PHARMACEUTICAL CALIBRATION, QUALIFICATION AND VALIDATION : AN INTRODUCTION

- CALIBRATION

  - *"Calibration of an instrument is the process of determining its accuracy. The process involves obtaining a reading from the instrument and measuring its variation from the reading obtained from a standard."*

- *Calibration of an instrument also involves adjusting its precision and accuracy so that its readings come in accordance with the established standard.*
- *This is important for justifying the processes of Qualification and Validation.*
- *The instrument or equipment with the known accuracy is known as standard. All the other instruments are measured against this standard.*

  It is important to know that the standards vary from one country to the other depending upon the type of industry.
- *Calibration Achieves 2 Main Objectives —*

a) It checks the accuracy of an instrument

b) It determines the traceability of the measurement

Scope/Purpose of Calibration

Calibration is primarily done to achieve 5 main purposes which are:

- ✓ To make sure that the readings of equipment or instruments are **consistent** with other measurements and display the correct readings every single time
- ✓ To determine the **accuracy, precision, reliability and deviation** of the measurements produced by all the instruments
- ✓ To establish the **reliability** of the instrument being used and whether it can be trusted to deliver **repeatable results** each time
- ✓ To map the '**drift**' as documented. Instruments have a tendency to produce inaccurate measurements over a period of time, following repeated use.
- ✓ Ensuring that the **industry standards, quality assurance** benchmarks such as current good manufacturing practice (cGMP) and government regulations are adhered to.

What Is Instrument Calibration?

- *Instrument calibration can be defined as the process of **comparing the measurements** made by the instrument to be calibrated **against a known measurement** of either standards or an instrument known to be making measurements that exceed the acceptable limits of accuracy and precision.*

- *Usually, calibration labs prefer a **standard with 10 times the accuracy;** however, most regulating organizations and authorities also accept a **3:1 accuracy ratio**.*

Frequency Of Instrument Calibration

- *How often you conduct instrument calibration mainly depends upon its **tendency to drift from the true measurement** and how it impacts the quality of the end product. Examine each instrument being used and study its behavior. Based on this information, you can design a calibration schedule for each instrument. The interval between calibrations can vary as:*

- *Weekly*
- *Monthly or bi-monthly*
- *Quarterly, semi-annually or annually*
- *After every heavy usage of the instrument*

When Should The Measuring Instruments Be Calibrated?

The frequency of calibrating the measuring instruments depends on a number of different factors. The following is a guide outlining when instruments need to be calibrated as a part of GMP:

- ✓ As soon as you bring in a new instrument, you should calibrate it before you test it out.
- ✓ Before and after you take critical measurements
- ✓ After any instance of electrical or mechanical shock or a similar event that includes a fall, bump, etc.
- ✓ When you suspect that the accuracy of measurements being produced is questionable
- ✓ If there were any repairs or re-qualifications of the instrument
- ✓ As per included as part of a calibration schedule
- ✓ Depending on the task and processes as some require calibration to be conducted before the work starts
- ✓ According to the manufacturer's recommendation

Commonly Used Calibration Methods and Procedures:

There are different ways that are used to calibrate an instrument. These methods are chosen based on the desired results of the calibration and regulatory authorities' requirements, like FDA guidelines. Let us look at three such procedures:

- **Standard Calibration:** This method is mostly preferred for calibrating instruments that are non-critical to quality or are not required for accreditation and license purposes. Use traceable standards and document its performance.
- **Calibration with Data:** Procedures for calibrations with data are similar to that of accredited calibration. The only exception being that these procedures are not accredited to the ISO standard. Moreover, they are not accompanied by data on measurement uncertainties.
- **ISO 17025 Accredited Calibration:** This has to be the strictest method of calibration. Generally, it requires a measurement report which has the details of the measurements that are made against a standard of 'as found' (before calibration is started) and 'as left' (once the calibration is completed). If the calibration is done by a calibration service provider, they must issue a certificate of the same.

Importance of Regular Calibration:

- Calibration is responsible for defining the accuracy of any measurement and its quality that is recorded by any instrument.

  When you start working with any instrument, it must be calibrated well, thus assuring you of accurate results. However, over a period of time you will start observing a 'drift'. Calibration minimizes such uncertainties by assuring the accuracy of the test equipment.

- When you regularly calibrate your equipment, you can eliminate the drift at its budding stage instead of allowing it to grow till it affects the measurements in significant ways.
- Calibration helps in quantifying and controlling errors and uncertainties within various measurement processes to an acceptable level.
- Further, it helps in improving the accuracy of the measuring device, which in turn improves the quality of the end product.
- In short, regular calibration allows pharmaceutical companies to have confidence in their results which they can record, monitor and control.

