CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF

PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.821850

Available online at: http://www.iajps.com *Review Article*

OVERVIEW OF VALIDATION, BASIC CONCEPTS AND ANALYTICAL METHOD PROCESS VALIDATION

Indu Gurram*, M.V.S.Kavitha, M.V.Nagabhushnam, Brahmaiah Bonthagara, D.Nagarjuna Reddy

Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amravati road, Guntur, A.P, India- 522002.

Abstract:

Quality is the primordial intention to any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. When analytical method is utilized to generate results about the characteristics of drug related samples it is essential that the results are trustworthy. They may be utilized as the basis for decisions relating to administering the drug to patients. Analytical method validation required during drug development and manufacturing and these analytical methods are fit for their intended purpose. To Process Validation emphasize on process design elements and maintaining process control during commercialization and communicate that process validation is an ongoing program and align process validation activities with product lifecycle. Process validation also emphasizes the role of objective measures and statistical tools and analyses and emphasizes knowledge, detection, and control of variability and gives assurance on consistent of quality/productivity throughout life cycle of product.

Keywords: *Quality, Validation, Process Validation, Protocol, Prerequisites, Regulatory basis, Analytical method validation, Pharmaceutical analysis, Specificity, Precision*.

Corresponding Author:

Indu Gurram ,

Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amravati road, Guntur, A.P, India- 522002.

E-mail: brahmaiahmph@gmail.com

QR code

Please cite this article in press as Indu Gurram et al, ***Overview of Validation, Basic Concepts and Analytical Method Process Validation****, Indo Am. J. P. Sci, 2017; 4(06).*

INTRODUCTION

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation [1].

Validation is a concept that has evolved in united states in 1978.The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labelling or process control, Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP. [2]

This principle incorporates the understanding that the following conditions exist: Quality, safety, and efficacy are designed or built into the production The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. Process controls include raw materials inspection, in process controls and targets for final product .Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance. [3]

Validation mainly based on, FDA regulations describing current good manufacturing practice (cGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211. The cGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the cGMP regulations in parts 210 and 211 [4].

Analytical method defined that Analytical chemistry is the study of separation, quantification and chemical components identification of natural and artificial materials constituted with one or more compounds or elements. Analytical chemistry is separated into two main categories, qualitative analysis that is to say the identification with regard to the chemical components exist in the sample, where as quantitative the amount of certain element or compound in the substance i.e., sample. analysis estimates

Analytical method development finally results in official test methods. Consequently quality control laboratories used these methods to check the efficacy, identity, purity, safety as well as performance of products of the drug. Regulatory authorities give utmost importance on analytical methods in manufacturing. Drug approval by regulatory authorities requires the applicant to prove control of the entire process of drug development by using validated analytical methods. Modern pharmaceutical analysis needs the following requirements.

1. The analysis should take a minimal time and should be economical.
2. The accuracy of the analysis must accept the guidelines of Pharmacopoeia
. 3. The chosen method should be precise and selective.

HISTORY OF VALIDATION

The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals (Agalloco 1995). It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated process of pharmaceutical.

U.S.F.D.A. was the pioneer in advocating the concept of process validation, but till 29th September 1978 the definition of process validation did not appear in any part of literature of U.S.F.D.A. no cGMP regulations talked anything about process validation [5].

Definitions [6-8]

European commission: 1991 –Validation-"Act of proving, in accordance of GMPs that Any…" process actually leads to expected results. 2000 - "Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes".

US FDA Definition: "Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

ICH Definition: "Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality."

WHO Definition: "The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result."

Need of Pharmaceutical Validation [9]

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.

Assurance of Quality: Without validation, a process that is well understood and in a state the confidence, control of quality of the product manufactured cannot be assured without validation

Cost Reduction : Since each and every step in validation is monitored constantly there lesser rejects and reworks which would lead to an effective cost reduction.

Government Regulation

Validation is considered to be an integral part of GMPs. Worldwide compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products.

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 becomes a really difficult task. However, a systematic look at the pharmaceutical operations will point out at least the following areas for pharmaceutical validation; [10]

- ✓ Analytical
- ✓ Instrument Calibration
- ✓ Process Utility services
- ✓ Raw materials
- ✓ Packaging materials
- ✓ Equipment
- ✓ Facilities
- ✓ Manufacturing operations
- ✓ Product Design
- ✓ Cleaning
- ✓ Operators

Table 1: Validation team and responsibilities

Department	Designation	Responsibility
Research and development (R&D)	Executive/Officer	To coordinate the entire validation process by scheduling meetings and discussions with production, quality control and quality assurance. Preparation of preliminary validation protocol, master formula record, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review the preliminary validation documents.
Quality Assurance	Officer	To coordinate the entire validation process by scheduling meetings and discussions with the team. Preparation of validation protocol, monitoring the process, compiling and analyzing data and test results and preparing the final report. To review of validation documents.
Production	Officer	To participate in performing the validation steps during manufacturing processes. To assist in collection of data.
Quality control	Officer	To test and report the test results
Quality assurance	General manager Quality assurance	To approve the process validation protocol and report. To review of validation documents. To approve the process

Importance of Validation [11, 12]

- ✓ Assurance of quality
- ✓ Time bound
- ✓ Process optimization Reduction of quality cost
- ✓ Nominal mix-ups, and bottle necks
- ✓ Minimal batch failures, improved efficiently and productivity
- ✓ Reduction in rejections
- ✓ Increased output
- ✓ Avoidance of capital expenditures
- ✓ Fewer complaints about process related
- ✓ failures

Planning for Validation: [13]

All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

- ✓ TheVMP should be summary document, which is brief, concise and clear.
- ✓ The VMP should contain data on at least the following:
- ✓ Validation policy.
- ✓ Organizational structure of validation
- ✓ activities..
- ✓ Planning and scheduling.
- ✓ Reference to existing document.
- ✓ In case of large projects, it may be
- ✓ necessary to create separate validation
- ✓ master plans.

Validation Set Up [14]:To establish the desired attributes. These attributes include physical as well as chemical characteristics. In the case of parenteral, these desirable attributes should include stability, absence of pyrogens, and freedom from visible particles.

The process and equipment should be selected to achieve the product specification. For example; design engineers; production and quality assurance people may all be involved.

