

VALIDATION: A REVIEW**Dr. S. J. Wadher*, Sachin Tayde and Dr. S. G. Gattani**

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University, Nanded.sjwadher@rediffmail.com**ABSTRACT**

The article provide outline of validation includes definition, types of validation, process validation, cleaning validation and terms like ongoing process verification during lifecycle, verification of transportation, validation of packaging, qualification of utilities. Validation need to provide assurance of the process, facility, equipment and system which produce reproducible result as compared with its predetermined specification and quality attributes. It differentiates between validation and qualification. The concept applicable for human drugs, veterinary drugs, biological and biotechnology products, active pharmaceutical ingredient (API) manufacturers. During development of process validation the modern

concept of pharmaceutical development(ICH Q8), quality risk management(ICH Q9), pharmaceutical quality system(ICH Q10) apply during process design and development stages in process validation.

KEYWORDS: Quality, Validation, Process Validation, Pharmaceutical.**History^[1,2,3]**

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. 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 processes including environmental control, media fill, equipment sanitization and purified water production.

The concept of validation was first developed for equipment and processes and derived from the engineering practices used in delivery of large pieces of equipment that would be

manufactured, tested, delivered and accepted according to a contract. The use of validation spread to other areas of industry after several large-scale problems highlighted the potential risks in the design of products.

INTRODUCTION^[4,5]

As per FDA Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics. In the past, process validation emphasis has been on collecting large quantities of data from validation batches, leading to a perception of process validation as largely a documentation exercise. Present approach requires the manufacturer to collect data.

Throughout the product life cycle and evaluate it for evidence that it supports a quality process.

Need of Validation^[5,9,10]

- In pharmaceutical industry the validation is required for national or international regulations.
- Validation is a part of integrated requirement of a quality system.
- Validation meets the consistency of quality product in all stages.
- To reduce batch to batch rejection.
- More rapid and reliable startup of new equipment.
- Easier scale-up from development work.
- More rapid automation
- Reduction in utility cost

Approach To Process Validation^[6,7]

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. Process validation activities are differentiate into three stages.

- **Stage 1 –Process Design:** The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- **Stage 2 – Process Qualification:** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- **Stage 3 –Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.

A successful validation program depends upon information and knowledge from product and process development. Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

Process Design

Takes into account sound scientific methods, principles and good documentation practices and follows comprehensive approach as laid down in ICH Q10. Decisions and justification of controls are documented and reviewed. Provides key inputs such as intended dosage form, quality attributes and a general manufacturing pathway and even takes into account variability posed by different component lots, sites, operators, environment and measurement systems. Laboratory or pilot scale model are considered representatives of commercial process. Risk analysis tools to screen potential variables during design of experiment.

Process Qualification

Facility qualification is required to ensure that the buildings and facilities are in line with regulations and the products to be made. Qualification of utilities and equipment which is essential for those which have direct product contact as well as Qualification to identify studies and tests, criteria to assess outcome, timing, responsibilities and procedures.

Process Performance Qualification

It combines actual facility, utilities, qualified equipment, trained personnel with the commercial process, control procedures and components to produce commercial batches. PPQ is essential before commercial distribution and is based on overall product and process understanding and demonstrable control and for this accumulated data from experiments, laboratories, pilot and commercial batches to be used. PPQ may involve higher level of sampling, additional testing and greater scrutiny of process performance. The duration for higher level of sampling is dictated by volume of production, process complexity and understanding and experience with similar process or products.

Continued Process Verifications

It includes developing a system for detecting unplanned departure and thus adherence to cGMP. Continued process verification recommends correction and evaluation of accumulated data. Ongoing programs are organized to analyze product and process data relating to product quality including statistical trending and review. It also evaluates process stability and capability and even monitors sources of variation not previously detected as Alert and action limit are parameters are variable. It emphasizes continuous monitoring of sampling process parameters and quality attributes and even in establishing basis for level and frequency of routine sampling and monitoring. Assessment of defects, complaints, OOS, process deviation, yield variation, adverse events, batch record and incoming material records is also a part of continued process verification as data gathered at this stage leads to improvement and/or optimization of process and plan changes depending on analysis of data. It proposes to analyze the impact of change on product quality, additional process design and qualification activities.

Types of Process Validation^[8,10,11,12]**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 to 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 in-process 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.

Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. 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 and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the process. 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 program 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. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance logbooks, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results. 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 assess process consistency, but fewer batches may be examined if justified.

Documentation, Including VMP^[13]

- Good documentation practices are important to support knowledge management throughout the product lifecycle.
- All documents generated during qualification and validation should be approved and authorized by appropriate personnel as defined in the pharmaceutical quality system.
- Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.
- Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).

QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES, UTILITIES AND SYSTEMS.^[6]

The qualification for equipment, facilities, utilities and systems are performed that stages given in fig.1.

User requirements specification (URS)

The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.

