steps that must be taken in order. Each person using the instruments—students, instructors, lab technicians, and researchers—must read and understand every element of the SOP. This will be updated on a regular basis and is meant to be dynamic. Mentioning brand names or commercial goods does not imply support or advice for their use.

Purpose

The goal of SOP is to carry out the procedure accurately and consistently in order to maintain the consistency of the output. It needs to be accessible where work is being done. The SOP must be followed by all operators.

Examples:

In Work shop, in Manufacturing, in Lab., in Physical Life.

Benefits SOP

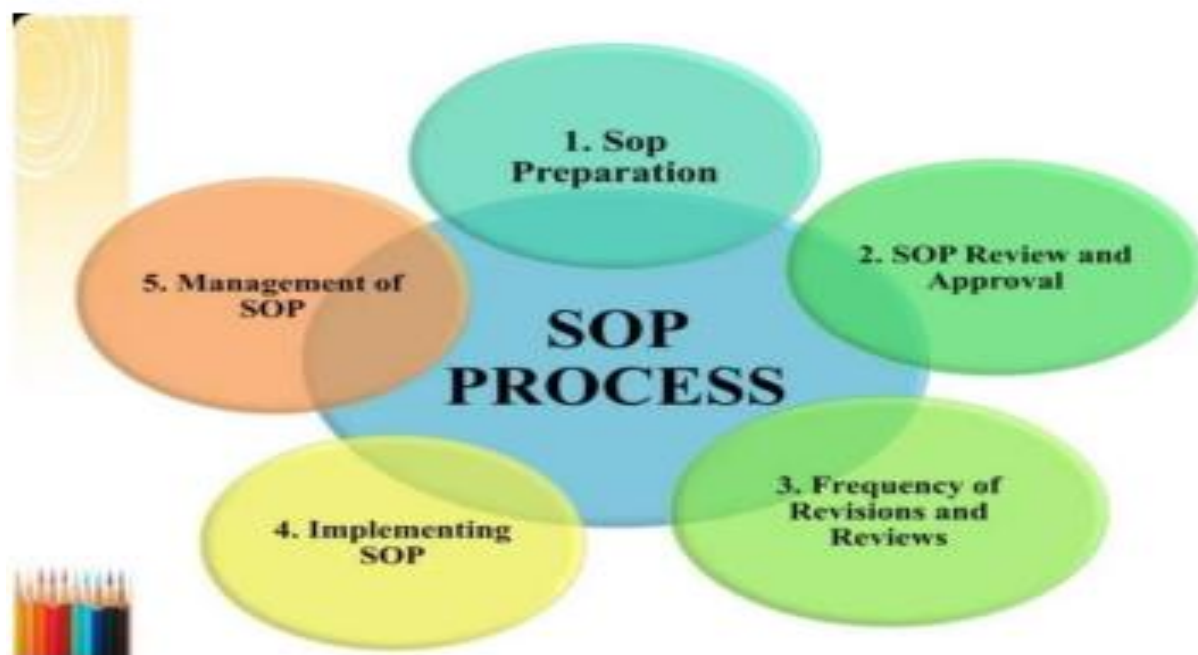


Figure 3: SOP Process

- 1) To give employees the knowledge they need to do their jobs safely, healthily, environmentally, and operationally. It is expensive in the long term to prioritise productivity over safety, health, and the environment.
- 2) It is preferable to teach staff members thoroughly before allowing accidents, penalties, or legal action to occur.
- 3) To guarantee that procedures run without interruption and are equipment failure or other facility damage by adhering to SOPs.
- 4) To prevent malfunctions in production and other procedures that might endanger anyone in the neighbourhood. Following the health and environmental precautions outlined in SOPs protects against spills and pollutants that endanger plant neighbours and spark uproar in the local community.

- 5) To guarantee compliance with corporate and governmental requirements and the execution of approved processes. Well-written SOPs aid in ensuring that legal requirements are met. Additionally, they show a company's sincere desire to conduct business appropriately.

