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Theoretical Approaches to Process Validation in Pharmaceutical Manufacturing Process

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ABSTRACT

Under the more general statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act, validation of manufacturing processes is deemed a legal part of current good manufacturing practice for active pharmaceutical ingredients (APIs). Validation of manufacturing processes is required by the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110). A medication should be created that is suitable for its intended purpose, according to the fundamental tenet of quality assurance. Procedure Validation is the collection and estimation of data that proves a process can reliably produce high-quality goods, starting with process design and continuing through commercial production. Three stages of validation are suggested by the 2011 USFDA process validation guideline - Process design, Process qualification, Continued Process qualification. An introduction and broad review of process validation in the pharmaceutical manufacturing process, specifically in the tablet manufacturing process, are provided in this article. Process validation ensures that a process will consistently create a product that meets its predefined quality features and qualities. It is a crucial step in the design, prototyping, and manufacturing processes. Since quality is always a necessary precondition for any product, pharmaceuticals must be produced to the greatest standards of quality. Furthermore, end-product testing does not ensure the product's quality on its own; rather, quality assurance methods need to be applied to incorporate the product's quality throughout the whole process, rather than only testing it at the conclusion.

Keywords – GMP, Food and Drug Administration, QA, Validation, Validation Master Plan, Re-Qualification.

I. INTRODUCTION

Validation is a crucial component of quality assurance that ensures the equipment, manufacturing process, software, and testing are all of the highest caliber.

Validation ensures that, within predetermined manufacturing process limitations, items with particular quality features and qualities can be produced consistently.

Documented evidence that offers a high level of assurance that a particular procedure will consistently result in a product that satisfies its planned specifications and quality attributes is known as validation. [1,16]

To maintain and enhance the quality of pharmaceutical products, the Food and Drug Administration (FDA) adopted Good Manufacturing Practices. [2]

The portion of quality assurance known as GMP makes ensuring that products are regularly manufactured and managed to the standards of quality appropriate for their intended use and as mandated by the marketing authorization.

The primary guidelines of GMP include correct facility and equipment design and construction, ongoing facility and equipment monitoring, and recurring audits.

Good practices, such as good manufacturing practices (GMP) and good clinical practices (GCP), depend on validation. Thus, it is a component of the system for ensuring pharmaceutical quality. [2,3,17]

Validation entails certification and ought to be used throughout a system's, equipment's, product's, process', or method's life.

The general principles of qualification and validation, as well as tasks like computerized systems, analytical methodologies, process validation, cleaning validation, and other related operations, are covered in these guidelines.[3]

Pharmaceutical facilities use a variety of processes, all of which need to be precise in order to guarantee a high-quality final product. Although the focus of validation is mostly on processes, when the same methodology is used on a machine or piece of equipment rather than a process, it is known as a qualification. [1,4]

In an effort to raise the caliber of medications, Ted Byers and Bud Loftus, two FDA officials, originally put out the idea of validation in the middle of the 1970s. The documented proof that offers a high level of assurance to a desired outcome with planned conformity is the validation process. The word "valid or validity," which meaning "legally defined," is the source of this phrase.

The US FDA and other food, drug, and pharmaceutical regulatory bodies, as well as their good manufacturing practices recommendations, mandate validation. [18]

Precise and accurate measurement of analytical data depends on the calibration of analytical instruments. Everything else that depends on using that instrumentation is dubious if it is not certified to ensure that the results shown are reliable. For the purposes of this paper, it will be assumed that well-qualified instrumentation forms the basis of the validation and verification work that will come after.

The process of proving through laboratory testing that an analytical procedure's performance characteristics satisfy the demands of the planned analytical applications is known as validation. [1,2]

A manufacturer must to be able to validate the manufacturing process with appropriate design and dependable methods to transfer process knowledge from development to commercial production. Within a quality system, process validation offers

preliminary evidence that the process design yields the desired product quality through commercial batch manufacturing.

