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THE QUALITY DEFECT DEVOID DOCUMENTED PHENOMENON: THE PROCESS VALIDATION

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ABSTRACT

It has always been known that facilities and processes involved in pharmaceuticals production impact significant on the quality of the product. It is directly related to preserving and improving the quality of life of human beings. So the process controls are mandatory in good manufacturing practices for finished pharmaceuticals and hence, validate it. A validated manufacturing process is one which has been proved to do what it purports or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continuing through the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, personnel), but it also includes the control on the entire process for repeated batches or runs. It helps in significant gaining of deepen understanding of processes, Decreases the risk of preventing problems and thus assures the smooth running of the process, Decreases the risk of defect costs, Decreases the risk of regulatory non-compliance, reduction in failure, improves productivity and decreases the reliance on end product testing to determine whether the product conforms to the desired standard or not. And also to achieved adequate synergic effect of manufacturing process quality. The purpose of this study is to present an Documented introduction and general overview on process validation of pharmaceutical manufacturing process with special reference to cGMP guidelines given under 21 Code of Federal Regulations(CFR) part 211(Current good manufacturing practices for finished pharmaceuticals).

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INTRODUCTION

● The principle objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation that is capable of large-scale manufacture with reproducible product quality. Further, continuously improvement of manufacturing process can effectively be achieved by careful process control and its execution i.e. the validation. The Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties(1).

● Validation for pharmaceutical come on track during the late 1960s and early 1970s when new types of incidents, such as poorly mixed, highly potent tablets and insufficient sterilization procedures for large volume parenteral caused serious patient disorders, Many speeches pointing out the need for process validation were made by US authorities and the expression "validated manufacturing process" was finally defined in the Drug Process Inspections Compliance Program in 1978(2, 3).

● Validation is therefore one element of quality assurance that associated with a particular process, as the process differs so widely, there is no universal approach to validation and regulatory bodies such as FDA and EC who have developed general non-mandatory guidelines. Then word Validation simply means "Assessment of validity" or "Action to proving effectiveness" (2, 4).

● Quality cannot be adequately assured by in-process and finished product inspection and testing but it should be built into the manufacturing processes. These processes should be controlled in order that the finished product meets all quality specifications. Therefore, building of the quality requires careful attention to a number of factors, such as the selection of quality materials/components, product and process design, control of processes, in-process control, and finished product testing. Careful design and validation of system and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications (3, 5).

DEFINATION OF PROCESS VALIDATION:

According to 1987 (USFDA) guideline(2), process validation is defined as Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

According to 2011 (USFDA) guideline(3), process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

According to EMEA guideline(6), process validation is the means of ensuring and providing documentary evidence that processes (within their specified design parameters) are capable of consistently producing a finished product of the required quality.

According to ICH Q7A guideline(7), process validation is defined as the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

According to WHO text of GMP (8), validation is the documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected result.

There for the process is developed in such way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameter during the routine production, which directly devoid the Quality defect.

● The Quality System (QS) regulation defines process validation as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications. The requirement for process validation appears in section 820.75 of the Quality System regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goals are met (5).

The basic principles for validation may be stated as follows (2, 3, 5):

1. Establish that the process equipment has the capability of operating within required parameters;
2. Demonstrate that controlling, monitoring, and/or measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment;
3. Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been operated within the prescribed parameters for the process and that the output or product consistently meets predetermined specifications for quality and function; and
4. Monitor the validated process during routine operation. As needed, requalify and recertify the equipment.

Today's process validation needs to be determined based on process knowledge. The more intimate your knowledge of a process including its potential risks and limitations, the greater your ability to implement controls throughout the process. Thus, the greater your ability to guarantee process outcome (9). For that:

● Identification of process parameters that could affect the critical quality attributes of the API. Critical parameters should be determined by scientific judgment and typically should be based on knowledge derived from research, scale-up batches, or manufacturing experiences (10).

● Determination of the range for each critical process parameter expected to be used during routine manufacturing and process control. Data to substantiate the ranges for critical process parameters generally should be obtained from laboratory- or pilot-scale batches, unless a specific parameter can only be determined from a production-scale batch (10).