Four Major Advantages of Validation Namely [9, 16]

Assurance of Quality

Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality and it is not possible to control a process properly without thorough knowledge of the capabilities of that process without validated and controlled processes, it is impossible to produce quality products consistently. End product testing, in the absence of validation, gives little assurance of quality for variety reasons, among which are

- ✓ Very limited sample size.
- ✓ The limited number of tests performed on a sample. For example, it is impractical to test for all potential impurities or contaminants.
- ✓ The limited sensitivity

Process Optimization

The optimization of a process for maximum efficiency, while maintaining quality standards, is a consequence of validation. Literal meaning of word to optimize is "To make as effective, perfect or useful as possible". The optimization of the facility, equipment, systems, and processes results in a product that meets quality requirements at the lowest cost.

Reduction of Quality Costs Quality costs are divided in to four categories. They are:

- ✓ Preventive costs.
- ✓ Appraisal costs.
- ✓ Internal failure costs.
- ✓ External failure costs.

e.g.: of internal failure costs: Any validated and controlled process will result in fewer internal failures like

- ✓ Fewer rejects
- ✓ Reworks
- ✓ Re-tests
- ✓ Re-inspection

Process validation makes it possible to do the job right the first time. Also, a scientifically studied and controlled process makes it unlikely that defective products will be dispatched to market thus no recalls or market complaints.

Safety: Validation can also result in increased operation safety. e.g.: gauges used on equipment that designed to operate at certain temperature and pressures must be reliable i.e. they must be calibrated.

TYPES/METHODS OF VALIDATION [17,18]

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-sizes (Consecutive batches).

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be categorized into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiment should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.

All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. 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. In practice, it may take some considerable time accumulate these data. Some considerations should be exercised when selecting the process validation strategy. Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the process data in case of Requalification and Revalidation.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

Upon completion of the review, recommendations should be made on the extent of monitoring and the inprocess controls necessary for routine production. These should be incorporated into the Batch manufacturing and packaging record or into appropriate standard operating procedures. Limits, frequencies and action to be taken in the event of the limits being exceeded should be specified. Prospective validation should include, but not be limited to the following:

- ✓ Short description of the process

- ✓ Summary of the critical processing
- ✓ steps to be investigated.
- ✓ List of the equipment/facilities to be
- ✓ used (including measuring, monitoring/recording equipment)
- ✓ together with its calibration status.
- ✓ Finished product specifications for
- ✓ release.
- ✓ List of analytical methods, as appropriate.
- ✓ Proposed in-process controls with
- ✓ acceptance criteria.
- ✓ Additional testing to be carried out,
- ✓ with acceptance criteria and analytical
- ✓ validation, as appropriate.
- ✓ Sampling plan.
- ✓ Methods for recording and evaluating results.
- ✓ Functions and responsibilities.
- ✓ Proposed timetable.

Batches made for process validation should be the same size as the intended Industrial scale batches. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise and the marketing authorization.

Concurrent Validation

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.
- In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
- The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.
- Documentation requirements for concurrent validation are the same as specified for prospective validation.

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 is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process 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.

Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet the specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process. 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.

Some of the essential elements for Retrospective Validation

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.

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. Revalidation 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 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). Changes of equipment which involve the replacement of equipment on a “like for like” basis would not normally require revalidation except that this new equipment must be qualified.
- ✓ Changes in the plant/facility.

A decision not to perform revalidation studies must be fully justified and documented.

Basic Concept of Process Validation

Pharmaceutical Process Validation is the most important and recognized parameters of cGMPs. The requirement of process validation appears of the quality system (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use [19]. **Installation Qualification (IQ)**

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer’s approved specification and that the recommendation

of the supplier of the equipment are suitably considered.

IQ considerations are:

Equipment design features (i.e.material of construction clean ability,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).

Operational Qualification (OQ)

Establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements.

OQ considerations include:

- ✓ 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.
- ✓ Short term stability and capability of the process,

Performance Qualification (PQ)

Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

PQ considerations include:

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

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.

The Regulatory Basis for Process Validation [23, 40]

The concept of process validation from its beginnings in the early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to

various analytical, quality assurance, pilot plant, production, and sterile product and solid dosage forms considerations. In the early 1990s, the concept of preapproval inspection (PAI) was born and had as one

of its basic tenets the assurance that approved validation protocols and schedules were being generated and that

Comprehensive development, scale-up, and bio batch and commercial batch validation data were required in order to achieve a successful regulatory PAI audit.

Prerequisite of Process Validation [24]

- ✓ Process Development Designee shall review the product development report, data from pilot scale, scale up batch and proposed master formula document of product intended for manufacturing.
- ✓ Process Development Designee shall review/ensure the availability analytical method transfer report to the plant and plant preparedness for conducting validation testing and routine testing; function shall co-ordinate with QC/QA in this regards [25].
- ✓ Process Development Designee shall prepare commercial/exhibit batch production and control records which include the operational limits and overall strategy for process control based on development report.
- ✓ The Process Validation is performed after the facility, utility, and equipment, and laboratory test methods have been validated and released fir process validation activities. Where compendia method is used only limited analytical method validation shall be conducted.
- ✓ All raw material and packaging material specification shall be from approved vendors and shall be approved by quality control.

Strategy for Industrial Process Validation of Solid

Dosage Forms [26]

The strategy selected for process validation should be simple and straightforward. The following five points

gives strategy for process validation.

- ✓ The use of different lots of raw materials should be included. i.e., active drug substance and major excipients.
- ✓ Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).
- ✓ Batches should be manufactured in the equipment and facilities designated for eventual commercial production.

Process Validation within the Quality Management

System [27]

Process validation is part of the integrated requirements of equality management system. It is conducted in the context of a system including design and development control, quality assurance, process control, and corrective and preventive action. The
product should be design robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Corrective actions often identify inadequate processes/process validations. Each corrective action applied to a manufacturing process should include the consideration for conducting process validation/ revalidation.

Reason for Process Validation [28]

The possible reason of performing process validation may include:

- ✓ New product or existing products as per SUPAC changes.
- ✓ Change in site of manufacturing.
- ✓ Change in batch size, equipment, in process existing products.
- ✓ Change in vendor of API or critical excipient.
- ✓ Change in specification on input material.