A. **Goals**

1) Equipment validation is necessary for both the manufacturing process and the individual pieces of equipment.
2) The objective is to develop a strong manufacturing process that reliably yields a pharmaceutical product that satisfies purity, identification, and potency quality standards with little fluctuation.
3) Any process or system's validation results in the determination of process parameters and controls.
4) It assists in identifying potential hazards and worst-case scenarios during the production of high-quality goods.
Examining variations that occur during the process is beneficial.
6) Validation enables in-depth analysis and comprehension of the system and its components.
7) Following validation, the risk of regulatory noncompliance is reduced.
8) Less process control and final product testing are needed throughout a validation process.
9) There is less fluctuation from batch to batch.
10) Lowers the cost of production.
11) Boosts manufacturing facility output as a result of less rejection and rework.
12) Reduces the likelihood that batches may fail. [1]

B. **Requirements**

1) Experience
2) Planning
3) Resources
4) Communication and Understanding
5) Instruction
6) Standard Operating Procedures, Tools, and Techniques
7) Master Plan for Validation
8) Information Evaluation
9) Report on Validation [1]

TABLE I. Difference Between Validation and Qualification.

Validation	Qualification
1) The act of demonstrating and recording that a process, method, or procedure genuinely and reliably produces the desired outcomes.	1) Ensuring that equipment or auxiliary systems are installed correctly, function as intended, and produce the desired outcomes through documentation and provision of this information.
2) System, procedure, or process validation is carried out.	2) Equipment qualification is carried out as a component of validation.
3) Documentary proof that the procedure will reliably result in the intended result.	3) Done on a specific process element to verify its functionality and ascertain whether it possesses the necessary characteristics to generate a predetermined result.

C. **Departments Responsible for Validation:**

The following departments hold primary responsibility for validation:
1) Site validation committee: Create a plan for the master validation of the site.
2) The manufacturing section is responsible for preparing the batches as if they were regular production batches. to help in data collection.
3) Quality assurance: Verify that all procedures, documentation, and compliance are in place. approves reports and procedures. Examining the documentation for validation. to give the procedure approval.

4) Quality controls: Evaluate protocols, conduct contracts validation testing, and provide reports as required.
5) Research & development: This field addresses product design.
6) Department of Engineering: Installs, certifies, and maintains plant, facilities, equipment, and support systems. [24, 22]

D. **Validation Team and Its Responsibilities**

Validation investigations are generally carried out and supervised by a diverse team. Individuals possessing training and experience in a pertinent field may carry out these kinds of investigations.

Among the validation team's many duties are:
1) Updates, evaluates, and approves each project's validation deliverables and plans.
2) Verifies that the project validation plan and the company validation master plan are followed for validation.
3) Coordinates, carries out, and validates VMP components.
4) Gives advice, assesses, and approves modifications.
5) Examines and authorizes IQ/OQ/PQ plans and processes.
6) Examines test findings and offers suggestions for publication.
7) Evaluates potential threats and creates backup plans. [25, 22]

II. Phases of Validation

A. **Design Qualification (DQ):** Design qualification may be the initial step in validating new buildings, systems, or equipment (DQ). The design's adherence to GMP requirements needs to be proven and recorded. It is an official confirmation of the production facilities' and equipment's designs.

DQ factors include:
1) Legal requirements and good manufacturing procedures.
2) Criteria for performance.
3) Dependability and effectiveness.
4) Access to and maintenance of vital instruments and equipment.
5) Impact on the environment and safety.
6) Pressure engines, movement flow, and air flow within the facility. [5]

B. **Installation Qualification (IQ):** is the process of proving, by objective evidence, that every important detail of the installation of the process equipment and ancillary systems complies with the manufacturer's approved specification and that the equipment supplier's recommendations are appropriately taken into account. Equipment, systems, and facilities that are new or updated need to undergo installation qualification.

IQ factors include:
1) Features of equipment design (e.g., cleanability of construction materials, etc.)
2) Installation circumstances (utility, functionality, wiring, etc.)
3) Cleaning schedules, calibration, and preventative maintenance.
4) Security elements.
5) Prints, drawings, and manuals from suppliers.
6) Documentation for software.
7) List of spare parts.
8) Environmental factors (including humidity, temperature, and clean room requirements).
9) Equipment description.
10) Functional specifications for the facility.
11) Operational premise.

C. **Operational Qualification (OQ):** An approved protocol should be followed when conducting an operational qualification (OQ). At the OQ stage, the crucial operational parameters for the systems and equipment should be determined.

OQ factors include:
1) Process control constraints (time, temperature, pressure, line speed, setup conditions, etc.) are among the OQ factors to be taken into account.
2) Parameters of the software.