QUALIFICATION

- It refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly.
- It is the action of proving that any equipment or process works correctly and consistently and produces the expected results.
- "It is the 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 of analytical instrumentation is essential for accurate and precise measurement of analytical data. If the instrumentation is not qualified, ensuring that the results indicated are trustworthy, all other work based upon the use of that instrumentation is suspect.
- Qualification of instruments is not a single, continuous process but instead results from many discrete activities. For convenience, these activities have been grouped into 4 phases of qualification. These phases are described below:
  - Design Qualification (DQ)
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)

Design Qualification (DQ):

- It is the documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.
- DQ should be performed when new equipment is being purchased, or when existing equipment is being used for a new application. DQ serves as the precursor to defining the equipment Installation Qualification (IQ) and OQ protocols.
- The purpose is to ensure that all the requirements for the final systems have been clearly defined at the start.

In other words,

"Has it been designed and selected correctly?"

DQ check items:

- GMPs and regulatory requirements
- Performance criteria
- Reliability and efficiency
- Commissioning requirements
- Construct ability and installation of equipment
- Safety and environment impact
- Description of the intended use of the equipment
- Preliminary selection of the supplier
- Final selection of the equipment

Installation Qualification (IQ):

- It is documented evidence that the premises, supporting utilities, the equipment have been built and installed in compliance with design specifications
- It verifies that the equipment has been installed in accordance with manufacturers recommendation in a proper manner and placed in an environment suitable for its intended purpose.
- It involves the co-ordinate efforts of the vendor, the operating department and the project team.
- The purpose of I.Q is to check the installation site/environment, confirms equipment specifications and verifies the condition of installed equipment; and also to ensure that all aspects of the facility or equipment are installed correctly and comply with the original design.

In other words,

"Has it been built or installed correctly?"

- In I.Q, connect each unit (Electrical system, Flow line system) and confirm that the connections are correct.

- ***IQ check items:***
  - ✓ *Equipment design features (i.e. material of construction cleanability, etc.)*
  - ✓ *Installation conditions (wiring, utility, functionality, etc.)*
  - ✓ *Calibration, preventative maintenance, cleaning schedules.*
  - ✓ *Safety features.*
  - ✓ *Supplier documentation, prints, drawings and manuals.*
  - ✓ *Software documented.*
  - ✓ *Spare parts list.*
  - ✓ *Environmental conditions (such as clean room requirements, temperature, and humidity).*
- *Any problems identified in I.Q must be investigated and appropriate actions must be taken. All such actions must be documented and approved by higher authority.*

Operational Qualification (OQ):

- It refers to establishing by objective evidence that the process control limits and action levels result in product with all predetermined requirements.
- OQ is the process of demonstrating that an instrument will function according to its operational specification in the selected environment.
- The purpose is to ensure that all the dynamic attributes comply with the original design.

In other words,

"Does it work correctly?"

- Prior to implementing O.Q, check the system configuration, determine the items to be evaluated and record them in O.Q record and have them approved.

OQ check items:

- Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
- Software parameters.
- Raw material specifications
- Process operating procedures.
- Material handling requirements.
- Process change control.
- Training.
- Potential failure modes, action levels and worst-case conditions.
- The use of statistically valid techniques such as screening experiments to optimize the process can be used during this phase.

- Any problems identified in O.Q must be investigated and appropriate actions must be taken. All such actions must be documented and approved by higher authority.

Performance qualification:

- After the IQ and OQ have been performed, the instrument's continued suitability for its intended use is proved through performance qualification.
- It refers to establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.
- PQ should always be performed under conditions that are similar to routine sample analysis. PQ should be performed on a daily basis or whenever the equipment is being used.

PQ considerations include:

- ✓ Actual product and process parameters and procedures established in OQ.
- ✓ Acceptability of the product.
- ✓ Assurance of process capability as established in OQ.
- ✓ Process repeatability, long term process stability.

- *The objective is to ensure that the instrument is performing within specified limits. The PQ represents the final qualification of equipment or system.*

It is used to establish and or confirm;

1. *Definition of performance criteria and test procedures.*
2. *Selection of critical parameters, with predefined specifications.*
3. *Determination of the test intervals, e.g.,*
   - *(a) - Everyday.*
   - *(b) - Every time the system is used.*
   - *(c) - Before, between and after a series of runs.*
4. *Define corrective actions on what to do if the system does not meet the established criteria.*

Re - Qualification:

- Modification to, or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure. This formal review should include consideration of re-qualification of the equipment.
- Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system of the preventive maintenance program.