Reasons for writing SOPs:

1. To arm those who conduct operations with the necessary operational, environmental, safety, and health knowledge to do them.
2. To safe guard both the environment and the health and well-being of workers.
3. To keep the neighborhood safe.
4. To make certain that procedures are followed consistently in order to keep process and product quality under control.
5. To ensure that processes continue and completed on a prescribed schedule.
6. To make sure that procedures continue and are finished according to a set timeline.

SOP Review and Approval: -

One or more people with the necessary training and process knowledge should evaluate (i.e., validate) the SOPs. Before the SOPs are completed, it is extremely beneficial if draught SOPs are actually tested by someone other than the original author. The organization's quality management plan or its own SOP for the creation of SOPs should be followed while approving the finished SOPs. The organization's quality assurance officer and the immediate supervisor, such as a section or branch head, typically examine the management. The Government Paperwork Elimination Act of 1998 states that, when practicable, using electronic signatures in place of paper for document maintenance and submission is permissible.

SOP Document Tracking and Archival

A comprehensive list of all SOPs should be kept up to date by the organization. The SOP number, version number, date of issue, title, author, status, organizational division, branch, section, and historical data on previous versions should all be listed in this file or database. The person in charge of keeping a file outlining all current quality-related SOPs and practises utilized by the company is often the QA Manager (or designee). Automatic "Review SOP" messages can be delivered if an electronic database is utilised. It should be noted that this list may also be utilised when audits are being considered or when concerns about organisational procedures are raised.

SOP Preparation

For deciding which processes or procedures need to be recorded, the business should have a procedure in place. Those SOPs ought to be created by experts who are familiar with the activity and the internal workings of the organisation.

These people are essentially the subject-matter experts who use the procedure or actually conduct the task. A team technique that may be used, especially for multi-tasking procedures where the collective wisdom of the participants is crucial, and that also encourages "buy-in" from future SOP users (15). SOPs should always be stated in enough detail such that a person with only a basic grasp of the procedure, but little experience or knowledge, may effectively repeat it on their own. The section on personnel qualifications should include a comment on the experience needed to accomplish a task. For instance, it should be stated if prior experience or further training is necessary for the fundamentals of chemistry or biology.

Formats for Standard Operating Procedures

Managers have a variety of organising and formatting options when drafting standard operating procedures. Your aim should be to produce a paper that is simple to understand and beneficial for the task at hand. Which SOP to employ is determined by two variables. How many selections would the user need to make initially in order to complete the procedure? How many phases and sub steps are there in total in the method, secondly? Simple steps of format can be used to write routine operations that are brief and need few considerations. Long procedures with more than 10 stages and few decisions should be expressed in a visual manner or according to a hierarchy of steps. A flowchart should be used to document procedures that call for plenty of choices.

Responsibility:

Person Performing: The relevant HODs for the relevant department QA officer/HOD QA is in charge of monitoring.

Records:

This Finalizer in the Quality Documentation System. Alteration, information, records, forms, etc. are archived. Quality records are the objective evidence to prove that the Quality System is being executed per

procedure. Quality Records also describe how the quality of the endproduct was verified to have met the specifications and then meet the customer's needs & expectations. Records include the following sources:

- Non-Conformance Investigations.
- CAPA's.
- Audit Results.
- Supplier Documentation
- Calibration Results

Application: (IND)

An Investigational New Drug (IND) is a drug or biological product that has not been approved by the FDA for general use, but is being tested in clinical trials to determine its safety and effectiveness.

New Drug Application: (NDA)

A New Drug Application (NDA) is a request to the U.S. Food and Drug Administration (FDA) for permission to sell and market a new drug in the United States. The NDA is submitted by a pharmaceutical manufacturer or its agent when they believe they have enough evidence to meet the FDA's requirements.

Abbreviated New Drug Application: (ANDA)

An Abbreviated New Drug Application (ANDA) is a submission to the FDA for the review and potential approval of a generic drug. ANDAs are called "abbreviated" because they don't require the same detailed evidence as a New Drug Application (NDA).

Supplemental New Drug Application: (SNDA)

A supplemental new drug application (SNDA) is a request to the FDA to change an approved drug in some way, such as by changing the label, dosage, ingredients, or manufacturing method.