3) Raw material requirements
4) Operating procedures for processes.
5) The requirements for handling materials.
6) Change control procedures.
7) Education.
8) The role of equipment control.
9) The process's short-term stability and capabilities (latitude studies or control charts).
10) Worst-case scenarios, action levels, and probable failure modes.
11) In order to optimize the procedure, statistically sound methods like screening experiments may be applied at this stage. [6]

D. **Performance Qualification (PQ):** Installation and operational qualification should be successfully completed before moving on to performance qualification (PQ).
PQ factors consist of the following:
1) Real product and process specifications and guidelines set forth in OQ.
2) The product's acceptability.
3) Guarantee of process capability according to OQ standards.
4) Long-term stability and repeatability of the process.
5) Tests that incorporate an upper and lower operating limit condition, or circumstances that encompass both. [7]

E. **Re-qualification:** Any equipment modification or relocation must be approved by the change control procedure after a thorough evaluation and approval process. It is recommended that the equipment be requalified as part of this official examination. Modest alterations or those that don't directly affect the quality of the finished or in-process product should be managed using the preventive maintenance program's documentation system.[8]

III. Types

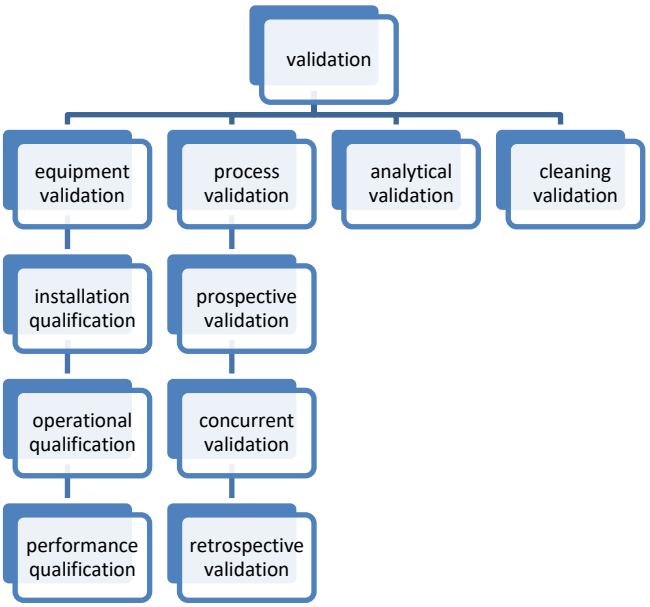

Fig. 1. Types of validation

A. **Analytical method validation:** This process aims to confirm that the chosen analytical technique will produce accurate results sufficient for the intended use. The validation of analytical methods encompasses various parameters. These are listed in the following order:
1)Accuracy
2) Detection limit;
3) range;
4) linearity;
5) precision;
6) repeatability;
7) reproducibility;
8) specification;
9) The quantity limit.

B. **Process validation:** This kind of validation presents written evidence, which offers a higher level of assurance that the procedure will reliably result in a product that satisfies all predefined quality standards and attributes. In addition to ensuring process repeatability and lowering the possibility of manufacturing issues, process validation also increases output of a set quality.

There are four forms of process validation depending on the stage of manufacturing. These are as follows:

The four types of validation are

1) Retro specific,

2) concurrent,

3) prospective, and

4) revalidation.

C. **Cleaning validation**: Cleaning validation is a recorded setup that offers a high level of assurance that a specific system, piece of equipment, or quality of clean-up is regularly carried out to acceptable limits and established quality. A wide range of pollutants, including lubricants, airborne contaminants, prepared product residues, and microorganisms, can contaminate pharmaceutical goods. Therefore, preventing contamination and cross-contamination requires a thorough cleaning process.

D. **Equipment validation**: Equipment validation is the established, documented setup that demonstrates that any equipment functions as intended and produces results that are accurate and acceptable (predetermined result). The idea that equipment needs to be built, maintained, and modified in order to carry out the intended tasks is the basis of the equipment validation process. Since equipment is the fundamental element of the pharmaceutical industry, it is crucial to provide equipment validation (recorded evidence of equipment) prior to carrying out any process in the sector. [9]

IV. Validation Approaches

1) Manufacturers ought to design and arrange validation in a way that guarantees the efficacy, safety, and quality of their products over the duration of their life cycles.