Scope of Performance Qualification.

- According to regulatory documents, like FDA guidelines, the scope of PQ is somewhat limited. While equipment validation tests the ability individually for each piece of equipment, PQ verifies the performance of equipment, systems and facilities as a whole.
- It represents the final qualification, including any requalification of the system and equipment that you use in your business.
- Typically, the scope of PQ extends to include the following scenarios:
  - New systems being delivered and operated for the first time
  - Existing systems in use (as part of a regular maintenance schedule)
  - Systems that have been modified to any degree
  - Equipment/systems which have been used more than they normally would be
  - After a system has been expanded in order to increase its capacity

Frequency of Performing Performance Qualification

- The objective of PQ is to provide quality assurance that the system is capable of being subsequently validated. GMP and other such guidelines might not specify the frequency of performing PQ, so the schedule or frequency you choose depends on a lot of factors.
- This will typically be one or more of the following:
  - Everyday
  - Each time the equipment or system is used
  - Before, after, or even during, a series of operations
  - Other periodic schedule, or as needed

VALIDATION:

- *Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified.*

- *A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved.*

- *Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.*

- ***Definitions :***
- *According to **ISO:***

*"Validation is the **confirmation by examination** and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled."*

- *According to the **US Food and Drug Administration (FDA)**, the goal of validation is to:*

*"Establish documented evidence which **provides a high degree of assurance** that a specific process will consistently produce a product **meeting its predetermined specifications and quality attributes**."*

- *According to **European commission:***

"Action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results."

Adequate validation is beneficial to the manufacturer in many ways:

- It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
- It decreases the risk of defect costs.
- It decreases the risk of regulatory noncompliance.
- A fully validated process may require less in-process controls and end product testing.

Validation should thus be considered in the following situations:

- Totally new process;
- New equipment;
- Process and equipment which have been altered to suit changing priorities; and
- Process where the end-product test is poor and an unreliable indicator of product quality.

Scope of validation

- Validation requires an appropriate and sufficient infrastructure including:
  - organization, documentation, personnel and finances
- Involvement of management and quality assurance personnel
- Personnel with appropriate qualifications and experience
- Extensive preparation and planning before validation is performed
- Validation should be performed:
  - for new premises, equipment, utilities and systems, and processes and procedures;
  - at periodic intervals; and
  - when major changes have been made.
- Validation in accordance with written protocols.
- Validation over a period of time, e.g. at least three consecutive batches (full production scale) to demonstrate consistency. (Worst case situations should be considered.)
- Significant changes (facilities, equipment, processes) - should be validated
- Risk assessment approach used to determine the scope and extent of validation needed

Importance of Validation

1. Assurance of quality
2. Time bound
3. Process optimization
4. Reduction of quality cost.
5. Minimal batch failures, improved efficiently and productivity.
6. Reduction in rejections.
7. Increased output.
8. Fewer complaints about process related failures.
9. Reduced testing in process and in finished goods.
10. More rapid and reliable start-up of new equipments
11. Easier maintenance of equipment.
12. Improved employee awareness of processes.
13. More rapid automation.
14. Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

ORGANIZATION FOR VALIDATION

Validation organization can be divided into three basic areas;

1. *Establishing the organization.*
2. *Operating it from a quality and cost effectiveness basis.*
3. *Maintaining a functioning organization.*

- ***Establishing the organization***

  Formulating a department mission is necessary so that, not only process validation staff members understand the breadth of their job, but also the other corporate groups with whom there is interaction, can also understand.

Departments responsible

- **Site validation committee**: - Develop site master validation plan.
- **Manufacturing department**: - Prepares the batches as though their routine production batches.
- **Quality assurance**: - Ensure compliance and that documentation, procedures are in place. Approves protocols and reports.
- **Quality controls**: - Perform testing contracts validation testing and reviews protocol and report as needed.
- **Research and development**: - Deals with product design.
- **Engineering department**: - Installation, quality and certify plant, facilities, equipment and support systems.

