JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PROCESS VALIDATION IN PHARMACEUTICAL INDUSTRY

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Abstract[6]:

The process validation is setting up documented evidence which gives a high degree of affirmation that a particular procedure, process or equipment will succinctly deliver a Product or result meeting its predetermined specifications and quality attributes. Validation is the key process for effective Quality Assurance. Objectives are mainly to assure that the Specific drug products have the identity, strength, quality and purity. And the next is to determine that a process consistently performs or not. As per GMP validation protocols are basic pieces of GMP these are required to be done according to predefined conventions, the base that ought to be approved incorporate process, testing and cleaning subsequently such control methodology, establish to screen the yield and approval of assembling forms that might be in charge of fluctuation of medication item. The evaluation of validation process gives us the precision, accuracy, specificity and reproducibility of the test techniques utilized by the organizations, might be built up and archived. Accordingly the validation is a Fundamental piece of the quality affirmation or assurance

Introduction [6] :

The prime objective of any pharmaceutical plant is to manufacture products ofrequisite attribute And quality consistently, at the lowest possible cost.

Although validation studies have been conducted in the pharmaceutical industry for a long time, thereis an ever-increasing interest in validation owingto their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation. 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, labeling 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.

The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from variousdisciplines of the plant. Validation isan essential part of good manufacturing practices (CGMPs). It is, therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fit for their intended use. (WHO,

2006). Validation represents the action to verify that any process, procedure, activity, material, system or equipment can achieve the desired results. (Rachna et al., 2012). Process and systems validation is fundamental to achieving the goal of using a new product.

For this purpose, the results of a large number of measurements are analyzed either by the paired t-test or by regression analysis. Regression analysis is the preferred statistical method in such cases because it is less restrictive and provides a greater amount of information, unlike the t-test (Massart et al., 1988; Miller et al., 1988). From a statistical point of view, validation involves assessing the relationship between one or more predictors using a performance criterion. The fundamental objective is to predict the values of the criterion based on predictor(s) values. Assuming their values are of a quantitative, continuous nature, the most used indicator of validity is the correlation coefficient (Pearson), referred to in this context as the coefficient of validity (Popa, 2011).

Finding a correlation between a predictor (eg, SAR measurements) and a certain criterion (eg, GNSS measurements) is not sufficient to support the conclusion that higher LOS (Line of Sight) values for GNSS measurements are the effect of a higher LOS level for SAR measurements, but only that the two variables tend to vary simultaneously with one another (Popa et al., 2011). Validation principles can be synthesized in the following words: quality, safety and efficacy in the design and building ofa product. Quality cannot be adequately assured merely by in-process and finished-product inspection. Each step of a manufacturing process is controlledto assure that the finished product meets all quality attributes. (Keyur et al., 2014; WHO, 2006)

History of validation[1]:

The concept of validation was first proposed in the mid-1970s by two FDA (Food and Drug Administration) officials, Ted Byers and Bud Loftus, in order to improve the quality of pharmaceutical products (Agalloco 1995 quoted in Sarvani et al., 2013). It was proposed as a direct response to the large volume of problems of parental sterility products. The first validation activities focusedon the processes involved in making these products, but they spread rapidly across all pharmaceutical production processes (Keyur et al., 2014). The purpose of validation is to test the quality of the system at each stage and not only at the end, as validation activities include checks on production materials, operating procedure, training of the persons involved and monitoring of the system during production (Sarvani et al., 2013). U.S.F.D.A(United States Food and Drug Administration) pioneered the validation process concept, but until September 29, 1978, the definition of the validation process did not appear in any of the U.S.F.D.A. literature, no CGMPs (Current Good Manufacturing Practices) law has spoken about the validation process (Chapman K.G, 1991 quoted in Keyur et al., 2014).The validation concept has expanded over the past few years in a wide range of activities, from the methods of analysis used to control the quality of medical substances and drugs to computerized systems, the validation processhas become an important and integral part of CGMPs (Kaur et al., 2013). Validation is a method with applicability in various fields: medicine, sales,economics, psychology, chemistry, biology, etc.

Definitions [1],[2]:

Process validation can be defined as "establishing documented evidence thatprovides a high degree of assurance that a certain system of equipment and processes that are consistently linked meet approved specifications and produce products with predetermined quality attributes"

European commission

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

US FDA Definition

"Process validation is establishing documented evidence which provides a highdegree 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 capableof repeatedly and reliably producing afinished product of the required quality."