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control

of the manufacturing processes that result in products with the desired quality attributes (3). Manufacturers should:

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

TYPES OF PROCESS VALIDATION:

● Prospective Validation (4, 5): Prospective validation is defined as the establishment of documented evidence that a system does what it purports to do based on a pre-planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process.

● Retrospective Validation (4, 5): Where historic data taken from the records of the completed production batches are used to provide documented evidence that the process has been in a state of control prior to the request for such evidence. This type of validation process is done for a product already in distribution.

● Concurrent Validation (4, 5): This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control. This validation involves in process monitoring of critical processing steps and product testing.

● Re-Validation (4, 5): It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in the case of sequential batches that do not meet product specifications.

In 2015, the regulatory authorities change the concept of process validation due to change in significate change in regulatory environment and manufacturing phenomenon and introduced the new era in validation; as mentioned below(11);

Traditional process validation is normally performed when the pharmaceutical development and/or process development is concluded, after scale-up to production scale and prior to marketing of the finished product (11).

Continuous process verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8). Continuous process verification can be used in addition to, or instead of, traditional process validation(11).

It is a science and risk-based real-time approach to verify and demonstrate that a process that operates within the predefined specified parameters consistently produces material which meets all its critical quality attributes (CQAs) and control strategy requirements

In order to enable continuous process verification, companies should perform, as relevant, extensive in-line, on-line or at-line controls and monitor process performance and product quality on each batch. Relevant data on quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end points, and assessment of CQA and critical process parameter (CPP) trends.

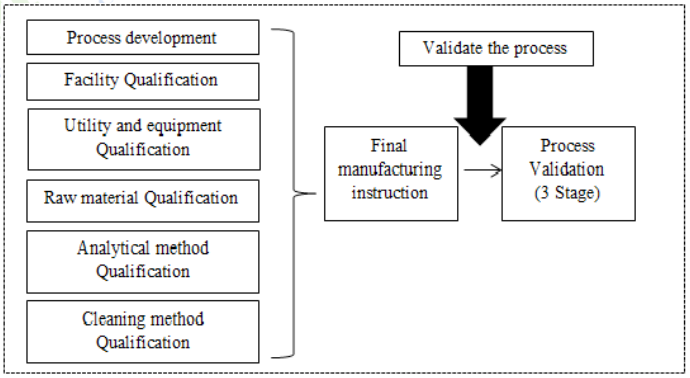
Hybrid approach, It may be necessary to use either the traditional process validation or the continuous process verification approach for different steps within the manufacturing process. It should be clear in the dossier which approach to validation has been taken for which steps in the manufacturing process. The validation requirements in terms of batch size and number of batches would depend on the extent to which continuous process verification has been used(11),.

Ongoing Process Verification during Lifecycle, Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated. The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance(11),.

PROCESS VALIDATION PHENOMENON (6, 9, 12, 13-16):

It consider for, (**Figure:-1**: Process Validation Phenomenon, Figure:-2: Validation Team and their Task, Figure:-3: Validation Life Cycle)

Figure:-1: Process Validation Phenomenon



● Define each module (step, unit operation) of the process.

● Define Critical Product Specifications.

● Define the Critical Process Operating Parameters.

● Develop the Critical Process Operating Parameter Ranges, based initially on laboratory studies of manufacturing material behavior under normal and stress conditions, and later on results of producing products under varied conditions.

● Define the Probable Adverse Consequences of exceeding the critical process operating parameter ranges in each direction (end values).

● Train and qualify operational and supervisory laboratory and plant personnel in product- specific validation principles. (Figure:-2: Validation Team and their Task)

● Ensure that interrelated systems (e.g., Water, environmental controls, utilities) are all validated; (Figure:-1: Process Validation Phenomenon)