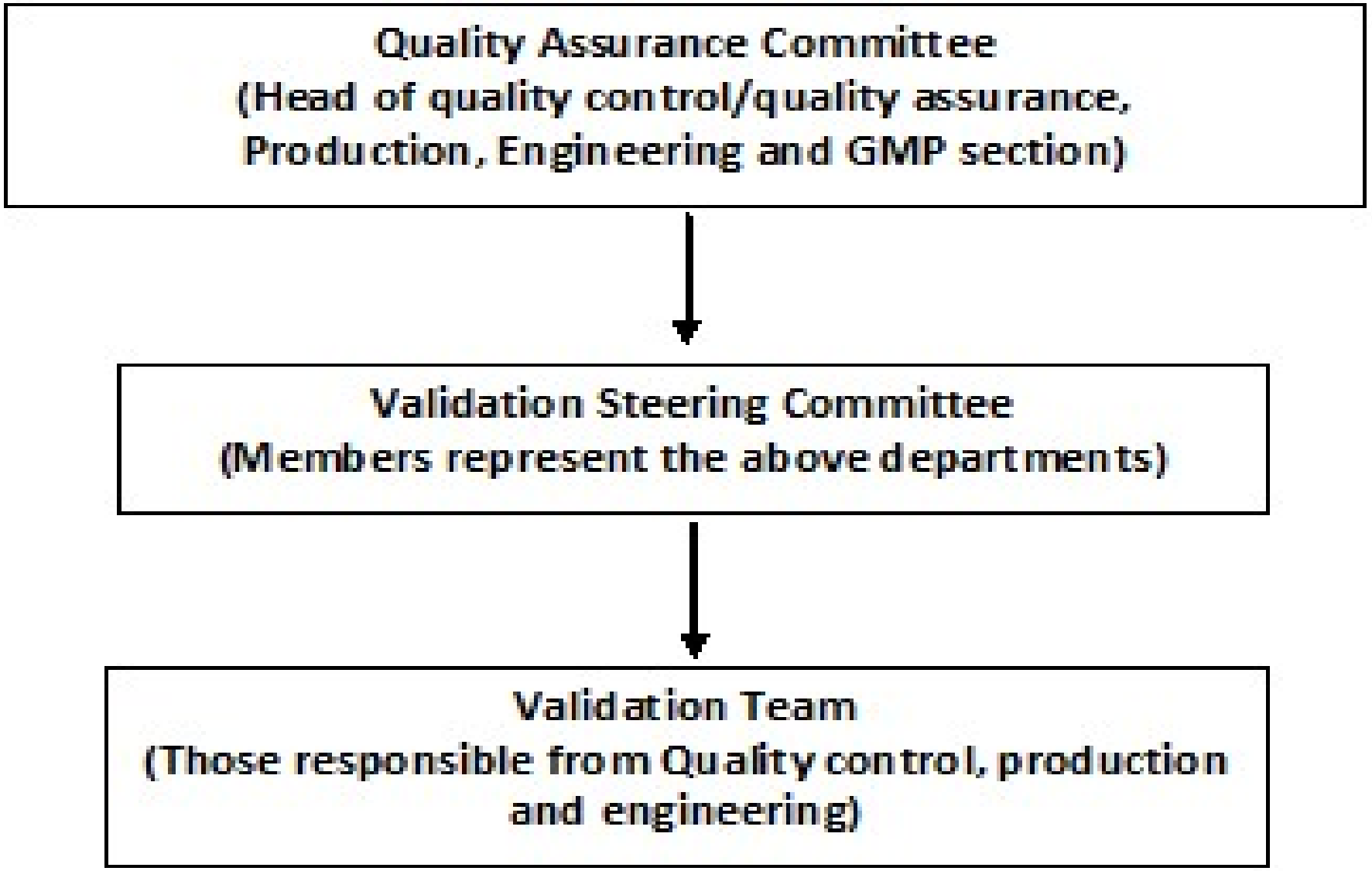
Validation team

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies.

Responsibilities of validation team

- Creates updates and reviews/approves individual project validation plans and validation deliverables.
- Ensures validation compliance with the company validation master plan and project validation plan.
- Coordinates, implements, verify elements of VMP.
- Consults on, evaluates and approves changes.
- Reviews and approves IQ/OQ/PQ procedures and plans.
- Reviews test results and makes recommendations regarding release.
- Assess risks and develops contingency plan.

ORGANIZATION FOR VALIDATION



Department interaction:

Once the validation team has been constituted and mission have been formalized, the team will interact with different departments which are :

- ✓ Research and development department
- ✓ Engineering department,
- ✓ Production department,
- ✓ Maintenance department,
- ✓ Quality control department,
- ✓ Quality assurance department.

VALIDATION MASTER PLAN

- The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning.
- The main elements of it being them list/inventory of the items to be validated and the planning schedule.
- All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan.