WHO Definition

"The documented act of proving that any procedure, process, equipment,material, activity orsystem actually leads to expected result."

Importance of Validation[1] :

- 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
- Reduced testing in process and in finished goods

- More rapid and reliable start-up of new equipment
- Easier scale-up form development work
- Easier maintenance of equipment
- Improved employee awareness of processes
- More rapid automation
- Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce newproducts)

Advantage of validation [13]:

- During the process the knowledge of process increases
- Assures the repeatability of process
- Assures the fluency of production
- Assures that the product is continuously according to the marketingauthorisation
- Decrease the risk of the manufacturing problems
- Decrease the expenses caused by the failures in production
- Decrease the risk of failing in GMP
- Decrease the expenses of the every day production even thought thevalidation itself willcreate expenses
- Optimized processes.
- Assured quality of products.
- Reduced cost of maintaining quality.
- Increased output.
- Reduced complaints, rejections, batch failure, mix-ups, and cross-contamination.
- Faster scale-up from pilot level to the manufacturing level.
- Better compliance with regulatory requirements.

Scope of Validation[17]:

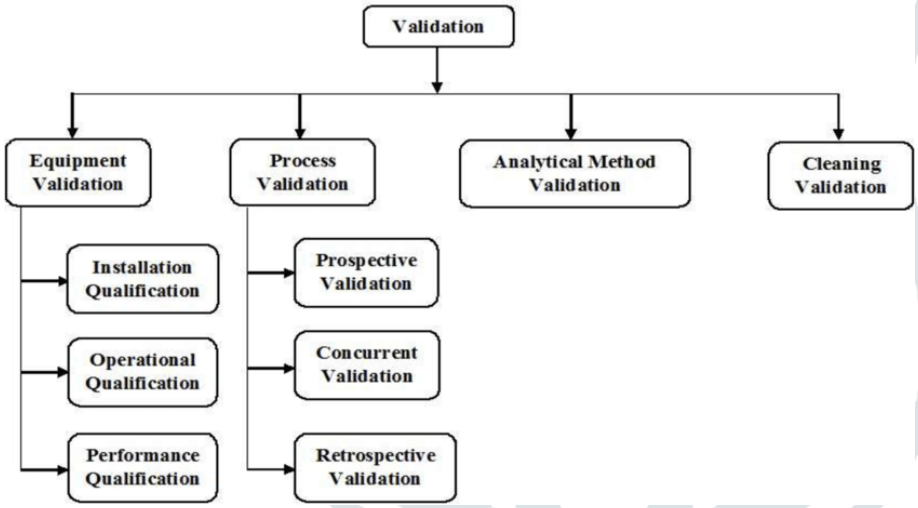
Pharmaceutical Validation is a vast area of work and it practically covers every aspect ofpharmaceutical processing activities, hence defining the Scope of Validation becomes a really difficult task. However, a systematic look at the pharmaceutical operations will point out at least the following areas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

- Analytical
- Instrument Calibration
- Process Utility services

- Raw materials
- Packaging materials
- Equipment
- Facilities
- Manufacturing operations
- Product Design
- Cleaning
- Operators

TYPES OF VALIDATION [1],[7]:

Depending on the type and timing of validation, the following types ofvalidation can be distinguished:



Equipment Validation [1][7]:

Equipment validation is a documented process that has been established todemonstrate that any equipment is functionally acceptable and produces results that can be trusted.

The principle behind equipment validation is that it must be built, maintained,and customized in order to carry out the tasks that need to be done.

There are four types of equipment validation:

- Installation qualification (IQ)
- Design qualification (DQ)
- Performance qualification (PQ)
- Operational qualification (OQ)
- Design Qualification (DQ):

Verification in writing that the facilities, systems, and equipment suggested are appropriate for the intended use.

Design compliance with GMP should be shown in this certification. The designprinciples used should be such that the equipment meets the GMP goals. It is important to look at the mechanical drawings and design elements that the equipment's manufacturer provided.

Installation Qualification (IQ):

Process equipment and related systems must operate consistently under a setof restrictions and tolerances for food and drug management (FDA). It is primarily recorded whether newly installed or updated appliances and equipment comply to the requirements and recommendations of the manufacturer. On new or updated facilities, systems, and equipment, installation qualification (IQ) should be carried out.