Benefits of Process Validation [27]

- ✓ Consistent through output.
- ✓ Reduction in rejections and reworks.
- ✓ Reduction in utility cost.
- ✓ Avoidance of capital expenditures.
- ✓ Fewer complaints about process related failure.
- ✓ Easier maintenance of equipment.
- ✓ Improve employee awareness of processes.
- ✓ More rapid automation.

Stages of Process Validation [29, 30]

Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process Validation involves a series of activities taking place over the lifecycle of the product and process. The activities relating to validation studies may be classified into three stages:

Stage 1 – Process Design

"Focusing exclusively on qualification efforts without also understanding the manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. It covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability. Also this is the stage in which the establishment of a strategy for process control is taking place using accumulation knowledge and understanding of the process. "

Stage 2 – Process Qualification

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. It confirms that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under "worst case" conditions. GMP compliant
procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product.

There are two aspect of Process Qualification:

- ✓ Design of Facilities and Qualification of Equipment and Utilities
- ✓ Proper design of manufacturing facility is desired under 21 CFR part 211, subpart C, of the cGMP regulation on Buildings and Facilities.
- ✓ Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly.

Process Performance Qualification "Criteria and process performance indicators that allow for a science and risk-based decision about the ability of the process to consistently produce quality products".

- ✓ Objective measures, where possible.

May be possible to leverage earlier study data if relevant to the commercial scale.

Stage 3 – Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control. The validation maintenance stage requires frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures.

A successful validation program depends on the knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detection of the variation, and the attributes susceptible of the variation.

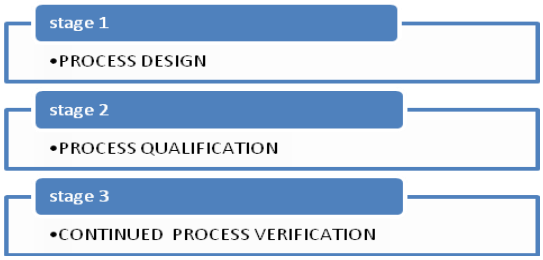

Fig. 1 Approaches to Process Validation

Primary Packing Validation Approach

Primary packing will be done for individual packing ,the process validation protocol shall be clearly state the variable(s) which impact the integrity of the primary pack and set parameters range, primary packing is mostly change part specific and it is mandatory for all new products

Phases in Process Validation [31, 32]

The activities relating to validation studies may be classified into three:

Phase1:Pre-Validation Qualification Phase

This phase is covers all activities relating to product research and development, formulation pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions and storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualification master production document,

operational qualification and process capacity.

Phase 2: Process Validation Phase

It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory. Products can be produced even under the worst conditions.

Phase 3: Validation Maintenance Phase

It requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture.

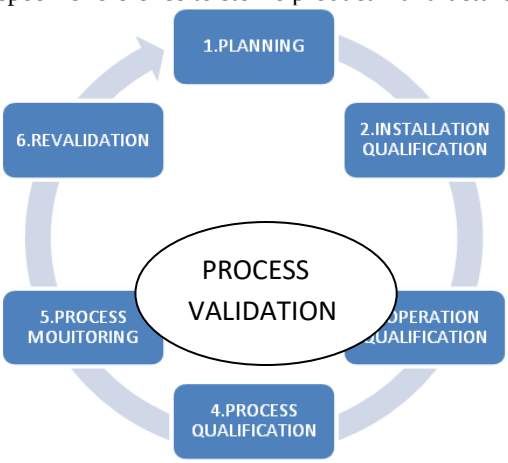

Fig. 2: Phases in Process Validation

Validation Protocol [33]

Detailed protocols for performing validations are essential to ensure that the process is adequately validated. Process validation protocols should include the following elements:

- Objectives, scope of coverage of the validation study
- Validation team membership, their qualifications and responsibilities.

Validation Master Plan [34]

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 the list/inventory of the items to be validated and the planning schedule

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 and critical and those requiring extra attention.

Process Validation and Quality Assurance [35]

The relationship of quality assurance and process validation goes well beyond the responsibility of any quality assurance (QA) function. Nevertheless, it is a fair to say that process validation is a QA tool, because

it establishes a quality standard for the specific process.

The quality assurance associated with the pharmaceutical development effort includes the following general functions:

- ✓ To ensure that a valid formulation is designated.
- ✓ To qualify the process that will be scaled up to production-size batches.
- ✓ To assist the design of the validation protocol.
- ✓ To manufacture the bio batches for the clinical program, which will become the object of the FDA's preapproval clearance.

Validation Report [36, 37] A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated). The report

should include at least the following:

- ✓ Title and objective of study.
- ✓ Reference to protocol.
- ✓ Details of material.
- ✓ Equipment.
- ✓ Programmes and cycles used.
- ✓ Details of procedures and test methods.
- ✓ Results (compared with acceptance criteria).
- ✓ Recommendations on the limit and criteria to be applied on future basis.

Documentation [38, 39]

A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

A report that cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

The degree and type of documentation required by cGMP is greatest during process qualification, and continued process verification. Studies during these stages must conform to cGMPs and must be approved by the quality unit in accordance with the regulations (21 CFR 211.22 and 211.100).

TYPES OF ANALYTICAL METHOD VALIDATION

I. TYPICAL INSTRUMENTAL TECHNIQUES

The methods of estimation of drugs are separated into physical, chemical, physicochemical and biological categories. Of these methods, generally physical and physicochemical methods are used and the most of the physical methods pertaining to analysis engross the studying of the different physical properties of a substance. They are determination of the solubility, transparency or degree of turbidity, color, density or specific gravity (for liquids), melting, freezing, boiling points and moisture content. Physicochemical methods[9, 10] are utilized to examine the physical phenomena that happened as a result of chemical reactions. In the Physicochemical methods Optical (Refractometry, Polarimetry, Emission Spectrophotometry and Nephelometry or Turbidometry), Electrochemical (Potentiometry, Amperometry and Polarography) and Chromatography (Paper, Column, Thin Layer[11], Gas Liquid Chromatography[12] High Performance Liquid Chromatography[13, 14] methods are usually preferable. Methods involving nuclear reaction like Nuclear Magnetic Resonance happened to be more popular. GC-MS combination is one of the prominent powerful tools available. The chemical methods include the volumetric and gravimetric procedures, which are mainly depend on complex formation, acid – base and redox reactions. Titrations in complexometry and non-aqueous media have been extensively utilizing in pharmaceutical analysis whenever the sensitivity at mg level is sufficient and the interferences are negligible. The modern methods (HPLC, UPLC, GLC, GC-MS/MS, LC-NMR and Liquid chromatography–mass spectrometry are the available choices for assay involving sophisticated equipment, which are highly sensitive, accurate and consume very tiny amount of samples for analysis

