ABSTRACT
Validation is the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results. The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Validation is the mean of catering enormous benefits to even more than the acceptable quality level which in the global standard scale. Lending importance to validation is increasingly profound in recent years. 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. Hence, an emphasis made on to review that gives a detailed, overview of validation concept of designing, organizing and conducting validation trials.

Keywords: Quality assurance, Validation, Validation trials.

INTRODUCTION
The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970s in order to improve the quality of pharmaceuticals. The first validation activities were associated with processes including environmental control, media fill, equipment sanitization and purified water production.

The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use has developed a text on the validation of analytical procedures. The United States Food and Drug Administration (USFDA) have proposed guidelines on submitting samples and analytical data for validation. The United States Pharmacopoeia (USP) has published specific guidelines for validation for compound evaluation.

The general guideline aimed at providing laboratories a practical framework required for the introduction or use of any new or change/relocation of established critical process, equipment, facilities or systems in the transfusion laboratory.

- Change Control - a formal system for managing change.
- Validation - documented evidence that the process meets predetermined specifications.
- Qualification - refers to equipment, facilities and systems.
The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. To further enhance the effectiveness and safety of the drug product after approval, many regulatory agencies such as the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use.

VALIDATION

- Documented evidence that the manufacturing process consistently produces product that meets predetermined specifications.
- Manufacturing process validation consists of successfully manufacturing at least three full-scale batches in succession, which pass all in-process and product quality product.

BACKGROUND

In the Federal Register of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled Guideline on General Principles of Process Validation (the 1987 guidance). Since then, we have obtained additional experience through our regulatory oversight that allows us to update our recommendations to industry on this topic. This revised guidance conveys FDA’s current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. The revised guidance also provides recommendations that reflect some of the goals of FDA’s initiative entitled “Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach,” particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts. This revised guidance replaces the 1987 guidance.

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess.

BASIC OF 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. 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.

PHASES OF VALIDATION\(^{[6,7]}\)

**Design qualification (DQ)**- Defines the functional and operational specification of the instrument, program, or equipment and details the rationale for choosing the supplier.

**Installation qualification (IQ)** – Demonstrates that the process or equipment meets all specifications, is installed correctly, and all required components and documentation needed for continued operation are installed and in place. The documented act of demonstrating that process equipment and ancillary systems are appropriately selected and correctly installed.

**Operational qualification (OQ)** – Demonstrates that all facets of the process or equipment are operating correctly. The documented action of demonstrating that process equipment and ancillary systems work correctly and operate consistently in accordance with established specifications.

**Performance qualification (PQ)** – Demonstrates that the process or equipment performs as intended in a consistent manner over time.

**Component qualification (CQ)** – is a relatively new term developed in 2005. This term refers to the manufacturing of auxiliary components to ensure that they are manufactured to the correct design criteria. This could include packaging components such as folding cartons, shipping cases, labels or even phase change material. All of these components must have some type of random inspection to ensure that the third party manufacturer's process is consistently producing components that are used in the world of GMP at drug or biologic manufacturer.

**TYPES OF VALIDATION**

A) **ANALYTICAL VALIDATION**\(^{[8]}\)

There are many reasons that show that analytical validation is very important. Among them are regulatory requirements, good science, and quality control requirements. The Code of Federal Regulations (CFR) states that “the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented.” Of course, as scientists, we would want to apply good science to demonstrate that the analytical method used had
demonstrated accuracy, sensitivity, specificity, and reproducibility. Finally management of the quality control unit would definitely want to ensure that the analytical methods that the department uses to release its products are properly validated for its intended use so the product will be safe for human use.

B) EQUIPMENT VALIDATION:
Studies which establish with confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. The studies must include equipment specifications, installation qualification (IQ), and operational qualification (OQ) of all major equipment to be used in the manufacture of commercial scale batches. Equipment qualification should simulate actual production conditions, including "worst case"/ stressed conditions.

C) PROCESS VALIDATION:
Establishing documented evidence with a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation may take the form of prospective, concurrent or retrospective validation and process qualification or re-validation.

BASIC CONCEPT OF PROCESS VALIDATION:

- Calibration, verification and maintenance of process equipment.
- Prequalification or revalidation.
- Establishing specifications and performance characteristics.
- Selection of methods, process and equipment to ensure the product meets specifications.
- Qualification or validation of process and equipment.
- Testing the final product, using validated analytical methods, in order to meet specifications.
- Challenging, auditing, monitoring or sampling the recognised critical key steps of the process.

TYPES OF PROCESS VALIDATION\[^9,10\]

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

**CONCURRENT VALIDATION:**
In-process monitoring of critical processing steps and end-product testing of current production can provide documented evidence to show that the manufacturing process is in a state of control. Is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price. This validation involves in process monitoring of critical processing steps and product testing. Retrospective validation is only acceptable for well established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there have been recent changes in the formulation of the product, operating procedures, equipment and facility. The source of data for retrospective validation should include amongst others, batch documents, process control charts, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results. For the purpose of retrospective validation studies, it is considered acceptable that data from a minimum of ten consecutive batches produced be utilized. When less than ten batches are available, it is considered that the data are not sufficient to demonstrate retrospectively that the process is fully under control.