  It should comprise all prospective, concurrent and retrospective validations as well as revalidation.
- The Validation Master Plan should be a summary document and should therefore be brief, concise and clear.
- It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports.

- The format and content should include:
  - ✓ Introduction: validation policy, scope, location and schedule.
  - ✓ Organizational structure: personnel responsibilities.
  - ✓ Plant/process/product description: rational for inclusions or exclusions and extent of validation.
  - ✓ Specific process considerations that are critical and those requiring extra attention.
  - ✓ Key acceptance criteria.
  - ✓ Documentation format.
  - ✓ Reference to the required SOPs.
  - ✓ Time plans of each validation project and sub-project.
  - ✓ List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach.
  - ✓ Re-validation activities, actual status and future planning

VALIDATION PROTOCOL

- *A written plan stating how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results.*
- *This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested.*
- *The validation protocol provides a synopsis of what is hoped to be accomplished.*
- *The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance. The date of approval by the validation team should also be noted.*
- *In the case where a protocol is altered or modified after its approval, appropriate reasoning for such a change must be documented.*

- *The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information:*
  - ✓ *objectives, scope of coverage of the validation study*
  - ✓ *validation team membership, their qualifications and responsibilities*
  - ✓ *type of validation: prospective, concurrent, retrospective, re-validation*
  - ✓ *number and selection of batches to be on the validation study*
  - ✓ *a list of all equipment to be used; their normal and worst case operating parameters*
  - ✓ *outcome of IQ, OQ for critical equipment*

- requirements for calibration of all measuring devices
- critical process parameters and their respective tolerances
- description of the processing steps: copy of the master documents for the product
- sampling points, stages of sampling, methods of sampling, sampling plans
- statistical tools to be used in the analysis of data
- training requirements for the processing operators
- validated test methods to be used in in-process testing and for the finished product
- specifications for raw and packaging materials and test methods forms and charts to be used for documenting results

TYPES OF VALIDATION

Prospective validation

- It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol.
- This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process.
- Performed on at least three successive production-size (Consecutive batches).
- The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product.
- In Prospective Validation, the validation protocol is executed before the process is put into commercial use.

Concurrent validation

- It is a process where current production batches are used to monitor processing parameters.
- Concurrent Validation means establishing documented evidence a process does what it is supposed to based on data generated during actual implementation of the process.
- It is important in these cases when the systems and equipment to be used have been fully validated previously.
- It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.
- This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