Operational qualification (OQ):

Operational qualification is a set of tests that evaluates the equipment's performance potential. Operational qualification places more of an emphasison the equipment than it does on demonstratingperformance capabilities related to manufacturing a particular good.

OQ considerations include:

Limits of process control (time, temperature, pressure, line speed, and setupconditions).

- Software settings.
- Raw material requirements.
- Process operational guidelines.
- Needs for material handling.

- Control of process change.
- Education and training.
- The process's capabilities and short-term stability.

Performance qualification (PQ):

It is described as the procedure to ensure that the system can produce a quality product consistently. Or alternatively the method used to show that the instrument can meet the requirements stated in the design qualification.

PQ consideration includes:

The OQ processes and actual product and process parameters.

- Acceptability of product.
- Confirmation of process capabilities according to OQ.
- Repeatability and long-term stability of the procedure.

Process Validation:

Prospective validation:

Its represents all the activities performed before the distribution of new products to ensure compliance with the initial (legislative/proposed/etc.)

conditions by the product's characteristics. (Sarvani et al., 2013; Lakshmana,2014).

Prospective validation is defined in Keyur et al., (2014) article as thedocumented evidence that a system does what it purports to do.

Concurrent validation :

It's issued for establishing documented evidence during actual imputation ofthe process toshow that the process is in a state of control (Sarvani et al., 2013).

Retrospective process validation :

It's based on a review of historical manufacturing and testing data, and the analysis of accumulated results from past production to assess the consistency of a process. It is assumed that the composition, procedures and equipment remained unchanged. During retrospective validation results ofin-process and final control tests are evaluated. All difficulties and failures recorded are analyzed to determine limits of process parameters and product-related problems. As retrospective validation is not

considered to be a quality assurance measure it should not be applied to new processes or products. (Lakshmana, 2014; Keyur et al., 2014). Revalidation is exploratory review of thecurrent performance of the validation effect to confirm the validated status of the facilities, systems, equipment's, manufacturing processes and software.

CLEANING VALIDATION [11]:

The validation of cleaning ensures that the cleaning procedure properlyreduces residues fromproduction facilities to below a set level. In the pharmaceutical sector, cleaning validation is mostly used for process equipment cleaning.

Cleaning validation analyses cleaning procedures or cycles. It should alsoexplain how acceptability criteria, such as chemical and microbiological parameters, detection limits, and choice of sampling procedure, were developed.

Objective of Cleaning Validation:

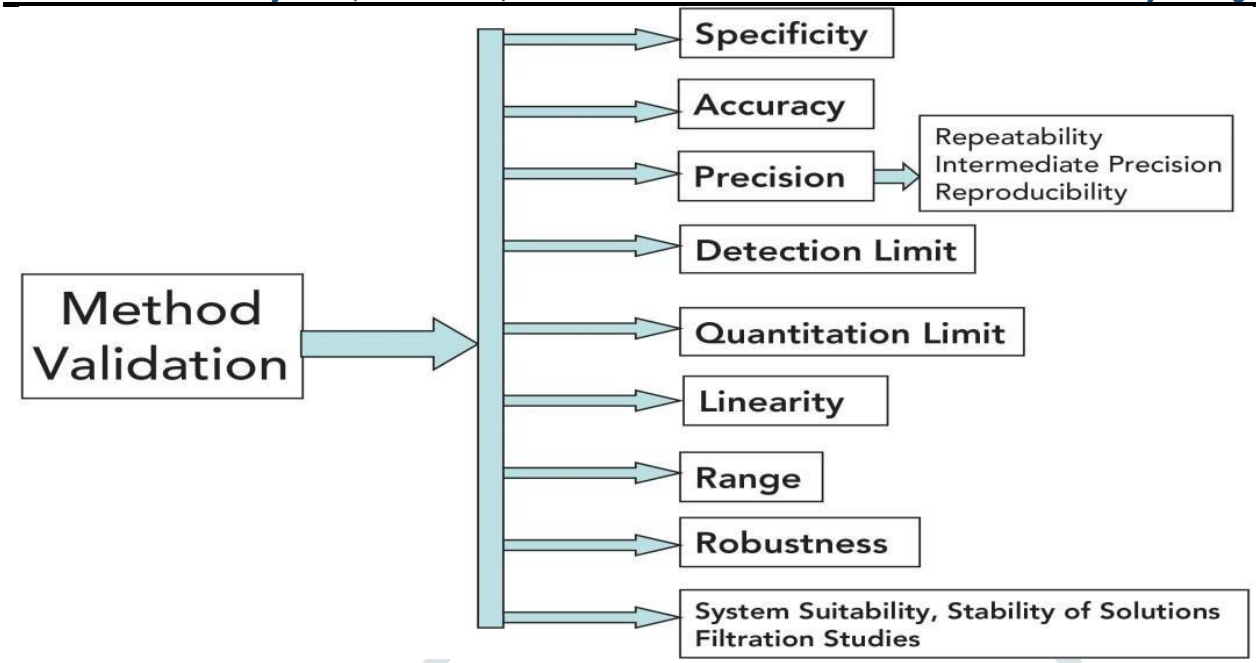
- Reduction of solvents.
- Increased cleaning equipment and shorter cleaning times.
- Equipment utilization, equipment life extension, and multiproduct.
- Infrastructure, worker safety, and cost-effectiveness are few otherobjectives.
- The major goal of cleaning validation is to verify whether the techniqueinvolved in cleaning could reliably eliminate debris from the accessible product while staying within the Tolerances.