2) Risk management concepts ought to serve as the foundation for the range and depth of qualification and validation.

3) When applicable, statistical computations should be used to support scientific claims that a system, process, or other relevant element has been suitably validated.

4) Qualification and validation should be carried out in compliance with established processes, and the outcomes suitably recorded, for example, in reports.

5) The administration and organization of validation should be ensured by a suitable and efficient quality system.

6) Senior management is in charge of making sure there are enough resources available to complete validation tasks quickly.

7) The task of completing validation should fall to individuals who possess the necessary training and expertise.

8) A defined timetable or program should be in place to assist with the organizing and carrying out of validation tasks.

9) In accordance with the established protocols and procedures, validation should be carried out in an organized manner.

10) Qualification and validation should be carried out: whenever new facilities, machinery, utilities, systems, processes, and procedures are introduced; if changes are made, contingent upon the results of the risk assessment; and whenever required or recommended by the results of the periodic review.

11) The results of the validation should be documented in writing.

12) As stated in the World Health Organization (WHO) guidelines on quality risk management, the breadth and depth of validation should be determined by knowledge, experience, and the application of quality risk management principles. Worst-case scenarios or particular challenge tests, such as stress load and volume verification in computer system validation, should be taken into consideration when adding to the validation as needed.

13) The V-model provides an illustration of a qualification and validation strategy. [22]

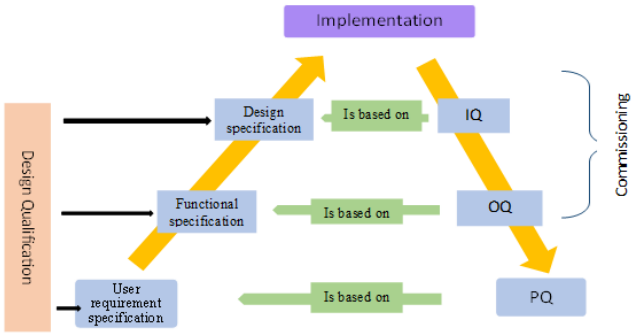

Fig. 2. V-Model for Validation

V. Process Validation

European Commission: The validation process, known as the "Act of Proving, in Compliance with GMPs that Any," genuinely yields the anticipated outcomes. 2000: "Documented evidence that the process can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes when operated within established parameters."

According to USFDA 1987, "a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics" is provided by documented evidence.

According to ICH, "Process Validation is the process of verifying and supplying documented proof that processes operating within the parameters of their designated designs are able to consistently and dependably produce a final product of the necessary quality."

According to the WHO, "the documented act of proving that any procedure, process, piece of machinery, substance, activity, or system actually produces the desired outcome."

USFDA (2011) - Process validation is the process of gathering and analyzing data to demonstrate scientifically that a process can consistently create high-quality products, starting from the process design stage and continuing through commercial production. [10]

TABLE II. The most recent definition of process validation is provided in this table.

1987 Definition	2011 Definition
"Determining documented proof that offers a high level of assurance that a particular process will consistently yield a product that satisfies its predetermined specifications and quality characteristics"	"The process design stage through production data collection and evaluation that establishes scientific evidence that a process is capable of consistently delivering quality products"

VI. Process Validation Stages

A. **stage 1: Process Design:** Using the knowledge gathered from development and scale-up activities, the commercial process is defined at this step. It includes all of the following: creating stability conditions; storing and managing in-process and finished dosage forms; equipment qualification; installation qualification; master production documents; operational qualification; process capability; formulations; pilot batch studies; scaleup studies; and the transfer of technology to commercial scale batches.

B. **Stage 2: Process Qualification**: In this phase, the process design's suitability for repeatable commercial manufacturing is verified. This stage is designed to confirm that all of the important process parameter limits that have been defined are valid and that good products are frequently generated even in the worst-case scenario. It stands for the specific research or experiments carried out to demonstrate.