II. ANALYTICAL METHOD DEVELOPMENT

When there are no authoritative methods are available, new methods are being developed for analysis of novel products. To analyze the existing either pharmacopoeial or non-pharmacopoeial products novel methods are developed to reduce the cost besides time for better precision and ruggedness. These methods are optimized and validated through trial runs. Alternate methods are proposed and put into practice to replace the existing procedure in the comparative laboratory data with all available merits and demerits.

2.1. Purpose of analytical method development

Drug analysis reveals the identification characterization & determination of the drugs in mixtures like dosage forms & biological fluids. During manufacturing process and drug development the main purpose of analytical methods is to provide information about potency (which can be directly related to the requirement of a known dose), impurity (related to safety profile of the drug), bioavailability (includes key drug characteristics such as crystal form, drug uniformity and drug release), stability (which indicates the degradation products), and effect of manufacturing parameters to ensure that the production of drug products is consistent

The reasons for the development of novel methods of drug analysis are:

a) When there is no official drug or drug combination available in the pharmacopoeias.

b) When there is no decorous analytical process for the existing drug in the literature due to patent regulations.

c) When there are no analytical methods for the formulation of the drug due to the interference caused by the formulation excipients.

d) Analytical methods for the quantitation of the analyte in biological fluids are found to be unavailable.

e) The existing analytical procedures may need costly reagents and solvents. It may also involve burdensome extraction and separation procedures.

2.2. Steps for the development of the method

Development procedure follows with the proper documentation. All data relating to these studies must be recorded either in laboratory notebook or in an electronic database.

2.3. Analyte standard characterization

a) All known important information about the analyte and its structure that is to say physico-chemical properties like solubility, optical isomerism etc., is collected.

b) The standard analyte (≈100 % purity) is obtained. Necessary arrangement is to be made for the perfect storage (refrigerator, desiccators, and freezer).

c) In the sample matrix when multiple components are to be analyzed, the number of components is noted duly presenting the data and the accessibility of standards is estimated.

d) Methods like spectroscopic, HPLC, GC, MS etc., are considered when matched with the sample stability.

2.4. Method requirements

The requirements of the analytical method need to develop the analytical figures of merit such as linearity, selectivity, range, accuracy, precision, detection limits etc., shall be defined.

2.5. Literature search and prior methodology

All the information of literature connected with the drug is reviewed for physico-chemical properties, synthesis, solubility and appropriate analytical methods with reference to relevant books, journals, USP/NF, AOAC and ASTM publications and it is highly convenient to search Chemical Abstracts Service automated computerized literature.

2.6. Choosing a method

a) Duly utilizing the information available from the literature, methodology is evolved since the methods are changed wherever required. Occasionally it is imperative to get additional instrumentation to develop, modify or reproduce and validate existing procedures for analytes and samples.

b) If there are no past suitable methods available to analyze the analyte to be examined

2.7. Instrumental setup and initial studies Installation, operational and performance qualification of instrumentation with reference to laboratory standard operating procedures is verified by setting up appropriate instrumentation.

2.8. Optimization While performing optimization, one parameter is changed at a time and a set of conditions are isolated, before utilizing trial and error approach. The said work need to be accomplished basing on a systematic methodical plan duly observing all steps and documented with regard to dead ends.

2.9. Documentation of analytical figures of merit

The actual decided analytical figures of merit like Limit of quantitation, Limit of detection, linearity, time taken for analysis, cost, preparation of samples etc. are also documented.

2.10. Evaluation of development method with real samples

The sample solution should lead to unequivocal, total identification of the peak interest of the drug apart from all other matrix components.

2.11. Estimation of percent recovery of real samples and demonstration of quantitative sample analysis

Percent recovery of spiked, genuine standard drug into a sample matrix which contains no analyte is estimated. Optimization to reproducibility of recovery (average ± standard deviation) from sample to sample has to be showed. It is not necessary to get 100% recovery so far as the results are reproducible to recognize with a high degree of certainty

III.. ANALYTICAL METHOD VALIDATION

The process of validation of analytical method[20-24] is adopted to confirm that the employed analytical procedure for a specific tests meet the intended requirements. Guidelines from the USP, ICH, FDA etc., can provide a framework for validations of pharmaceutical methods. Results from the method validation can be considered to judge its quality, reliability as well consistency pertaining to analytical results. In the realm of pharmaceutical industry the prominent reasons for validating assay are the first crucial one is validation of assay which is the integral part of the quality-control system and secondly regulation of genuine manufacturing practices inevitably needs assay validation.

Parameters of Analytical Method Validation

Analytical methods have been validated in pursuance of ICH guidelines of Q2 (R1)[25]. Validation parameters are: 1. System suitability

1. Specificity
2. Linearity
3. Precision
4. Accuracy
5. LOD
6. LOQ
7. Robustness

3.1. System Suitability

System suitability testing originally believed by the industry of pharmaceuticals to decide whether a chromatographic system is being utilized day today in a routine manner in pharmaceutical laboratories where quality of results is most important which is suitable for a definite analysis.

The parameters used in the system suitability tests (SST) report are as follows:

- Number of theoretical plates or Efficiency (N).
- Capacity factor (K).
- Separation or Relative retention (α).
- Resolution (Rs).
- Tailing factor (T).
- Relative Standard Deviation (RSD).

Number of theoretical plates/Efficiency (N) In a specified column, efficiency is defined as the measurement of the degree of peak dispersion and it should have the column characteristics. The efficiency is conveyed in terms of number of theoretical plates". The formula of calculation of N is illustrated bellow in the following Figure 1.1. (Half height method).