Benefits of Cleaning Validation:

- Operator safety: Validation enhances operator security. To reduceaccidents and boostsafety, equipment that has been properly calibrated and approved is used.
- Better Customer Quality: Proper validation helps to decrease marketrecalls, which leadsto better customer service and product quality

Method of validation [8][9][10] :

Method validation is a key element in the establishment of reference methodsand within the assessment of a laboratory's competence in generating dependable analytical records. Validation hasbeen placed within the context of the procedure, generating chemical data. Analytical method validation, thinking about the maximum relevant processes for checking the best parameters of analytical methods, using numerous relevant overall performance indicators inclusive of selectivity, specificity, accuracy, precision, linearity, range, limit of detection (LOD), limit of quantification (LOQ),ruggedness, and robustness are severely discussed in an effort to prevent their misguided utilization and ensure scientific correctness and consistency among publications.



Key parameters of the analytical method validation:

It is important for to understand the parameters or characteristics involved inthe validation process.

The various performance parameters, which are grouped as follows, Accuracy Precision.

- Repeatability
- Intermediate precision
- Reproducibility
- Specificity/Selectivity
- Limit of Detection (LOD)
- Limit of Quantitation (LOQ)
- Linearity
- Range
- Robustness
- Ruggedness
- System suitability testing

Accuracy:

The International Convention on Harmonization (ICH) definition of states that"Accuracy of an analytical procedure is the closeness of agreement between the values that are accepted either as conventional true values or an acceptedreference value and the value found.

For a drug substance, accuracy is determined by applying the analytical method to ananalyte whose purity is known, such as a reference standard.

For drug products, accuracy is determined by applying the analytical method tomixtures containing drug components along with a known amount of analyte that has been added, within the

operating range of the method.

According to ICH guidelines, a minimum of nine determinations must beperformed over a minimum of three concentration levels that cover thespecified range.

Accuracy is generally reported in terms of the percent recovery (by the assay)of the known amount of analyte added into the sample. It may also be reported in terms of the difference between the accepted true value and the mean, along with the confidence intervals.

Generally, the accuracy of recovery for drug substances must be between 99 – 101%. For drugproducts, the values may range between 98 – 102%. Any accuracy of recovery data that deviates from this range must be investigated indetail.

Precision:

Precision is defined as the degree of closeness of a series of measurementsobtained usingmultiple samples of the same substance under specified conditions.

Precision may be studied as three characteristics – repeatability, intermediateprecision, andreproducibility.

Repeatability measures precision under the same conditions over a short timeduration. This is done using normal operating conditions and the same equipment as usually used for the given analytical method. ICH guidelines prescribe that at least nine determinations should be run over the range specified for the procedure. Values to be reported include standard deviation,coefficient of variation (relative standard deviation), and confidence interval.

Intermediate precision refers to variation occurring within the same testinglaboratory. Itincludes a study of day-to-day variation, equipment variation,and analyst variation.