The FDA categorizes changes as major, moderate, or minor based on their potential impact on safety, quality, or efficacy:

- **Major changes:** Require prior approval.
- **Moderate changes:** Require 30 days' notice.
- **Minor changes:** Only require description in the annual report.

Scale Up Post Approval Changes: (SUPAC)

IUPAC, which stands for Scale-up and Post Approval Changes, refers to guidelines that govern changes made during the post-approval phase of drug manufacturing. These guidelines apply when there are changes in: Manufacturing procedures or equipment, Specifications.

Bulk active chemical Post approval changes: (BACPAC)

Bulk Active Chemicals Post Approval Changes (BACPAC) is a guidance document from the FDA that provides recommendations for post-approval changes to drug substance synthesis.

marketing surveillance: (PMS)

Post marketing surveillance (PMS) is defined as the identification and collection of information regarding drugs after their approval for use in a population.

Product registration guidelines – CDSCO, USFDA.

Identify Registration Type: Determine if your product is a drug, medical device, or cosmetic.

Prepare Documents: Gather necessary documents, including product details and safety information.

Register on SUGAM Portal: Create an account on the CDSCO SUGAM portal.

Complete Application: Fill out the application form accurately and attach required documents.

Pay Fees: Submit applicable fees based on your product type.

Submit Application: Monitor your application status on the portal and respond to any queries from CDSCO [1][3][4].

Assay of raw materials as per official monographs:

Assaying raw materials according to official monographs involves a systematic approach to ensure quality and compliance with established standards. Here's a general outline of the process:

1. Selection of Monograph: Identify the appropriate official monograph for the raw material from recognized pharmacopeia's (e.g., USP, EP, JP).

- 2. Sample Collection:** Collect samples that represent the entire batch. Ensure proper storage and handling to avoid contamination.
- 3. Preparation of Sample:** Follow specific instructions for sample preparation, which may include grinding, dissolving, or diluting.
- 4. Analytical Methods:** Use the prescribed analytical methods outlined in the monograph, such as:
 - ❖ Chromatography (HPLC, GC)
 - ❖ Spectroscopy (UV, IR, NMR)
 - ❖ Titration (acid-base, redox)
 - ❖ Physical Tests (melting point, solubility)
- 5. Calculation of Results:** Calculate the assay results using the formulas provided in the monograph. Compare results to the specified limits.
- 6. Documentation:** Record all data, including observations, calculations, and any deviations from the procedure. Maintain complete and accurate records.
- 7. Compliance Verification:** Confirm that the results meet the criteria established in the monograph. If results do not comply, investigate and document the reasons.
- 8. Reporting:** Prepare a comprehensive report detailing the assay process, results, and conclusions.
- 9. Quality Control:** Implement quality control measures to ensure consistency and reliability in testing. Always adhere to Good Laboratory Practices (GLP) and maintain compliance with regulatory requirements throughout the assay process.

Validation:

INTRODUCTION:

The concept of validation was first proposed in the mid-1970s by two FDA (Food and Drug Administration) officials, Ted Byers and Bud Loftus, in order to improve the quality of pharmaceutical products (Agalloch 1995 quoted in Sardine et al., 2013). It was proposed as a direct response to the large volume of problems of parental sterility products. The first validation activities focused on the processes involved in making these products, but they spread rapidly across all pharmaceutical production processes (Keyur et al., 2014). The purpose of validation is to test the quality of the system at each stage and not only at the end, as validation activities include checks on production materials, operating procedure, training of the persons involved and monitoring of the system during production (Sarani et al., 2013).

Scope of Validation: Pharmaceutical Validation is a vast area of work and it practically covers every aspect of pharmaceutical processing activities, hence defining the Scope of Validation. However, a systematic look at the pharmaceutical operations will point out at least the following areas for pharmaceutical validation.

1. Analytical Instrument.
2. Calibration Process.
3. Utility.
4. Services.
5. Raw materials.
6. Packaging material.
7. Equipment.
8. Facilities.
9. Manufacturing operations.
10. Product Design.

Importance of Validation:

1. Assurance of quality.
2. Time bound.
3. Process optimization.
4. Reduction of quality cost.
5. Nominal mix-ups.
6. bottle necks.