**RETROSPECTIVE VALIDATION:**
Conducted for a product already being marketed, and is based on extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed. Almost all GMP texts recommend that whenever there are significant changes in the facility, equipment or process, revalidation should be carried out. The FDA process validation guidelines refer to a quality assurance system in place that requires revalidation whenever there are changes in packaging (assumed to be the primary container-closure system), formulation, equipment or processes (meaning not clear) which could impact on product effectiveness or product characteristics and whenever there are changes in product characteristics.

**REVALIDATION**[^11]
Almost all GMP texts recommend that whenever there are significant changes in the facility, equipment or process, revalidation should be carried out. The FDA process validation guidelines refer to a quality assurance system in place that requires revalidation whenever there are changes in packaging (assumed to be the primary container-closure system), formulation, equipment or processes (meaning not clear) which could impact on product effectiveness or product
characteristics and whenever there are changes in product characteristics. Conditions requiring revalidation study and documentation are listed as follows:

- Change in a critical component (usually refers to raw materials).
- Change or replacement in a critical piece of modular (capital) equipment.
- Change in a facility and/or plant (usually location or site).
- Significant (usually order of magnitude) increase or decrease in batch size Sequential batches that fail to meet product and process specifications.

**BENEFITS OF PROCESS VALIDATION**

- Reduction in rejections and reworks
- Reduction in utility costs
- Avoidance of capital expenditures
- Fewer complaints about process related failures
- Reduced testing in process and finished goods
- More rapid and accurate investigations into process deviations
- More rapid and reliable start-up of new equipment
- Easier scale-up from development work
- Easier maintenance of the equipment
- Improved employee awareness of processes
- More rapid automation

**D) CLEANING VALIDATION:**

Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should biologically based on the materials involved. The limits should be achievable and verifiable. Validated analytical methods having sensitivity to detect residues or contaminant should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to noncontact parts. The intervals between use and cleaning as well as cleaning and re use should be validated. Cleaning intervals and methods should be determined.

For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilizing a “worst case” approach can be carried out which takes account of the critical issues.
Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

"Test until clean". is not considered an appropriate alternative to cleaning validation. Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning a pharmaceutical production equipment. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross-contamination and adulteration of drug products hence is critically important. The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy or quality of subsequent batches of drug product produced within the equipment. The objectives of equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area are same as those in pharmaceutical production area. In both these areas efforts are necessary to prevent contamination of a future batch with the previous batch material. The cleaning of 'difficult to reach' surface is one of the most important consideration in equipment cleaning validation.

PHASES OF PROCESS VALIDATION.

Phase 1 (Process Design): Pre-validation phase or the qualification phase, which 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.

Phase 2 (Process Qualification): Process validation phase (process qualification phase) designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.

Phase 3 (Continued Process Verification): Validation maintenance phase requiring 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.

At this stage the validation team also assures that there have been no changes/ deviations that should have resulted in requalification and revalidation.

DOCUMENTATION[12,13]

The Validation Report:
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.

**Validation plan:**
The validation master plan will define the requirement for a discrete validation plan or in the case of complex systems a series of plans to validate each component or process. The validation plan will define the need for a validation protocol(s) describing the scope of the validation and procedures used.

**Validation master plan:**
VMP details all of the critical processes, equipment, facilities and systems, when they were last validated and when re-validation is due. The VMP is the operational document which allows the laboratory to turn the Validation Policy into practice and provides a route map to how the laboratory ensures critical processes and systems remain valid and fit for purpose throughout their life-cycle from initial procurement, installation and routine operation to withdrawal, or replacement. The VMP is a key document which can be used by laboratories to serve as a tool for ensuring compliance and may be used by regulatory authorities to check the robustness of the processes employed in laboratories. The validation policy and VMP may be two separate documents or integrated as a single document.

**Validation Protocol:**
Outlines the objectives of validation of a specific equipment or process, testing protocol including elements such as installation, operational and performance qualification and documentation.

**ASPECTS OF VALIDATION** [14-16]

**CHANGE CONTROL:**
Written procedures should be in place to describe the actions to be taken if change is proposed to the starting material, product component, process equipment, process environment (or site),
method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedure should ensure that sufficient support data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis.

**WORST CASE:**
A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

**DESIGN SPACE:**
The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

**PILOT BATCHES:**
These may be used in the process development or optimization stage may be used to support formal stability studies and also support pre-clinical and clinical evaluation. Pilot Batch size should correspond to at least 10% of the production scale batch, i.e. such that the multiplication factor for the scale-up does not exceed . For oral dosage forms this size should generally be 10% of the production scale or 100,000 units whichever is the greater.

**PRODUCTION SCALE BATCH:**
These batches are of the size, which will be produced during the routine marketing of product. Data on the production scale may not always available prior to granting marketing authorization. Where production scale data are not available or presented at the time of submission, the two-stage approach outlined below should be followed. First a thorough evaluation and characterization of the critical process parameters at laboratory or pilot scale, followed by a formal validation programme on production scale batches for which the “validation scheme” has been described.

**CONCLUSION**
Validation is a method which is establish to maintain a documentary evidence and to provide assurance that a product can be manufactured on a commercial scale, meeting all its quality attributes in a consistent manner.

REFERENCES
5. Carleton FJ and Agalloco JP. Validation of pharmaceutical processes, sterile products. Second edn., 1 to 16.
13. Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.
16. Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

For Correspondence:
Soni Neha
Email: soninehapharma@gmail.com