Reproducibility gives information about the precision of measurements between laboratories. To validate reproducibility, the same study must be performed using the sameexperimental design and same sample lot at thedifferent laborator.

Specificity:

ICH definition of specificity is “The ability to assess unequivocally, an analyte,in the presence of other components that are expected to be present”.

A test method is called specific if it can discriminate the compound of interestfrom other closely related compounds that may be present in the same sample. Samples containing the analytemust show positive results; samples without the analytic must show a negative result. Also, when closely related compounds are tested, the test method must not show a positive result.

Detection:

Limit Detection limit (DL) is defined as the “lowest amount of analyte presentin a sample thatcan be detected but not necessarily quantitated under the

stated experimental conditions.” DL is generally expressed in terms of analyteconcentration in the sample (as parts per million, or percentage). DL may be established visually, or using signal-to- noise ratios, or using data from the standard deviation and slope of the calibration curve.

Quantitation Limit:

Quantitation limit (QL) is defined as the lowest level of an analyte that can bequantitatively measured under the given experimental conditions. This parameter is generally useful to assay analytes present in very low levels – forexample, degradation products or impurities. QL may also be defined as the concentration of a related substance in the sample that produces a signal-to- noise ratioof 10:1. QL for a method is influenced by two important factors – the accuracy in sample preparation and sensitivity of the detector used.

QL may be evaluated by the visual method, signal-to-noise ratio method, and the calibrationcurve method. Once QL has been determined, it must be further validated by carrying out accuracy and precision measurements at thislevel.

Linearity:

As per ICH guidelines, linearity is defined as, "The ability (within a particular range) to obtain test results of variable data (such as the area under the curve,or absorbance) which are directly proportional to the concentration of the analyte in the sample. Analyte quantitation may be done using variables such as peak height, peak area, or ratio of peak heights/areas of analyte to the internal standard.

Linearity may be determined by two methods. The first one involves directly weighing different quantities of the standard to prepare solutions of differentconcentrations. The second and more popular approach is to prepare high concentration stock solutions and then dilute them to lower concentrations.

Linearity is accepted if the coefficient of determination is found to be greaterthan or equal to 0.997. ICH guidelines required reporting of the slope, y- intercept, and residual sum of squares, too.

Range:

Range is defined as the interval between lower and upper concentrations of analyte in the sample for an analytical procedure that is demonstrated to possess a suitable level of accuracy, precision, and linearity. Assays must generally have a range of 80 – 120% of nominal concentration. Content uniformity tests must have a range of 70 – 130% of the nominal concentration.

Robustness:

It is defined as the capability of an analytical method to remainunaffected by small butdeliberate variations in the method parameters.

PROCESS VALDATION STAGES [3][4][5] :

Process validation involves a series of activities taking place over a lifecycle of the product and process (Keyur et al., 2014). Activities related to validation studies can be classified into three stages: the pre-qualification phase or the qualification phase; process validation phase (Process Qualification phase); continued process verification or validation maintenance phase. This pre- validation phase or the qualification phase covers all activities related to product research and development, formulation pilot batch studies, transfer oftechnology to commercial scale batches, establishing stability conditions and storage and handling of in-process and dosage forms, equipment qualification,operational qualification and process capacity. (Sarvani et al., 2013).