C. **Stage 3: Ongoing Process Verification:** During regular production, continuous assurance is obtained that the process stays under control. In order to ensure that there are no deviations, failures, or changes to the assembly process, as well as that all SOP, including the change control procedure, are followed, this phase necessitates periodic evaluation

of all process-related documentation, including validation audit report backs. At this point, the validation team additionally guarantees that there haven't been any modifications or deviations that should have led to revalidation and requalification. [11, 12, 13]

Step 1: Process Design
a. Developing and Preserving Process Knowledge and Understanding
b. Formulating a Process Control Plan
↓
Step 2: Qualification of the Process
a. Facility design and equipment and utility qualification
b. Process performance qualification
c. PPQ Protocol
d. Execution and Report of the PPQ Protocol
↓
Step 3: Ongoing Process Validation

Fig. 3. Methods for Validating Processes

VII. Types of Process Validation

A. **Prospective validation** is the practice of conducting validation before a new product or one created using an altered manufacturing process—a process that may have an impact on the product's characteristics—is distributed. FDA validation is performed prior to the regular production of goods meant for retail distribution.

B. **Concurrent validation** is the process of validating products that are routinely produced with the intention of selling them.

C. **Retrospective validation** is the process of validating a product's manufacturing procedure using data from production, testing, and control that has already been distributed. (FDA) Process validation for a product that has been sold using data gathered from manufacture, testing, and control batches.

D. **Re-Validation**: A repeat of the process validation to guarantee that equipment or process modifications made in compliance with change control procedures won't negatively impact the process's characteristics or its output quality. [14]

VIII. Validation Life Cycle

The process of validation is ongoing and dynamic. Its scope includes training, process and system maintenance, and revision control for documentation. Validation evidence ought to be visible at the corporate level and show up in the management hierarchy. One technique for establishing and preserving quality is validation. [15]

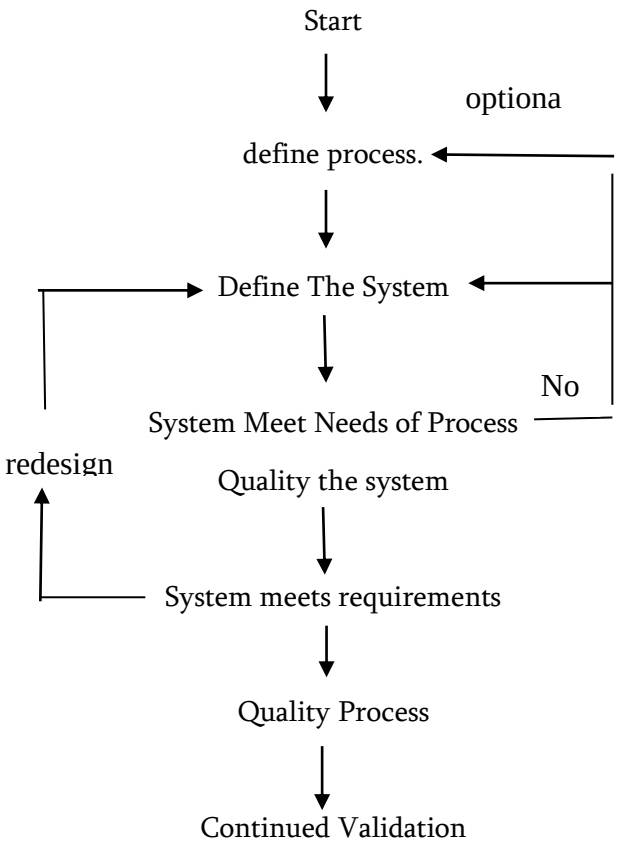

Fig. 4. Life Cycle of Validation

IX. Process Validation of Manufacturing Process (Eg., Solid Dosage Form) [13]

addition of active excipients, or raw ingredients

↓

Pre-blending with a granulator and high-speed mixer

↓

High-speed mixer granulator for granulating

↓

Fluid-bed dryer for drying

↓

Sizing (mill/sieve)

↓

addition of raw materials (disintegrants and lubricants)

↓

V-blender for blending

↓

Tableting (precompression combined with high-speed rotary)

Fig. 5. Synopsis of Process

TABLE III. Parameters performed during process validation.