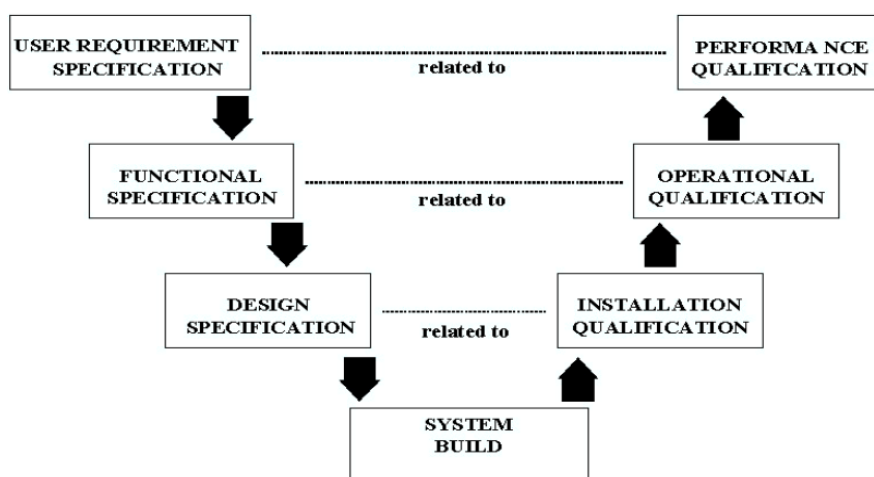


Fig. 1: Qualification Stages.

Design Qualification (DQ)

The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.

Factory acceptance testing (FAT) /Site acceptance testing (SAT)

Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery. Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable. FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

Installation qualification (IQ)

IQ should be performed on equipment, facilities, utilities, or systems. IQ should include, but is not limited to the following:

- Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications.
- Verification of the correct installation against pre-defined criteria.
- Collection and collation of supplier operating and working instructions and maintenance requirements.
- Calibration of instrumentation.
- Verification of the materials of construction.

Operational Qualification (OQ)

OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).

OQ should include but is not limited to the following:

- Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed
- Tests to confirm upper and lower operating limits, and /or “worst case” conditions.
- The completion of a successful OQ should allow the finalization of standard operating and cleaning procedures, operator training and preventative maintenance requirements.

Performance qualification (PQ)

PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.

PQ should include, but is not limited to the following:

- Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behavior under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified.
- Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

Re-qualification

- Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

- Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.

Verification of Transportation^[6]

- Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorization, the approved label, product specification file or as justified by the manufacturer.
- It is recognized that verification of transportation may be challenging due to the variable factors involved however, transportation routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport.
- A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.
- Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the product may be subjected should be performed, unless otherwise justified.

Validation of Packaging^[6]

- Variation in equipment processing parameters especially during primary packaging may have a significant impact on the integrity and correct functioning of the pack, e.g. blister strips, sachets and sterile components, therefore primary and secondary packaging equipment for finished and bulk products should be qualified.
- Qualification of the equipment used for primary packing should be carried out at the minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure or for any other factors.

Qualification of Utilities^[6]

- The quality of steam, water, air, other gases etc. should be confirmed for qualification.
- The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.

- A risk assessment should be carried out where there may be direct contact with the product, e.g. heating, ventilation and air-conditioning (HVAC) systems, or indirect contact such as through heat exchangers to mitigate any risks of failure.

Cleaning Validation^[6]

- Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.
- A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.
- It is recognized that a cleaning validation program may take some time to complete and validation with verification after each batch may be required for some products, e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.
- Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.
- For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.
- Limits for the carryover of product residues should be based on a toxicological evaluation. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.
- Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.

- If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.
- The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.
- The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process.
- Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.
- Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity and potency.
- Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria. Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.
- The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.
- Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures should be used for each product.
- Where manual cleaning of equipment is performed, it is especially important that the effectiveness of the manual process should be confirmed at a justified frequency.

Change Control^[6]

- The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.
- Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, process, equipment,

premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility.

- Where design space is used, the impact on changes to the design space should be considered against the registered design space within the marketing authorization and the need for any regulatory actions assessed.
- Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.
- Changes should be authorized and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.
- Supporting data, e.g. copies of documents, should be reviewed to confirm that the impact of the change has been demonstrated prior to final approval.
- Following implementation, and, where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.

CONCLUSION

- 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.
- After the drug is approved, pharmaceutical validation and process control are necessary to ensure that the drug product will meet/set pharmaceutical standards for identity, strength, quality, purity, stability, evaluation safety and efficacy.
- Verification o transportation, validation of packaging, validation of test methods also discussed.
- Whereas a cleaning validation programme should contain the assessment of equipment and products, assessment of the impact of a process on routine process, determination of an appropriate cleaning agent and method, determination of acceptance criteria for the

residues, determination of a degree of evaluation required to validate the procedure, decisive on the residues to be tested based on solubility and toxicity, development of sampling and analytical methods for recovery and detection of residues.

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