The four main types of validation used in the life sciences are: Prospective validation, Concurrent validation, Retrospective validation, and Revalidation.

Prospective Validation: Conducted prior to the distribution of either a new product or a product made under a modified production process where the modifications are significant and may affect the products characteristics. It is a pre-planned scientific approach and includes the initial stages of formulation development, process development, setting of process specifications, developing in-process tests sampling plans, designing of batch records, defining raw material specifications, completion of pilot runs, transfer of technology from scale-up batches to commercial size batches, listing major process is executed and environmental controls.

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. It is generally considered acceptable that three consecutive batches/runs within the finally agreed

parameters, giving product of the desired quality would constitute a proper validation of the process. It is confirmation on the commercial three batches before marketing.

Concurrent Validation:

A process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency quality from batch to batch. Concurrent Validation may be the practical approach under certain circumstances.

Examples of these may be when: -

- A previous validated process is being transferred to a third-party contract manufacturer or to another site.
- The product is a different strength of a previously validated product with the same ratio of active/inactive ingredients...
- The numbers of batches produced are limited.
- Process with low production volume per batch and market demand.
- Process of manufacturing urgently needed drug due to shortage or absence of supply.
- A detailed procedure shall be planned for handling of the marketed product if any adverse reactions observed in concurrent validation process.

Retrospective Validation:

Conducted for a product already being marketed, and is based on extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which are now to be validated to confirm to the requirements of division 2, Part C of the Regulation to Food and Drugs Act. Retrospective Validation is only acceptable for well-established detailed processes and will be inappropriate where there have recent changes in the formulation of the products, operating procedures, equipment and facility¹⁸ Some of the essential elements for

Retrospective Validation are:

- Batches manufactured for a defined period (minimum of 10 last consecutive batches).
Number of lots released per year.
- Batch size/strength/manufacturer/year/period.
- Master manufacturing/packaging documents.
- List of process deviations, corrective actions and changes to manufacturing documents.
- Data for stability testing for several batches.
- Trend analysis including those for quality related complaints.

Process Re-Validation:

Required when there is a change in any of the critical process parameters, formulation, primary packaging components, raw material fabricator, major equipment or premises. Failure to meet product and process specifications in batches would also require process revalidation.

- Re-Validation becomes necessary in certain situations. The following are examples some of the planned or unplanned changes that may require re-validation.
- Changes in raw materials (physical properties such as density, viscosity, particle size distribution, and moisture, etc. that may affect the process or product).
- Changes in the source of active raw material manufacturer.
- Changes in packaging material (primary container/closure system).
- Changes in the process (e.g., mixing time, drying temperatures and batch size).
- Changes in the equipment (e.g. addition of automatic detection system).
- Must be qualified.
- Changes in the plant/facility.
- Variations revealed by trend analysis (e.g. process drifts).

Instrument Handling

1. Demonstration of High-Pressure Liquid Chromatography: (HPLC)

Principle: -

HPLC (high performance liquid chromatography) is based on adsorption as well as Partition chromatography is depending on their nature of stationary phase, if stationary phase is solid principle is based on adsorption chromatography and if stationary phase liquid is based on partition chromatography.

TYPES OF HPLC: -

- Normal phase chromatography

- Reverse phase HPLC
- Ion exchange chromatography
- Analytical HPLC
- Preparative HPLC
- Qualitative and Quantitative HPLC

CONSTRUCTION -

Pump:

- The development of HPLC led to the development of the pump system.
- The pump is positioned in the most upper stream of the liquid chromatography system
- generates a flow of eluent from the solvent reservoir into the system.
- High-pressure generation is a "standard requirement of pumps besides which, it should also
- to be able to provide a consistent pressure any condition and a controllable and reproducible flow rate.

Injector:

- An Injector placed next to the pump.
- The simplest method is to use a syringe, and the sample is introduced to the flow of eluent.
- The most widely used injection method is based on sampling loops.

Column:

- The separation is performed inside the column.
- The recent columns are often prepared in a stainless-steel housing, instead of glass columns.