Retrospective validation

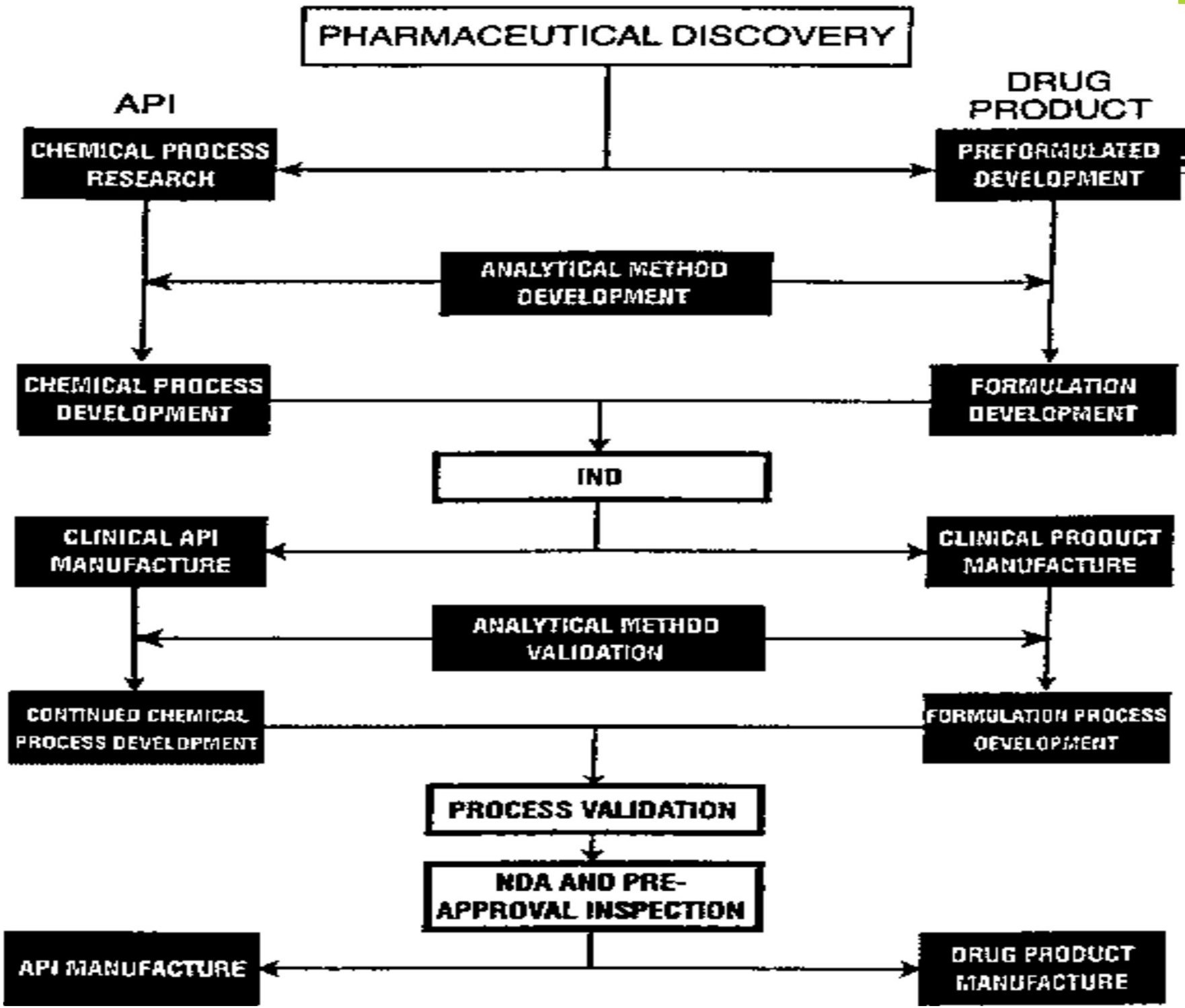
- It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This type of validation of a process is for a product already in distribution.
- Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.
- Validation of such processes should be based on historical data.
- For retrospective validation, generally data from ten to thirty consecutive batches should be examined to access process consistency, but fewer batches may be examined if justified.

Revalidation

- *Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.*
- *Re-validation becomes necessary in certain situations. Some of the changes that require validation are as follows:*
  - ✓ *Changes in raw materials (physical properties such as density, viscosity, particle size distribution 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).*
  - ✓ *Changes in the plant/facility.*

STREAMLINING VALIDATION OPERATIONS

- The best approach to avoiding needless and expensive technical delays is to work in parallel. The key elements at this important stage of the overall process are the API, analytical test methods, and the drug product (pharmaceutical dosage form). An integrated and parallel way of getting these three vitally important functions to work together is depicted in Figure below.
- Figure shows that the use of a single analytical methods testing function is an important technical bridge between the API and the drug product development functions as the latter two move through the various stages of development, clinical study, process development, and process validation and into production.


PHARMACEUTICAL DISCOVERY
API
DRUG PRODUCT
CHEMICAL PROCESS RESEARCH
PREFORMULATED DEVELOPMENT
ANALYTICAL METHOD DEVELOPMENT
CHEMICAL PROCESS DEVELOPMENT
FORMULATION DEVELOPMENT
IND
CLINICAL API MANUFACTURE
CLINICAL PRODUCT MANUFACTURE
ANALYTICAL METHOD VALIDATION
CONTINUED CHEMICAL PROCESS DEVELOPMENT
FORMULATION PROCESS DEVELOPMENT
PROCESS VALIDATION
NDA AND PRE-APPROVAL INSPECTION
API MANUFACTURE
DRUG PRODUCT MANUFACTURE

CALIBRATION v/s VALIDATION

- Calibration and validation are two processes in manufacturing to guarantee the quality of the product or related apparatus.
- With the calibration, the measurements are compared with an accepted reference measurement, to assure the considered measurements comply with the requirements.
- With the validation, the performance, quality, and other operating parameters of a system are tested to verify that they comply with the requirements.

CALIBRATION v/s VALIDATION

CALIBRATION

- ***Calibration*** *is a demonstration that, a particular Instrument or device produces results within specified limits by comparisons with those produced by a reference or traceable standard over an appropriate range of measurements.*
- *In calibration performance of an instrument or device is comparing against a reference standard.*

VALIDATION

- ***Validation*** *is a documented program that provides high degree of assurance that a specific process, equipment, method or system consistently produces a result meeting pre-determined acceptance criteria.*
- *No such reference standards are using in validation program.*

CALIBRATION v/s VALIDATION

CALIBRATION

- Calibration ensures that instrument or measuring devices producing accurate results.
- Shall be performed periodically, to identify the 'drift' of the measuring device or equipment and make them accurate.
- Shall be performed as per calibration SOP.