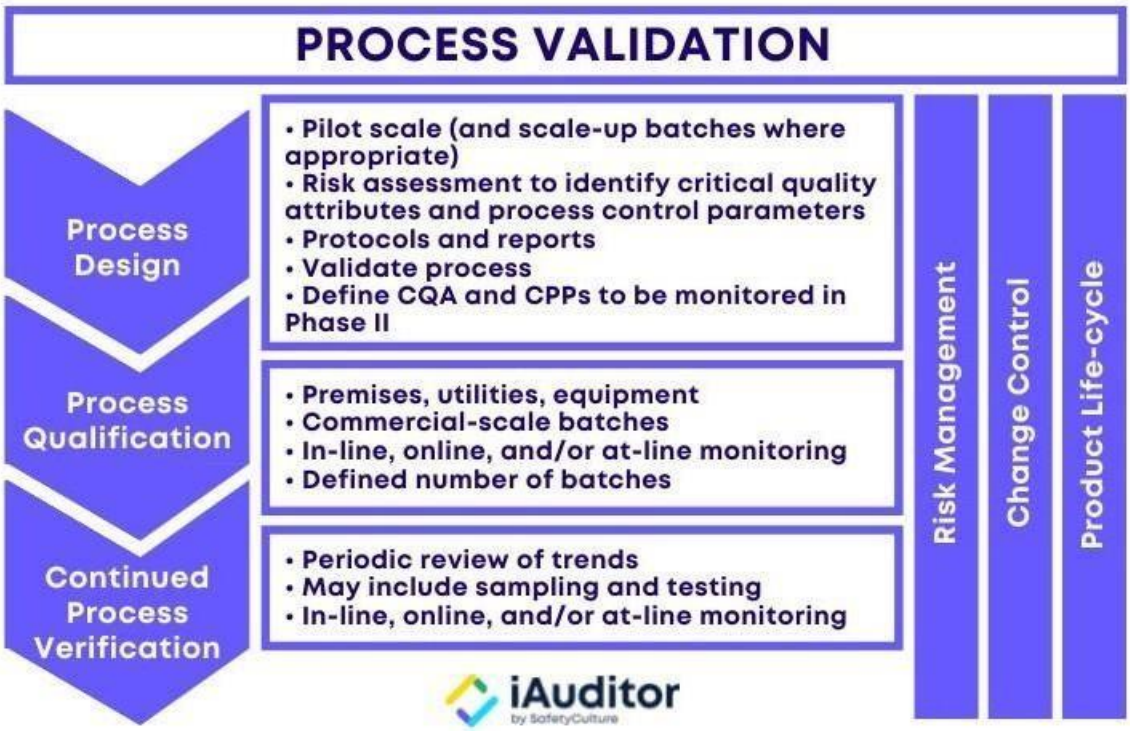
"It covers all activities relating to product research and development, formulation, pilot batchstudies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, 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" (Keyur et al., 2014). During the procedure's validation phase (Process Qualification stage) the process design is evaluated to determine if the process is capable of commercial manufacturing. (Keyur et al., 2014). In this stage it is checked if all established limits of the critical process parameters are valid and if satisfactoryproducts
can be produced even under "worst case" conditions. (Sarvani et al., 2013). There are two aspects ofprocess qualification: (Keyur et al., 2014)

- Design of facilities and qualification of equipment and utilities. Activities performed to assure proper facility design and that the equipment and utilitiesare suitable for their intended use and perform properly.
- Process performance qualification. Part of the planning for stage 2 involvesdefining performance criteria and deciding what data to collect when, how much data and appropriate analysis of data.

Manufacturer must scientifically determine suitable criteria and justify it. Objective measures, where possible. Continued process verification or validation maintenance 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 stages 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. (Sarvani et al., 2013). A successful validation program depends onthe knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detectionof the variation and the attributes susceptible of the variation. (Keyur et al., 2014).

Elements of validation are: (Sarvani et al., 2013):

1)Design qualification (DQ): It is a documented review of the design, at an appropriate stage ofstagesin the project, for conformance to operational and regulatory expectations.
2)Installation qualification (IQ): There are verified all the aspects of a facility, utility or equipment that can affect product quality
3) Operational qualification(OQ): There are verified all aspects of a facility, utility or equipment thatcanaffect product quality
4)Performance qualification (PQ): There are verified all aspects of a facility, utility or equipment perform as intended in meeting.Predetermined acceptance criteria. From the methodological point of view, thevalidation analyses start from the structure of the problem, namely from the identification of the general objective, the derived objectives, the identificationof the necessary factors in the analysis. A second phase in the process validation consists in the standardization of each factor for their compatibility and then they can be hierarchized according to the importance they represent for the main objective.



Validation Team and Responsibilities[13]

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.

Documentation of validation[17]:

- Validation Master Plan(VMP)
- Validation Protocol(VP)
- Validation Reports(VR)
- Standard Operating Procedure(SOP).
- Validation Report

Standard Format

- Executive summary
- Discussion
- Conclusions & recommendation
- List of attachment

Topic should be presented in the order in which they appear in the protocol.Protocol deviation are fully explained & justified. The report is signed & dated by designated representatives of each unit involved in water system validation.