Stage	Process variables	Tests performed
Dry mixing	Mixing time	Uniformity of content, Bulk density, moisture content, sieve analysis
Granulation	Mixing time impeller reading during mixing	
Drying	Inlet & outlet temperature drying time	Final drying, Loss on drying/moisture content
Blending	Blending time	Uniformity of content & RSD
		Bulk density, sieve analysis & compressibility index
Compression	Pre compression studies	Optimum speed-Dissolution at lower & higher thickness
Compression	Machine speed (10 - 30 rpm)	At different speeds
		Appearance
		Group weight variation
		Individual weight variation
		Thickness
		Hardness
		Friability
		Disintegration time
		Dissolution
		Content uniformity
		Assay
Compressio	Hopper	Full hopper, middle of hopper

n	study at maximum speed	& near end of hopper
		Individual weight variation
		Thickness
		Hardness
		Friability
		Disintegration time
		Content uniformity
Coating	Inlet temp. Exhaust temp. Pan speed atomization pressure, spray rate gun distance	Weight build up
		At the end of coating
		LOD
		Dissolution profile at 15, 20, 30, 45 & 60 minutes
Blister packing	Machine speed, forming and sealing temperature	Blister appearance and quality, leak test and impurity

X. Documents

A. **Validation Master Plan:** The purpose of this document is to demonstrate to the Federal Department of Agriculture (FDA) inspectors that the company has a very well-organized validation program. Included in the format and content should be:

1) Introduction: scope, location, schedule, and validation policy.

2) Organizational structure: duties assigned to employees.

3) Plant, process, or product description: justification for additions or deletions, as well as the scope of validation.

4) Particular process factors that need special attention and are crucial.

5) A matrix-formatted list of the systems, processes, and products that need to be validated, along with the validation methodology.

6) Key acceptance criteria, real status, and revalidation operations.

7) Format for documentation.

8) Making use of the necessary SOPs.

9) Schedules for every validation project and its subsidiary projects. [19, 20]

B. **Validation Protocol:** To guarantee that the process is sufficiently validated, comprehensive procedures are necessary for carrying out validations. The following components must to be included in validation protocols:

1) The goals and extent of the validation study's coverage.

2) The composition, credentials, and duties of the validation team.

3) Validation types include prospective, contemporaneous, retrospective, and re-validation.

4) The quantity and choice of batches to be included in the validation research.

5) A list with the typical and worst-case operating parameters for every piece of equipment that will be used.

6) IQ and OQ results for essential equipment.

7) Requirements for all measurement instruments' calibration.

8) Important process variables and the tolerances that apply to them.

9) Process characteristics and variables that are likely to cause risk should be noted.

10) A copy of the product's master documents is used to describe the processing processes.

11) Sampling locations, sampling procedures, stages, and plans.
12) The statistical instruments should be applied to data analysis.
13) The processing operators' training needs.
14) Test strategies that have been proven to work for both process and final product testing.
15) Details regarding test procedures, raw ingredients, and packaging.
16) The charts and forms that will be used to record the outcomes.
17) Format for presenting findings, recording conclusions, and endorsing research findings. [21,22]

C. **Validation Report:** Following the conclusion of the validation, a documented report ought to be made available. Should it be deemed appropriate, it ought to be permitted and approved (signed and dated). It ought to draw conclusions about the process's validation status and provide the required advice for regular procedures. Following the execution of batches, a validation report must be created to evaluate adherence to the protocol. During execution, data might be gathered in a format that has been preplanned. The formulation order of the validation batch processing records must be compared with the actual yield that was attained at various stages.

At minimum, the following should be included in the report:
1) The study's title and goal.
2) A mention of protocol.
3) Specifics of the content.
4) Tools.
5) Cycles and programs utilized.
6) Specifics of protocols and testing techniques.
7) Outcomes (weighed against acceptance standards).
8) Suggestions regarding the upper limit and future application criteria. [13]

XI. CONCLUSION

In pharmaceutical companies, the practice of process validation is crucial. It is essential to ensuring that the quality objectives are fulfilled. Understanding of the product and process will be enhanced, and waste, rejections, lead times, and other failures will be decreased, by conducting validation in accordance with USFDA process validation guidelines. Throughout the course of the product life cycle, this guideline also aids in the validation process' ongoing improvement. Prior to receiving approval, a novel medication must undergo a thorough and dependable evaluation to determine its safety and efficacy for the intended use and intended patient population.

To guarantee that the drug product will meet or set pharmaceutical standards for identity, strength, quality, purity, stability, assessment safety, and efficacy, pharmaceutical validation and process control are required when the drug is approved.

Under the more expansive statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act, validation of manufacturing processes is deemed an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs). Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110). There is a high degree of exact assurance that a manufacturing process that has been validated will consistently yield acceptable items. Thus, process validation is a scientific way of proving that a process can reliably produce high-quality results.

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