Detector:

- Separation of analytes is performed inside the column, whereas a detector is used to observe the obtained separation.
- The composition of the eluent is consistent when no analyte is present. While the presence of analyte changes the composition of the eluent. What detector does is to measure these differences.

Recorder:

- The change in eluent detected by a detector is in the form of an electronic signal, and thus it is still not visible to our eyes.
- In older days, the pen (paper)-chart recorder was popularly used. Nowadays, a computer-based data processor (integrator) is more common.

Degasser:

When gas is present in the eluent, this is detected as noise and causes an unstable baseline.

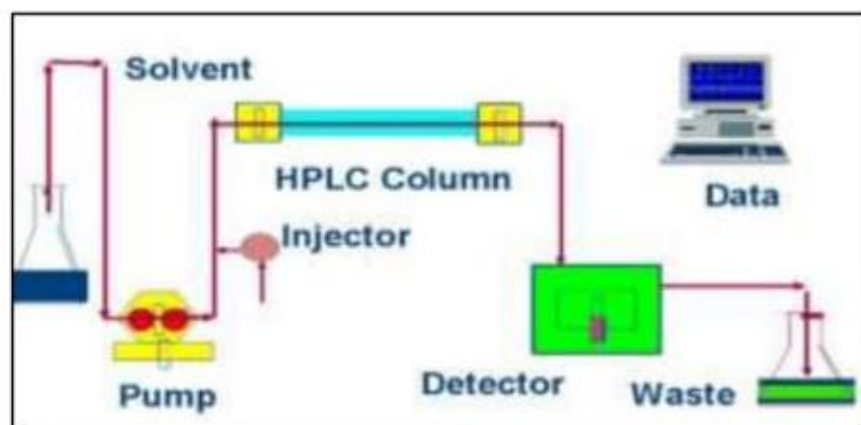


Fig. 1: Flow Diagram of HPLC²

WORKING -

Step-by-Step Demonstration of HPLC Working:

1. Setup and Preparation:

- a. Turn on the Instrument:** Power up the HPLC system, including the pump, detector, and computer software that controls the system.
- b. Check the Solvent Reservoirs:** Ensure the mobile phase solvents are properly prepared and degassed. Check if the solvent bottles contain enough mobile phase (e.g., water, acetonitrile, methanol) to last the entire run.
- c. Prime the Pump:** Remove air bubbles. This ensures stable and accurate flow rates during the experiment.
- d. Column Installation and Equilibration:** Attach the HPLC column (e.g., reverse-phase C18 column) securely between the pump and the detector. Equilibrate the column by flushing it with the mobile phase for at least 30 minutes. This stabilizes the column and brings it to equilibrium with the mobile phase.

2. Sample Preparation and Injection:

- a. Prepare the Sample:** Ensure that the sample is well prepared, filtered, and degassed to avoid clogging the system or introducing air bubbles. Load the sample into an autosampler vial or directly into the injection loop using a syringe.
- b. Sample Injection:** Use the software to set the injection volume (e.g., 10-50 μL). Inject the sample using the autosampler or manual injector into the mobile phase stream.

3. Running the Analysis:

- a. Start the Pump:** Begin the flow of the mobile phase at the set flow rate (e.g., 1 mL/min). The pump delivers the mobile phase at high pressure (around 1000-5000 psi), pushing the sample through the column.
- b. Separation in the Column:** The sample components interact differently with the stationary phase (inside the column), resulting in the separation of the individual compounds as they move at different speeds through the column.

4. Detection and Data Analysis:

- a. Detection of Compounds:** The detector (e.g., UV, PDA, fluorescence) monitors the eluting compounds as they exit the column. As each compound elutes, it creates a peak on the chromatogram, which corresponds to the time it took to pass through the column (retention time).
- b. Monitor the Chromatogram:** Observe the chromatogram generated by the detector in real-time. Each peak represents a different compound in the mixture. The area under the peak can be used for quantification, and the retention time identifies the compound.
- c. Recording Results:** - The software records the chromatogram, which displays retention times and peak areas for all detected compounds. Analyze the peaks to determine the concentration and identity of the compounds.