VALIDATION

- Validation provides documented evidence that a process, equipment, method or system produces consistent results (in other words, it ensures that uniforms batches are produced).
- No such requirements. Shall be performed when changes or modifications happen to the existing system or once revalidation period is reached.
- Shall be performed as per validation protocol.

User Requirements Specification (URS).

- *The User Requirements Specification describes the business needs for what users require from the system.*
- *User Requirements Specifications are written early in the validation process, typically before the system is created. They are written by the system owner and end-users, with input from Quality Assurance.*
- *Requirements outlined in the URS are usually tested in the Performance Qualification or User Acceptance Testing.*
- *User Requirements Specifications are not intended to be a technical document; readers with only a general knowledge of the system should be able to understand the requirements outlined in the URS.*
- *A URS defines clearly and precisely, what the customer (i.e. you) wants the system to do, and should be understood by both the customer and the instrument vendor.*
- *The URS is a living document, and must be kept updated, via a change control procedure.*
- *This focuses on the "what" rather than the "how."*

- **A well-written URS provides several specific benefits, as it:**
  - Serves as a reference against which off-the-shelf commercial products are selected, evaluated in detail, and any enhancements are defined.
  - Reduces the total system effort and costs, since careful review of the document should reveal omissions, misunderstandings and/or inconsistencies in the specification and this means that they can be corrected easily before you purchase the system.
  - Provides the input to user acceptance test specifications and/or qualification of the system.

- **The URS should include:**
  - **Introduction** – including the scope of the system, key objectives for the project, and the applicable regulatory concerns
  - **Program Requirements** – the functions and workflow that the system must be able to perform
  - **Data Requirements** – the type of information that a system must be able to process
  - **Life Cycle Requirements** – including how the system will be maintain and users trained

General Guidance for Writing the Requirements

- The following guidelines should be followed during the production of the specification:
- Each requirement statement should be uniquely referenced and no longer than 250 words.
- The URS should be consistent and requirement statements should not be duplicated or contradicted.
- Specify requirements and not design solutions. The focus should be on what is required, but not how it is to be achieved.
- Each requirement should be testable. This allows the tests to be designed as soon as the URS is finalised.
- Both the customer and the vendor must understand the document. Therefore, jargon should be avoided wherever possible and key words are defined in a specific section in the document.
- Requirements should be prioritised as mandatory or desirable.
- The URS should be modifiable but changes should be under a formal control procedure.
- A URS is correct if every stated requirement has only one interpretation and is met by the system. Unfortunately, this is very rare.

ACCEPTANCE TESTING

- *The question of what USER ACCEPTANCE TESTING (UAT) is, becomes very important as you reach a state of having equipment /systems delivered to a facility.*
- *The system/equipment is claimed to be constructed in a manner that has been defined by a User Requirement, and constructed or fabricated in a manner that meets the requirements of the industry and of your company specifically.You can ill afford to accept a system or piece of equipment that does not meet these requirements.*

- ***What is Acceptance Testing?***
  - *User Acceptance Testing defines **precisely** and **clearly** what the user expects the system to do. UAT documents contain information about the operating environment, the required data for processing, and the functionality that the system should carry out.*
  - *Completed during a FAT and a SAT*

What is a FAT?

- *A **FAT** or Factory Acceptance Test is usually preformed at the vendor prior to shipping to a client. The vendor tests the system in accordance with the clients approved test plans and specifications to show that system is at a point to be installed and tested on site.*

- *It's an essential aspect of the whole system lifecycle and should be performed by experienced personnel. Time spent doing a proper FAT will lead to fewer problems when the equipment is installed.*

- ***Summary - It is the partial commissioning and qualification of equipment and/or systems prior to their shipment from the fabricator's site.***

- *The FAT protocol is an inspection that includes both static and dynamic exhaustive testing of systems or major system components to support the qualification of equipment or a system. The tests must verify that all functionality detailed in the User Requirements Specification (URS) is embodied and performs as specified. It is written by the manufacturers and executed by the client or client representative.*

What is a SAT?