VALIDATION MASTER PLAN[15]:

The validation master plan should provide an overview of the entire validation operation, itsorganizational structure, its content and planning.The main elements of it being the list/inventory of the items to be validated and the planning schedule. All validation activitiesrelating to critical technical operations, relevant to product and process controls within a firmshould be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as revalidation. The Validation Master Plan should be a summary document and should therefore be brief, concise and clear. It should not repeat

information documented elsewhere but should refer toexisting documents such as policy documents, SOP's and validation protocols and reports.

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

VALIDATION LIFE CYCLE[14]:

Validation is a continuing and evolving process. The validation process which extends from the very basic to a very broad the logical and methodical investigation if how the system and processes perform. Its scope encompasses documentation revision control, training and maintenance of the system and process. Evidence of validation should be seen at the corporate level, and be reflected in the management structure. Validation is a method for building and maintaining quality.

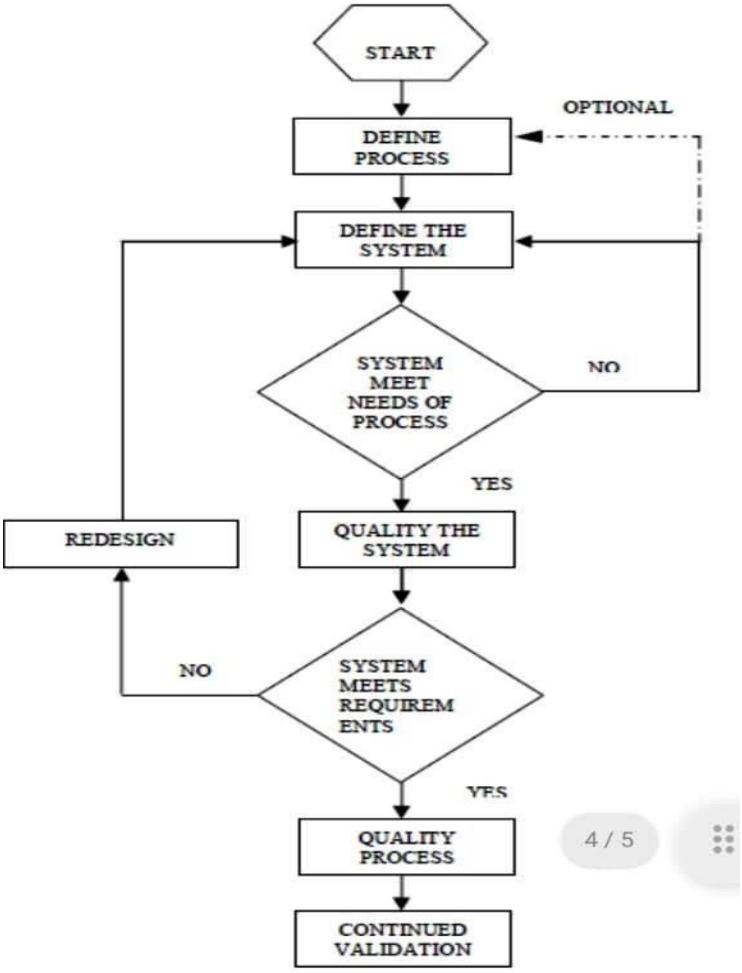


Figure 1: Validation Life Cycle

CONCLUSIONS [12]

Validation refers to the establishment of documented evidence that a process or system can effectively and reproducibly produce a product with identical or similar characteristics. In its short existence, about 50 years, validation has proven its worth in various stages of the manufacturing process, for the preservation, improvement of products and even the use of new methods.

Validation has become a very important research topic when using new products that produce similar results to old ones. Today validation is used in various industries, research, medicine, etc.

Also, the validation process is closely related to the development of technology (softwares, computers, tools to collect the data needed). Validation involves the collection and evaluation of data, throughout process stages, which establishesscientific evidence that a process is capable of consistently delivering quality similar to the one with which the correlation study has been done.

The use of validated methods is important for a researcher to demonstrate thequalification and competence of a new product. This implies prospective or perspective validation, concurrent validation, retroactive or retrospective validation and revalidation. Activities related to validation studies can be classified into three stages: the pre-validation phase; process validation phase and validation maintenance phase, and can be done by statistical process control. Like any new type of analysis, they also have their limitations. One of them is that validation of a product is directly dependent on obtaining a common element between the validated product and the one used as the reference product. There are also areas where validation must have the same zero point (eg, Geodesy).

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