5. Post-Run Procedures:

- a. Flush the System:** After the analysis, flush the column with a strong solvent (e.g., pure acetonitrile) to remove any remaining sample or contaminants. Wash the system with a cleaning solvent if required (e.g., water or methanol).
- b. Shut Down the System:** Turn off the pump, detector, and other components systematically to ensure no pressure remains in the system. Clean the sample injector and tubing to prevent contamination for future runs.

The Validation Process Of HPLC: -

It involves several key steps to ensure the method is reliable and accurate:

1. **Specificity:** Ensure the method can separate and identify the target compound from other substances (like impurities or degradation products).
2. **Linearity:** Test if the results are proportional to the concentration of the compound over a specific range. You prepare samples at different concentrations and check if the response is linear.
3. **Accuracy:** Check how close the test results are to the true value. You do this by comparing the HPLC results to known standards.
4. **Precision:** Verify if the method gives consistent results when repeated multiple times. It includes:
 5. **Repeatability:** Same person, same equipment, same conditions.
 6. **Intermediate precision:** Different conditions, such as different days or different operators.
7. **Limit of Detection (LOD):** Find the smallest amount of the compound that can be detected but not necessarily quantified.
8. **Limit of Quantification (LOQ):** Determine the smallest amount that can be accurately quantified.
9. **Robustness:** Test how small changes in conditions (e.g., temperature, pH) affect the results.

Each step ensures the method produces consistent, accurate, and reliable results.

Application of HPLC: -

- Analysis of drugs
- Analysis of synthetic polymers
- Analysis of pollutants in environmental analytics
- Determination of drugs in biological matrices
- Isolation of valuable products Product

ADVANTAGES: -

- Accuracy and precision: HPLC is highly accurate and precise, even across multiple runs.
- Efficiency: HPLC is efficient and can analyze multiple samples quickly.
- Sensitivity: HPLC can detect trace amounts of compounds, from nanogram to picogram levels.
- Selectivity: HPLC can separate and purify structurally similar compounds.
- Versatility: HPLC can analyze a variety of compounds, including polar and nonpolar compounds, acidic and basic compounds, and large and small molecules.

DISADVANTAGES: -

- Training: HPLC requires extensive training.
- Downtime: HPLC can experience excessive downtime.
- Precision: HPLC is less precise than gas chromatography (GC).
- Detectors: HPLC doesn't have a universal detector, so you need different detectors for different solutes.
- Troubleshooting: It can be difficult to troubleshoot problems or develop new methods.
- Compatibility: HPLC can have compatibility issues with some solvents and columns.

HPLC VALIDATION: -

It ensures that the method used for analysis is reliable, accurate, and consistent. Key parameters involved in HPLC validation are:

1. Accuracy: The method must produce results close to the true value.
2. Precision: Results should be reproducible under the same conditions (intra-day and inter-day).
3. Specificity: Ability to distinguish the analyte from other components like impurities.
4. Linearity: The response should be directly proportional to the concentration of the analyte within a given range.
5. Range: The method must be validated over the expected range of analyte concentrations.
6. Limit of Detection (LOD): The smallest amount of analyte that can be detected, but not necessarily quantified.
7. Limit of Quantitation (LOQ): The smallest amount of analyte that can be quantitatively determined with accuracy and precision.
8. Robustness: The method should remain reliable under small variations in conditions (e.g., temperature, pH).
9. Stability: Ensures that the analyte remains stable throughout the analysis.

2.pH METER

PRINCIPLE: -

The pH meter is operated via potentiometry and the exchange of ions across a glass membrane between the sample solution and the inner solution (pH 7 buffer) of the glass electrode. This represents a solution's electric potential, or voltage. The ability of a solution to conduct a current is known as its electric potential. When the two electrodes, or a combination electrode (glass electrode and calomel electrode), are submerged in an aqueous solution, a potential is formed across the thin glass of the bulb (of glass electrode). the principle of a pH meter is crucial for ensuring the quality and stability of pharmaceutical products. Here's the principle explained in a simple way:

A pH meter measures the acidity or basicity of a solution, which is important for drug formulation and stability. It works by using a glass electrode that is sensitive to hydrogen ion (H⁺) concentration. When the electrode is placed in a pharmaceutical solution, it detects the activity of H⁺ ions.