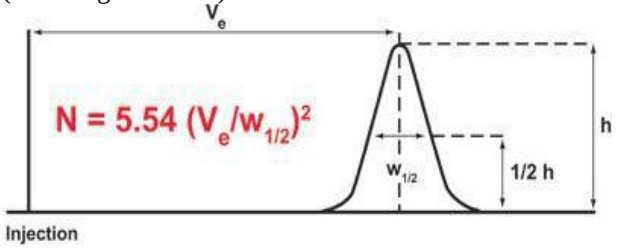

Fig 3: Half height method relating to determination of N.

N = Efficiency / Number of theoretical plates. Ve = Retention time of analyte.

h = Height of the peak.

w 1/2 = Gaussian function of the peak width at the half- height.

Sigma/tangential method (USP method) With the help of sigma/tangential method N is calculated which is shown in the following figure 1.2 duly noting the formula for calculation of N.

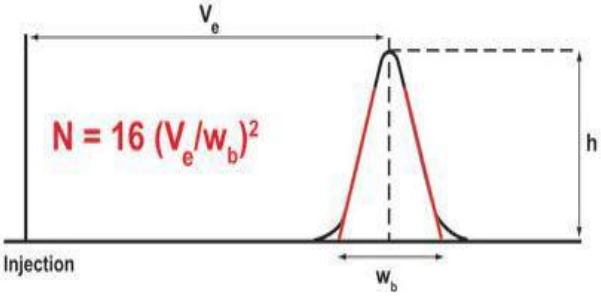

Fig 4: Sigma/tangential method relating to determination of N.

N = Number of theoretical plates.
Ve = elution volume, retention time or retention distance (mL, sec, or cm).
h = peak height.
wb = width of the peak at the base line (mL, sec, or cm).

The plate number depends on column length. Theoretical plate number is the measure of column efficiency. As stated by plate theory, the analyte will be in instant equilibrium with stationary phase and column has to be divided into number of hypothetical plates and each plate consists of a fixed height and analyte spends finite time in the plate. Height equivalent to theoretical plate (HETP) is given by following formula:

HETP =L Where,

L = length of column.
N = plate number.

Capacity ratio or Capacity factor (k)

K=tR-tM/t

The above said capacity factor sometimes is called as a retention factor which has no dimension and independent from flow rate of mobile phase as well as column dimensions which is the measure of extent of retention relating to an analyte relative to an un-retained peak. Where tR implies retention time of the sample peak and retention time of an un-retained peak is tM.

k' = 0 means no compound is left in the column. Generally the value of k' is > 2.

Resolution (Rs)

Resolution is the capability of the column to separate 2 drugs in 2 individual peaks or chromatographic zones and it is improved by enhancing column length, reduction of particle size and rising temperature, altering the eluent or stationary phase. It can be told in terms of ratio of separation of the apex of two peaks by the tangential width average of the peaks. By using the following formula resolution is calculated.

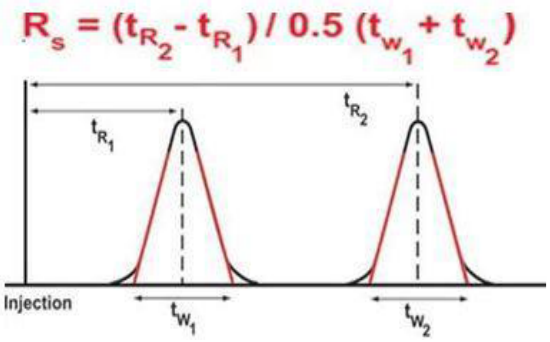

Fig 5: Determination of resolution between two peaks.

tR1 and tR2 are the retention times for the two peaks of components. tw1 and tw2 = At the baseline lies between tangents drawn to the sides of the peaks. (Tangents are drawn at 0.6 times the peak height). If the peaks are correctly symmetric, provided the valley between the two peaks should touch the baseline Rs is 1.5. Generally good value of resolution is Rs ≥2 should be adequate and preferred normally. **Resolution factor (R)**

Resolution is a function of capacity factor, function of selectivity and a function of efficiency (or) number of theoretical plates (N). In order to separate any two peaks you must have right capacity factor ideally between 2 and 10, but appropriate selectivity is required i.e., ideally 1.2 and enough efficiency i.e., number of theoretical plates (more than 2000 theoretical plates). Resolution should be ≥ 1.5. 1.5 defines baseline resolution.

Tailing factor or Asymmetry factor

Chromatographic peak assumed to have a Gaussian shape under ideal conditions. However in practical conditions, there is always a deviation from normal distribution which indicates non-uniform migration and non-uniform distribution process. Hence the regulatory organizations like USP and EP have recommended this as one of the system suitability parameter. The asymmetry factor and tailing factor are roughly same and rarely accurate and equal in most cases. Values should normally between 1.0-1.5 and values greater than 2 are unacceptable. The peak asymmetry is computed by utilizing the following formula

As = B/A

Where: As = peak asymmetry factor

B = distance from the point at peak midpoint to the trailing edge. (measured at 10 % of peak height).

A = distance from the leading edge of peak to the midpoint.

(measured at 10 % of peak height). Ideally, peaks should be Gaussian in shape or totally symmetrical. Determination of tailing and asymmetric factor is shown in Figure 1.5

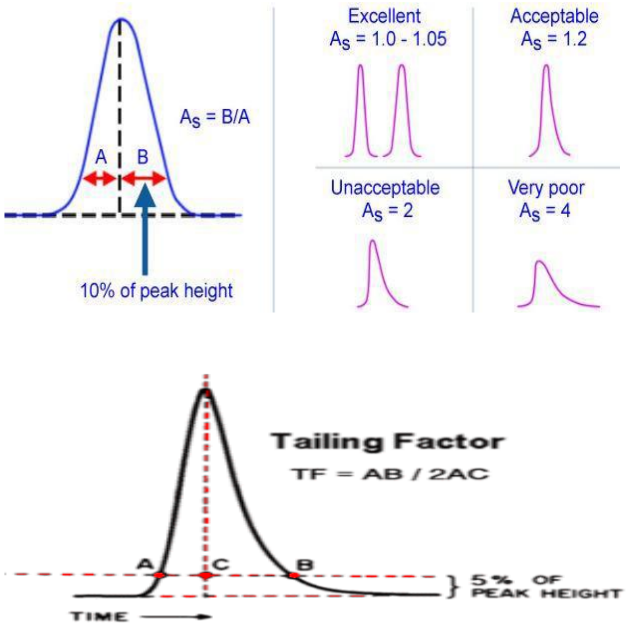

Fig 6: Determination of tailing and asymmetric factor

Acceptance criteria (limits) of system suitability parameters are shown in the following Table.