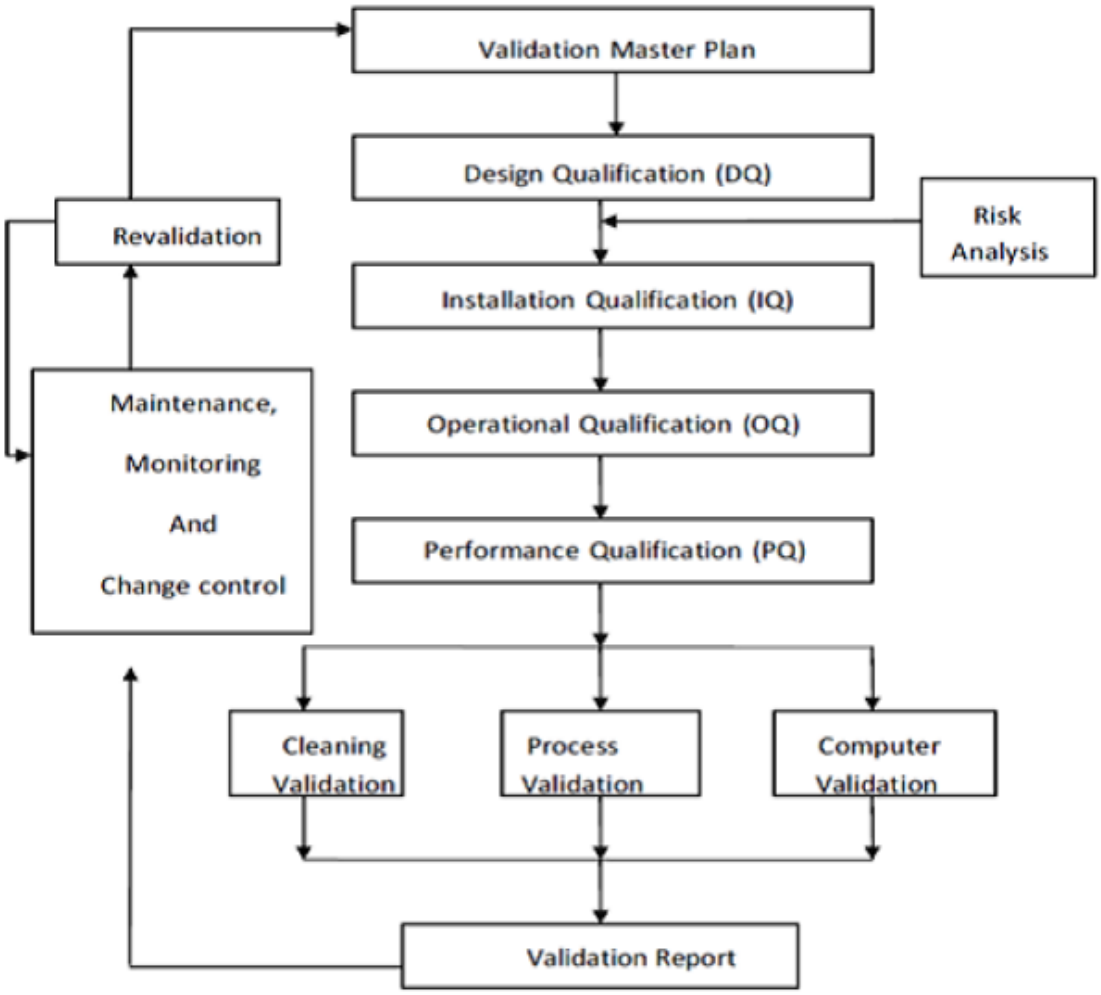
● Installation Qualification (IQ) and Operational Qualification (OQ) are to be conducted and documented in a manner that ensures proper installation and functionality of all processing equipment and permits effective change control. (**Figure:-3:** Validation Life Cycle).

Figure:-2: Validation Team and their Task.

Department /Designation	Responsibility
Manager Production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for analysis of samples collected
Executive QC	Responsible for samples collection and submission to QC
Manager Maintenance	Providing utilities and engineering support
Executive Production	Responsible for preparation of protocol and manufacturing of validation batches
Manager QA	Responsible for protocol authorization and preparation of summary report.

Figure:-3: Validation Life Cycle.

later.



Installation Qualification (IQ) is to include at least the following:

1. List of all equipment, operation of which has potential bearing on product quality or
2. process performance;
3. As-built drawings and specifications for all purchased equipment, new or used;
4. Verification that all such equipment and the installation thereof meets original intent, including applicable building, electrical, plumbing, and other such codes;
5. Preventive maintenance plans and schedules for all such equipment.