The pH meter then converts this into a numerical pH value, which tells how acidic or basic the solution is. Maintaining the correct pH in pharmaceuticals is essential for the drug's effectiveness, safety, and stability. A slight variation in pH can affect drug solubility, absorption, and shelf life, making the pH meter a vital tool in pharmaceutical quality control.

1. Electrodes: A pH meter typically has two electrodes: a glass electrode (which is sensitive to hydrogen ions) and a reference electrode. Some pH meters use a combination electrode, which houses both in a single unit.

2. Hydrogen Ion Sensitivity: The glass electrode produces a voltage when it comes into contact with hydrogen ions in the solution. The more acidic the solution (lower pH), the higher the concentration of hydrogen ions, and the greater the potential difference generated.

3. Reference Electrode: The reference electrode provides a stable voltage to compare against the varying voltage from the glass electrode.

4. Measurement and Display: The pH meter measures the voltage difference between the two electrodes and converts this electrical signal into a pH value, which is displayed on the screen. The meter must be calibrated with buffer solutions of known pH before use to ensure accurate readings.

The Validation Process Of a pH Meter: -

It ensures that it provides accurate and reliable pH measurements. Here's a brief overview:

1. **Calibration:** Calibrate the pH meter using standard buffer solutions (usually pH 4.00, 7.00, and 10.00) before use. Ensure that the slope and offset are within acceptable ranges.

2. **Accuracy:** Measure the pH of certified reference buffer solutions and verify that the readings match the known pH values.

3. **Repeatability:** - Test the same sample multiple times and check for consistent results.

4. **Linearity:** Measure pH across a range of buffer solutions (e.g., 4.00, 7.00, and 10.00) to ensure the meter provides a linear response.

5. **Robustness:** Assess the meter's performance under varying conditions, such as temperature changes, to ensure reliable readings.

6. **Electrode Condition:** Regularly check the condition of the electrode, including its cleanliness and response time.

7. **Documentation:** Record calibration results, validation tests, and any corrective actions taken.

This process helps confirm that the pH meter consistently performs within its specifications.

APPLICATION:-

- pH influences processing speed and dye bath persistence, making it significant in the dyeing industry.
- Information on the state of healing and bacterial infection can be obtained from the pH value of the wound.
- To reduce chemical use and halt equipment deterioration, the pulp and paper industry needs to maintain the proper pH level.
- Maintaining the pH levels at the perfect range makes many daily jobs easier, such as avoiding sour milk.

Advantages: -

- **Accuracy:** pH meters provide precise pH values.
- **Consistency:** pH meters are reliable and consistent.
- **Detailed monitoring:** pH meters can be used for detailed monitoring and analysis.
- **Portability:** Offline pH meters are portable and can be used in remote areas.

Disadvantages: -

- **Cost:** pH meters are more expensive than pH paper strips.
- **Maintenance:** pH meters require regular cleaning and calibration to avoid contamination and inaccurate results.
- **Fragility:** pH meters have glass tips that can be easily broken or damaged.
- **Complexity:** Digital pH meters may have more advanced features that require additional training.

pH Meter Validation

pH Meter Validation is the process of ensuring that a pH meter provides accurate and reliable readings. The key steps involved are:

1. Calibration: Regular calibration using standard buffer solutions (e.g., pH 4, 7, and 10) to adjust the meter to known values.

- 2. Accuracy Check:** After calibration, test the meter with a buffer solution to verify the reading is within acceptable limits.
- 3. Electrode Condition:** Ensure the electrode is clean, hydrated, and functioning well, as it's critical for accurate measurements.
- 4. Temperature Compensation:** pH readings can vary with temperature, so validate the meter's automatic temperature compensation feature or manually correct for temperature variations.
- 5. Documentation:** Keep records of calibration and validation results for traceability and quality assurance.

CONCLUSION: -

Quality Assurance (QA) is an integral component of the pharmaceutical industry, playing a vital role in ensuring that medicinal products are consistently produced and controlled to the highest standards. QA involves a comprehensive and proactive approach, covering all aspects of drug development, from raw material procurement to the final product's release to the market. The purpose of QA is to prevent errors, defects, and contamination, ensuring that each product is safe, effective, and reliable for patient use.