S.No	Parameter name	Acceptance criteria
1	Number of theoretical plates or Efficiency (N)	> 2000
2	Capacity factor (K)	< 1
3	Separation or Relative retention (α)	> 1
4	Resolution (Rs)	> 1.5
5	Tailing factor or Asymmetry(T)	< 2
6	Relative Standard Deviation (RSD	< 2

3.2. Specificity

One of the significant features of HPLC is its ability to generate signals free from interference. Specificity refers to the ability of the analytical method to differentiate and quantify the analyte in complex mixtures. An investigation of specificity is to be conducted during the determination of impurities and validation of identification tests.

An ICH guideline defines specificity as ability to assess unequivocally the analyte in the presence of other compounds that may be likely to be present. Typically these might be impurities, degradants, matrix, etc. The definition has the following implications:

- ✓ **Identification test:** Identification tests should be able to differentiate compounds of closely related structure which are expected to be present i.e., to assure identity of an analyte.
- ✓ **Purity test:** To ensure that the analytical procedure performed allows an accurate statement of content of the impurity of an analyte i.e. related substances, residual solvents content, heavy metals, etc.
- ✓ **Assay:** To arrive at an accurate result, this permits a correct report on the potency or content of analyte in a sample.

3.3. Linearity and Range

The linearity of a method is a measure of how well a calibration plot of response vs. concentration approximates a straight line. Linearity can be assessed by performing single measurements at several analyte concentrations. The data is then processed using a linear least-squares regression. The resulting plot slope, intercept and correlation coefficient provide the desired information on linearity.

3.4. Precision

The precision of an analytical procedure represents the nearness of agreement between a series of measurements got from multiple sampling of the same homogenous sample under the similar analytical conditions and it is divided into 3 categories.

- ✓ Repeatability: precision under same operating conditions, same analyst over a short period of time.
- ✓ Intermediate precision: method is tested on multiple days, instruments, analysts etc.
- ✓ Reproducibility: inter-laboratory studies.

The ICH guidelines suggest that repeatability should be conformed duly utilizing at least 9 determinations with specified range for the procedure (e.g., three concentrations / three replicates each) or a minimum of 6 determinations at 100 % of the test concentration

.3.5. Accuracy

The accuracy of a measurement is defined as the closeness of the measured value to the true value. In a method with high accuracy, a sample (whose "true value" is known) is analyzed and the measured value is identical to the true value. Typically, accuracy is represented and determined by recovery studies. There are three ways to determine accuracy:

1. Comparison to a reference standard.
2. Recovery of the analyte spiked into blank matrix.
3. Standard addition of the analyte.

It should be clear how the individual or total impurities are to be determined.

3.6. Limit of detection

LOQ is determined by the analysis of samples with known concentration of analyte and by establishing that minimum level at which the analyte can reliably detected, but not necessarily quantitated as precise value, under the stated experimental conditions. The

detection limit is generally expressed in the concentration of analyte (ppm) in the sample. A number of approaches are recommended by the ICH for determining the detection limit of sample, depending on instrument used for analysis, nature of analyte and suitability of the method. The acceptable approaches are

- Visual evaluation.
- Signal-to-noise ratio.
- Standard deviation of the response.
- Standard deviation of the slope of linearity plot.

The formula for calculating LOD is

$$LOD = 3.3\ \delta/S$$

Where δ = standard deviation of intercepts of calibration curves.

S = the slope of linearity plot.

3.7. Limit of quantitation

Limit of quantitation is the least concentration of drug in a sample which is estimated with appropriate precision and accuracy under the affirmed experimental conditions.

Similar to LOD, ICH recommends the following four methods for estimation of LOQ. The acceptable approaches are

- Visual evaluation.
- Signal-to-noise ratio.
- Standard deviation of the response.
- Standard deviation of the slope of linearity plot

The formula for calculating LOQ is

$$LOQ = 10\ \delta/S$$

Where δ = standard deviation of response.

S = Mean of slopes of the calibration curves

3.8. Robustness

Robustness is defined by the measure of the capability of an analytical method to stay unchanged by small deliberate changes in method parameters. The variable method parameters in HPLC technique may involves flow rate, column temperature, sample temperature, pH and mobile phase composition.

IV.STATISTICAL TREATMENT OF ANALYTICAL DATA

The function of analyst is to attain a specific result as near to the true value as feasible by the exact application by employing analytical procedure. The state of confidence that the analyst may enjoy with his results will be very small unless he has knowledge of the accuracy and precision of the method used as well as being aware of the sources of error which may be introduced. Experimental measurements always have some variability, so no conclusion can be drawn with certainty. Statistics give us tools to let conclusions that have a high probability of being exact and to reject improbable conclusions. The purpose of carrying out a determination is to achieve a valid estimate of a 'true' value. When one considers the criteria as said by which an analytical procedure is selected; precision and accuracy are generally the primary prominent point to come to mind for application. Precision and accuracy together determine the error of an individual determination. They are among the most significant critical parameters for judging the analytical procedures by their achieved results

4.1. Precision

Precision may be defined as the concordance of a series of measurements (n) of the same quantity. Precision expresses the „reproducibility" of a measurement. One of the most common statistical terms employed for precision is the sample standard deviation which is shown in the following equation

$$S = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

The square of standard deviation is called Variance (S2). RSD or % RSD is the absolute value of the CV (Coefficient of Variation) and it is often stated as a % which is used to juxtapose the uncertainty among different measurements of varying total magnitude.

4.2. Accuracy[26]

Accuracy normally refers to the difference between the mean „x" of the set of results and the true or most probable value for the quantity measured. As stated by IUPAC, accuracy relates to the difference between result (or) mean and the true value. For analytical methods, there are two feasible ways of determining the accuracy: absolute method and comparative method.