Operational qualification (OQ) is to include at least the following:

1. A list identifying each module (step, unit operation, or stage) of the process;
2. Process operating parameters for each module, including those designated as critical;
3. An OQ protocol designed to demonstrate the equipment used in each module operates as intended throughout each process operating parameter range;
4. Task report(s) describing the successful execution of each OQ protocol.

● Performance Qualification (PQ) (Figure:-3: Validation Life Cycle) shall be performed when the following steps are complete and production has been authorized. At least three consecutive, commercial scale lots shall be successfully produced and tested prior to market distribution of any product. Process fully defined, including definition of critical process operating parameters, potential adverse consequences, and critical process operating parameter ranges;

1. Product specifications completed;
2. IQ and OQ steps completed;
3. Operating personnel trained and qualified; and
4. Change control procedures in place.

● Change Control and Revalidation procedures:

Change Control procedure for: (Figure:-3: Validation Life Cycle)

1. Identifying all modifications or alterations that are potentially significant to a state of control, qualification, or validation;
2. Implementing corrective action, such as repair, readjustment, requalification, And/or revalidation;
3. Implementing interim measures to be taken until effective corrective actions are Complete; and
4. Documenting all of the above.

Revalidation – repetition of the validation process or a specific portion of it. Revalidation may include a total process review and/or requalification of those portions of the process potentially affected by a change.

Change control and revalidation measures include, and are not limited to, review of changes to the following:

1. Product and manufacturing material specifications;
2. Source of components;
3. Product formula (drug products);
4. Manufacturing process instructions;
5. Test procedures;
6. Equipment (automated and nonautomated);
7. Support systems, including SOPs;
8. Manufacturing location; and
9. Utilities

● A Validation Master Plan (VMP) shall be used to define and coordinate validation activities related to any new, existing, or revised production process. The Validation Master Plan (VMP) is to include or identify at least the following (to avoid excessive detail in the VMP, cross references to relevant detailed documents may be used, including to validation protocols):

1. The plan for establishing process robustness, including use of results from development pharmaceutics and other process development efforts, such as the number and sizes of PQ batches intended to be involved;
2. Relevant task reports (e.g., from R&D or other sites);
3. Identification of all test methods and analytical instruments to be used in the validation
4. work, including calibration plans associated with each;
5. IQ and OQ plans with identification of specific areas in which IQ and OQ are expected to overlap;
6. Individual validation protocols for each validation study;
7. Sampling and testing plans;
8. Provisions for change control and document control to be executed throughout the validation project;
9. Key SOPs and policies;
10. Project team organization with training backgrounds, responsibilities, and authorities(Figure:-2: Validation Team and their Task);
11. Definition of resources required and allocated; and
12. Validation schedules, including responsible party or parties associated with each line item.

● Validation Protocols shall be used to define individual validation experiments and practices. Each Validation Protocol shall include, and is not limited to, the following:

1. Statement of experimental objectives;
2. Definition of what is to be qualified or validated;

3. Experimental plan to be executed, including number of trials and data to be gathered;
4. Detailed sampling plans, including sample sizes, sites, and methods;
5. Test plans with acceptance criteria to be met or established;
6. Descriptions of all testing instruments to be used and specific calibration plans (full details or reference to detailed instructions) for each; and
7. Description of all statistical analyses to be applied.

● Definitive statements must be used, especially in describing objectives, conclusions, and product or process definitions. Collectively, project validation task reports are to support acceptability of all critical process operating parameter ranges, corresponding acceptance limits, and evidence of process robustness and reproducibility.

● All validation master plans, protocols, and task reports must be approved. All such validation documents created on-site must be approved by the site quality authority and, when production is involved, also by the site production authority.

● Validation task reports shall be used for documenting and summarizing results of validation studies.

1. Five illustrative categories of task reports are listed and are not necessarily all-inclusive.
2. Collectively, the validation task reports must support acceptability of all critical process operating parameter ranges, corresponding acceptance limits, and evidence of process robustness:
3. Product development summary (e.g., as one of several technology transfer measures);
4. Lot summary report (e.g., identification and size of development and production lots, yields, failures if any, major conclusions);
5. Process performance report (e.g., tables detailing lots versus actual critical process Parameter data);
6. In-process control report (e.g., tables detailing lots tested versus results, including actual product attribute data); and
7. Validation protocol completion report (could cover any subject for which a protocol is executed).