- ***SAT*** *is Site Acceptance Test of a system to ensure it is tested in accordance to client approved test plans and specifications & to show the system is installed properly and interfaces with other systems and peripherals in its working environment.*

- ***Summary - Inspection and /or dynamic testing of the systems or major system components to support the qualification of an equipment system conducted and documented at the manufacturing site.***

- *The SAT is related to the FAT and also entails inspection and dynamic testing of systems or major system components to support the qualification of equipment. This is written by the client and verifies that the installed functionality of the equipment meets or exceeds the operational requirements as specified in the equipment URS.*

- *The SAT is executed on completion of all commissioning tasks; but prior to the start of Installation Qualification execution.*

CALIBRATION AND PREVENTIVE MAINTENANCE

- Regulations of the regulatory authorities like FDA and EU require that all the firms have program for calibration and preventive maintenance for test as well as measurement equipments.
- Preventive maintenance program is one of the most importance aspects for GMP inspection as it ensures the efficient GMP operations.
- Any equipments either it is automatic or manually operated will perform its functions properly and are used for manufacturing, processing, packaging, labeling or holding of drug products; it is mandatory that it will be timely calibrated, inspected and checked for errors according to the written program which is specially designed to assure the best performance of the equipments.

INTRODUCTION

- **Definition of Calibration:** - "It is a set of operation that performs under specific conditions to verify the values/data obtained by comparison of two instruments or measuring devices one of which is a standard of known accuracy (Traceable to national standards). It is used to detect, correlate, report or eliminate any of the discrepancy in accuracy of instruments or measuring devices when being compared to the standard."
- Calibration is one type of comparison but it is not an adjustments.

- **Definition of Preventive Maintenance:** "It is a care or service provided by personnel to maintain the equipment or facility in satisfactorily working conditions by providing inspections, detection and correction of failures before they occur. Basically they are conducted to keep the instrument in working conditions and to extend the life of the instrument."

Main advantages of PM are:

- ✓ Improvement in the reliability of system,
- ✓ Decrease in replacement cost and time,
- ✓ Inventory management system is also improved.

Requirements of Regulatory Authorities

- Calibration program is required by the regulatory authority (FDA) under section 21 CFR part 211.68 and Preventive maintenance and calibration program is required by FDA under section 21 CFR part 211.67.
- Calibration requirements for Lab instruments under section 21 CFR part 211.67 are: specific directions, schedule, limit of accuracy and precision remedial action and system to prevent usage of instrument which are failed to calibrate.

Calibration and maintenance procedure (SOP)

- There should be a documented SOP for conducting the calibration and preventive maintenance for each type of instrumentation.
- The SOP for calibration must includes accuracy and precision limits and what are the remedial actions should be taken if this limits do not meet with each other. There should be an authorized department to perform and monitor calibration and maintenance.
- The SOP must contain the step by step calibration instructions, instrumentation manual, proper calibration procedures, provisions for adjustments, provisions for record and document the actual measurement reading before and after doing adjustment.

Software used for calibration and PM

- Lots of software are used for calibration and PM at industrial scale. This computerized system has more efficiency and guaranteed the best results.

Calibration software

- Quality Calibration Management system (QCMS) is complete instrument and designed according to the requirements of 21 CFR part 11. This software ensures regulatory compliance and also traceability. It will help to improve the reliability of plant and optimize the administrative costs. It will help to increase in the productivity as well as efficiency.

Preventive maintenance software

- RCM turbo is very popular PM software. Traditional approach took years to complete just one PM but by using this RCM turbo, anyone can quickly go for PM. This software directs us through EMEA process. But the thing is it will go through quickly and efficiently. It is 100 % reliable and will allow you do risk assessment.

CALIBRATION OF ANALYTICAL BALANCE

Measure the pan position error of the balance

- **Daily calibration**
  - The maximum and minimum weight limits of the balance are taken and divided into four to five parts and single standard weight is selected in those four or five different regions for the purpose of daily calibration.
  - The variation allowed from the standard weight used for measuring is NMT ±0.1% of standard weight.
  - Drift check from day to day is carried out using any particular weight and the deviation allowed should not be more than ±1% of that weight.

- ***Monthly calibration***

- *All the standard weights in the maximum and minimum weighing limits are used in monthly calibration and the deviation allowed should not be more than ±0.1% of standard weight used. (The standard weights that are used are E1 and E2 weights)*

- ***Measurement of uncertainty***

- *For measurement of uncertainty any single standard weight is taken and is weighed for 10 times the readings are noted and the standard deviation for all the readings is calculated. And measurement of uncertainty can be measured using the formula:*

- ***Measurement of uncertainty*** = $\frac{\text{S. D. x 3}}{\text{Standard weight taken}}$