Absolute method

The test of the accuracy of the method under consideration is carried out by taking amounts of the constituents and proceeds as said by specified instructions to perform the test for accuracy of the method. The difference between the means of an adequate number of results and amount of constituent in fact present, usually expressed as parts per hundred (%) which is termed as % error.

The constituent in question will be determined in the presence of other substances, and it will therefore be necessary to know the effect of the determination. This will require testing the influence of a large number of probable compounds in the chosen samples of each varying amounts. In a few instances, the accuracy of the method is controlled by separations (usually solvent extraction or chromatography technique) involved.

Comparative method

In the analysis of pharmaceutical formulations (or solid synthetic samples of desired composition), the content of the constituent to be sought has been determined by one or more accurate analysis methods. Basically if several distant (dissimilar) methods of analysis for a given constituent are available, e.g. gravimetric, titrimetric, spectrophotometric, or chromatographic, the agreement between at least two methods of essentially different character can generally be

accepted as indication of the absence of an appreciable systematic error in either method.

Recovery experiments

A known amount of the constituent being estimated is added to the sample, which is analyzed for the total amount of constituent present. The difference between the analytical results for samples with and without the added constituent gives the recovery of the amount of the added constituent. If the recovery is satisfactory, our confidence in the accuracy of the procedure is improved.

4.3. Evaluation of precision and accuracy by comparison of two procedures

By comparing the test method (method to be investigated) has to be compared with reference method (existing method) to attain the accuracy of the method to be investigated.

Student t-test Student t-test is used to compare the means of two related (paired) samples analyzed by reference and test methods. It gives answer to the correctness of the null hypothesis with a certain confidence such as 95 % or 99 %. If the number of pairs (n) is less than 30, the condition normality of x or at least the normality of the difference (di) is required. If this is the case the quantity has a student t-distribution with (n -1) degrees of freedom

$$t = \frac{\overline{d_i}}{s_d/\sqrt{n}}$$

Where di = xR (Reference method) – xT. (Test method) and sd is the standard deviation

F-test

By the F-test we can test the significance of the difference in variances of reference and test methods. Let us suppose that one carried out n1 replicate measurements by test methods and n2 replicate measurements by using reference method. If the null hypothesis is true then the estimates ST2 (variance of the test method) and SR2 (variance of reference method) do not differ very much and their ratio should not differ much from unity. In fact, one uses the ratio of variances

F = ST2 / SR2

It is conventional to calculate the F - ratio by dividing the larger variance by the smaller variance in order to attain a value equal or larger than unity. If the calculated F - value is smaller than F - value from the F-table, one can conclude that the procedures are not significantly different in precision at a given confidence level.

4.4. Calibration

A very essential part of all analytical procedures is the calibration and standardization process Calibration determines the relationship between the analytical response (Absorbance, peak area, peak height etc.,) and the analyte concentration. Generally this is accomplished by the use of chemical standards. A good precision and accuracy can only be obtained when an excellent calibration procedure is used. In pharmaceutical analysis the following calibration procedures are normally employed. External standard calibration

An external standard is prepared separately from the sample. External standards are used to calibrate instruments and procedures when there are no interference effects from matrix components in the analyte solution. A series of such external standards containing the analyte in known concentration is prepared. Ideally three or more such solutions are used in the calibration process. Calibration is achieved by obtaining the response signal as a function of the known analyte concentration. A calibration curve is prepared by plotting the data or by fitting them to a suitable mathematical equation such as the linear relationship used in the method of least squares. The next step is the prediction step, in which the response signal obtained for the sample is used to predict the unknown analyte concentration from the calibration curve or the best fit equation. Internal standard calibration

An internal standard is an amount of compound, different from the analyte that is added to unknown. The signal of analyte is juxtaposed and compared with signal of internal standard to know how much quantity of an analyte is present. Standard addition In standard addition, known quantities of drug are added to the unknown. From the increase in signal and then figure out how much analyte existed in the original unknown. The standard addition method gets a linear response to analyte.

4.5. The method of least squares

In the calibration procedures ideally a linear response should be obtained. The method of least square is a key statistical tool available for fitting the data into a linear model. Least-squares regression analysis can be used to express the relationship between response (y) and concentration (x). The relationship can be represented by the general function

Y = f (x, a, b1, …… bm)

Where a, b1....., bm are the parameters of the function.

We adopt the convention that the x values relate to the controlled or independent variable (e.g. the concentration of a standard) and the y values are related to the dependent variable (the response measurements). This means that the X values have no error. On the condition that the errors made in preparing the standards are significantly smaller than the measuring error (which is usually the case in analytical problems). The values of the unknown parameters a, b1, ...bm must be estimated in such a way that the model fits the experimental data points (xi, yi) as closely as possible. The true relationship between x and y is considered to be given by a straight line. The relation between each observation pair (Xi, Yi) can be represented as

$Yi = \alpha + \beta Xi + ei$

The signal yi is composed of deterministic component predicted by linear model and a random component ei. One must now find the estimates of a and b of the two values α and β. This can be done by calculating values a and b for which ei2 is minimal. The component ei represent the differences between the observed yi values and the predicted yi values by the model. The ei are called the residuals, a and b are the intercept and slope respectively.

$$b = \frac{n\sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} y_i}{n\sum_{i=1}^{n} x_i^2 - \left[\sum_{i=1}^{n} x_i\right]^2}$$

$$a = \frac{\sum_{i=1}^{n} y_i \sum_{i=1}^{n} x_i^2 - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} x_i y_i}{n\sum_{i=1}^{n} x_i^2 - \left[\sum_{i=1}^{n} x_i\right]^2}$$

Standard error of estimation (Se) The standard error of estimation is a measurement of the difference between experimental and computed values of the dependent variable. It is represented by the following equation

$$S_e = \sqrt{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2/(n-2)}$$

y_i and $\hat{y}_i$ are the observed and predicted values, respectively. Standard deviations on slopes (Sb) and intercepts (Sa) are quoted less frequently, even though they are used to evaluate proportional differences between or among methods as well as to compute the independent variables such as concentration etc. It is important to understand how uncertainties in the slope are influenced by the controllable properties of the data set such as the number and range of data points and also how properties of data sets can be designed to optimize the confidence in such data.