● Concurrent Process Validation techniques can be employed only with site management approval, in such exceptional cases as rework lots or orphan drug products. Concurrent validation may be the practical approach under certain circumstances. Examples of these may be:

1. When a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site
2. Where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients
3. When the number of lots evaluated under the Retrospective Validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control
4. When the number of batches produced is limited (e.g. orphan drugs).

● When a secondary manufacturing site is scheduled to produce with an established process using similar equipment, the primary site shall make the necessary process validation information, including the primary site validation task reports, available for use by the secondary site in preparing its VMP. The new VMP must then also include all site-specific information required to comply with these standards.

● Relevant process validation information from other divisions, departments, and production sites (including R&D) is to be gathered, used, and maintained

● Assemble and document evidence of process robustness and reproducibility. And these documented evidence shall be established prior to approval of the first production batch/lot, and such evidence shall continue to be recorded and analyzed throughout the commercial life of the process and product.

● Provide for retention of archived validation files for required periods following last commercial lot expiration date.

● A validation life cycle for an established (legacy) or altered process (requires revalidation) will be the same as above, except for those steps that apply and can be shown by Retrospective Process Validation to have been already satisfactorily completed.

● Critical process operating parameter data shall be collected for each commercial batch manufactured to provide ongoing evidence of process capability and robustness. Tabulations of data (e.g., spreadsheets) shall be maintained and periodically analyzed to ascertain that critical process operating parameter ranges are being consistently met.

Results of annual record reviews of product complaints, adverse events, batch records, change controls, revised SOPs, and QA investigations are to be reviewed, analyzed for trends, and responded to as part of the on-going change control and revalidation programs (Figure:-3: Validation Life Cycle).

The Three Lot Controversy (9):

During 1983 – 1984, representatives of FDA and Industry debated at length over the value of positioning three consecutive, commercial-sized lots as pivotal evidence of process validation. Industry agreed that FDA's argument for three lots might be suitable for medical devices, but argued successfully that it was not appropriate for pharmaceutical processes for several reasons:

1. Unnecessarily costly and risky to perform prior to regulatory submission;
2. Limited statistical benefit from three lots; and
3. Establishing critical process parameter ranges and probable adverse consequences of exceeding range limits represents a better investment of resources and contributes more to process robustness and reliability, while the three-lot requirement can detract from such efforts.

In 1990, when FDA launched its Pre-Approval Inspections (PAI) program, the three-lot issue again arose. PAI's chief architects (Richard Davis and Joseph Phillips, FDA, Newark District Directors) announced

they would require evidence of three consecutive, successful lots of commercial size prior to shipment of a new product across state lines, as "final" evidence of process validation, even when the firm had already received its New Drug Application (NDA) Approvable Letter. This time, Industry did not protest the requirement. Several reasons made the requirement logical:

● Three commercial lots add some degree of assurance that the process works and at least a limited indication of reproducibility.

● Three lots can be made in a practical period of time, compared with the number of lots required to gather statistical evidence of reproducibility.

● The overall approach forces focus of validation emphasis on process development measures that occur earlier in the life cycle and, thus, do not jeopardize market launch timing.

Since 1990, most firms have found the redistribution three-lot requirement practical and useful. Some have made the mistake of believing that critical parameters should be varied during the three runs in order to develop new validation evidence, usually of the kind that can be developed in the laboratory or pilot plant more economically and with less risk of failure.

BENEFITS OF PROCESS VALIDATION (14-16):

● Low to confirm compliance of cGMP.

● Good Business-Avoid possibility of rejected or recall.

● Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control, but testing data can be used to support improvements or the development of the next generation of the process.

● Process validation is intended to establish that the proposed manufacturing process is a suitable one and consistently produce a product of the desired quality.

● Customer satisfaction: Non-conforming product can lead to lost customers.

● Product liability:

● Reduced production costs:

● Idealist environment to expect Regulatory requirement complies i.e. CFR Title 21, Part 820.75(5).

CONCLUSION:

The white paper concept, process validation in federal regulations is defect devoid documented phenomenon for quality dosage form in importance of human healthcare in this planet.

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