One of the key principles of QA is adherence to Good Manufacturing Practices (GMP), which are regulatory guidelines established to ensure that pharmaceutical products are manufactured under strict quality controls. QA systems ensure that every step in the manufacturing process is properly documented and followed, reducing the risks associated with human error or equipment malfunction. These practices guarantee that products meet the specified quality attributes and regulatory requirements for safety and efficacy.

Furthermore, QA promotes a culture of continuous improvement by regularly evaluating and updating processes to adapt to new scientific knowledge, technological advances, and regulatory changes. This ensures that the pharmaceutical industry stays at the forefront of innovation while maintaining high standards. QA also fosters transparency and accountability within organizations, with thorough record-keeping, regular audits, and quality checks at every stage of production.

In addition to ensuring product quality, QA has a direct impact on patient health. By maintaining strict quality controls, the pharmaceutical industry helps prevent adverse drug reactions, therapeutic failures, and other risks that could arise from substandard products. This builds public trust in the safety and effectiveness of pharmaceutical products, which is essential for the well-being of society. In conclusion, Quality Assurance in pharmaceuticals is not just about compliance with regulations; it is about safeguarding human lives. By ensuring that every product meets rigorous quality standards, QA plays a critical role in maintaining the integrity and reliability of the pharmaceutical supply chain, ultimately protecting public health and enhancing patient care.

Reference: -

- 1) A Text Book of PHARMACEUTICAL QUALITY ASSURANCE By NIRALI PRAKASHAN Author: Anusuya R. Kashi Bindu Sukumaran.
- 2) Gita Chaurasia, A review on Pharmaceutical Preformulation studies in formulation IJPSR (2016) Vol.7, Issue 6
- 3) Dr. K.L. Senthilkumar, Dr. Atish Kumar Sarkisian Mundada, Dr. Rani S. Kankate, Industrial Pharmacy - 1 Thakur Publication 2019 edition.
- 4) Kaur H, Singh G, Seth N; Pharmaceutical Process Validation: A Review. 2013; 3 (4): 189-194.
- 5) Potdar MA; Pharmaceutical Quality Assurance, 2nd Edition, Nirali Prakashan, 2009: 8.6-8.20.
- 6) Mangesh G. Bhise, Amol R. Lahane, Nitin B. Kohale, Shailesh G. Shende, A review on pharmaceutical studies (new), JETIR FEBRUARY 2022, Vol.9, Issue 2.
- 7) Shubhangi M. Dhore, Santosh A. Waghmare, Hemant V. Kamble, A Review on Preformulation Studies, IJARES, ISSN: 2455 - 6211 Vol. 10 Issue 3 March 2023.
- 8) Manghani Kishu in 2011 Quality assurance: Importance of systems and standard operating procedures Perspect Clin Res. Doi: 10.4103/2229-3485.76288
- 9) Martin, M.; Guiochon, G. Effects of high pressure in liquid chromatography. JChromatography A 2005;1090(1):16-38.
- 10) Dwivedia, S.K.; Agarwala, D.D. A Review: HPLC Method Development and Validation. Int J Analytical Bioanalytical Chem 2015;5(4):76-81.

- 11) Kumar, V.; Bharadwaj, R. An Overview on HPLC Method Development. Optimization and Validation process for drug analysis, Pharm Chem J 2015;2(2);30-40.
- 12) M. Filomen, "A Century of pH. Measurement," Chemistry International, no. April, pp.3-7, Mar-2010.
- 13) Digital pH Meter- M\ Komal Naikude, M\ Taiyele, M\ Jyoti Damin.
- 14) Mangesh G. Bhise, Amol R. Lahane, Nitin B. Kohale, Shailesh G. Shende, A review on pharmaceutical studies (new), JETIR FEBRUARY 2022, Vol.9, Issue 2
- 15) Kumar, V.; Bharadwaj, R. An Overview on HPLC Method Development. Optimization and Validation process for drug analysis, Pharm Chem J 2015;2(2);30-40.