Standard deviation of slope (Sb) The standard deviation of slope is proportional to standard error of estimate and inversely proportional to the range and square root of the number of data points.

$$S_b = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{(n-2)}} * \sqrt{\frac{1}{\sum_{i=1}^{n}(x_i - \hat{x}_i)^2}}$$

Where,$\hat{x}_i$ is the arithmetic mean of xi value

Standard deviation of intercept (Sa) Intercept values of least squares fits of data and are often used to calculate additive errors between or among different methods

$$S_a = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{(n-2)}} * \sqrt{\frac{1}{\sum_{i=1}^{n}(x_i - \hat{x}_i)^2}} * \sqrt{\frac{\sum_{i=1}^{n} x^2}{n}}$$

Where,$\hat{x}_i$ is the arithmetic mean of xi value

Correlation coefficient (r) In order to ascertain whether there is a linear relationship between two variables „x" and „y", the correlation coefficient (r) is used. To achieve a correlation coefficient, the co-variance is divided by the product of the standard deviation of x and y.

$$r = \frac{[\sum_{I=1}^{n}(x_I - \bar{x})(y_i - \bar{y}]/(n-1)}{\sum_{i=1}^{n}(x_i - \bar{x})^2\,(y_i - \bar{y})^2\,/(n-1)^2}$$

CONCLUSION:

This article provides an idea how to perform validation process to prove that the method is apt for its intended purpose and to assure the capabilities of the test method. Validation is the most widely used word in the areas of drug development, manufacturing and specification of finished products. The consistency and reliability of a validated process to produce a quality product is the very important for an industry. Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. The process validation is intended to assist manufacturers in understanding quality management system (QMS) requirements concerning process validation and has general applicability to manufacturing process. The definitions of method validation parameters are well explained. Although the requirements of validation have been clearly documented by regulatory authorities, the approach to validation is varied and opened to interpretation, and validation requirements differ during the development process of pharmaceuticals. Validation is an important procedure in the pharmaceutical industry and it is utilized to ensure that quality is built in to the processes supporting drug development and manufacture.

REFERENCES:

1.Sharma A, Saini S; Process Validation of Solid Dosage Form: A Review. International Journal of Research in Pharmacy and Science, 2013; 3 (2): 12-30.

2. Kaur H, Singh G, Seth N; Pharmaceutical Process Validation: A Review. 2013; 3 (4): 189-194.

3.Thaduvai R, Rao BS, Jeybaskaran M; Process Validation of Pantoprazole 40 mg Tablets: The Pharma Innovation. 2012; 1(5): 50-52.

4. Kavita, Khurana G, Chaudhary S;Process Validation of Solid Dosage Form: A Review. Pharma Science Monitor, An International Journal of Pharmaceutical Sciences, September 2013; 4 (4): 390- 391.

5. Chapman K. G: A History of Validation in the United States, Part I, Pharma Technology. November 1991; 39-98.

6.Nash R. A., Wachter A. H: In Pharmaceutical Process Validation. Third Edition; Revised and Expanded, Marcel Dekker Inc., New York, 1993.

7.Potdar MA; Pharmaceutical Quality Assurance. 2nd Edition, Nirali Prakashan, 2009: 8.6-8.20.

8.WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO technical report, series no. 863 – 34th report, Annex 6 –GMP: Guidelines on the validation of manufacturing processes: 4-7.
9. ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: 33.
10. Potdar MA; Current Good Manufacturing Practices for Pharmaceuticals. 2nd Edition, PharmaMed
Press Publication, Delhi, December 2007:
8.2-8.3.
11. Validation of Solid Dosage Forms the FDA view, 1989; 15(6-7): 1119-1133.
12. Guidelines for Process Validation of
Pharmaceutical Dosage Forms. Saudi Food and Drug Authority, Kingdom of Saudi Arabia, 2010; 9-15.
13. Guideline on General Principles of Process Validation. Washington DC: Center for Drug Evaluation and Research, US Food and Drug Administration, May 1987;
14.Good Manufacturing Practices for Pharmaceutical Products, WHO/Pharm./93.562/Annex: Guidelines
on Validation of Manufacturing Process. Geneva: WHO.
15.Kumar NL, Moorthy DG, Kumar SR; An Overview of Pharmaceutical Validation: Quality Assurance view point. 2011; 1(4): 1003-1014.
16.FDA Guidance Update: Process Validation: General Principles and Practices; version 01; 2009.
17. Potdar MA; Pharmaceutical Quality Assurance. 2nd Edition, Nirali Prakashan, Pune, 2007: 8.1- 8.44.
18. Nash R. A: Process Validation of a 17- Year Retrospective Study of Solid Dosage Forms. Drug Development Industrial Pharmacy 1966; 22 (1): 25-34.
19.Guidance for Industry: Process Validation: General Principles and Practices. U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Biologics Evaluation and Research (CBER), Centre for Veterinary Medicine (CVM), January 2011.
20. Oechslein C, Lazar MS; Process Validation from view report of the FDA. Maas and Peither AG – GMP Publishing, Logfile No. 3/ February 2012.
21. Guidance for Industry on general principles and practices of process validation; US Department of Health and Human Services, Food and Drug Administration, 2011; 7-9.
22.Validation Guidelines for Pharmaceutical Dosage Form; Health products and Food branch Inspectorate, Canada, December 2009; 8-13.
23.Von Doehren PJ, St. John; An Approach to the Characterization and Technology Transfer of Solid Dosage Form Processes: Pharma Technology, 1982; 6 (9): 139–156.
25.Patel RC, Bhuva CK; Pharmaceutical Process Validation: Pharmatutor, ART - 1053
26. Jatto E, Okhamafe AO; An Overview of Pharmaceutical Validation and Process Controls in Drug Development. Tropical Journal of Pharmaceutical Research, 2002; 2: 115-122.
27.Mohammed. SA; Pharmaceutical Process Validation: An Overview. Journal of Advanced Pharmacy Education and Research, 2012; 2 (4): 186-200.
28.Guide to Inspections of Oral Solid Dosage Forms pre/post Approval Issue for Development and Validation; issue (1/94); January 2010.