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Pharmaceutical Validation: An Updated Review

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A B S T R A C T

Pharmaceutical validation is a crucial process in ensuring the safety, efficacy, and quality of pharmaceutical products. It involves systematic and documented evidence to demonstrate that a particular process, system, or equipment consistently produces results that meet predefined specifications and quality standards. Validation is essential for maintaining regulatory compliance, minimizing risk, and building trust among patients, healthcare professionals, and regulatory authorities. The purpose of pharmaceutical validation is to demonstrate that the process can consistently produce desired results and comply with good manufacturing practices (GMP) guidelines. The concept of validation was introduced by Ted Byers and Bud Loftus in the 1970s to enhance quality standards within the pharmaceutical industry. The FDA introduced the Good Manufacturing Practices (cGMP) regulations in 1976, which have been subjected to several amendments over time. The pharmaceutical industry adopts these regulations as a fundamental aspect of effective management and ethical business practices. Pharmaceutical validation is based on scientific evidence and rational design, following a systemic approach that includes planning, execution, documentation, and review.

Keywords: Validation, Quality, manufacturing practices, product, process, qualification, FDA, U.S. FDA, Equipment, cGMP, SOPs, URS, QMS.

1. INTRODUCTION

Validation in the pharmaceutical industry is the process of providing documented evidence that procedures, processes, and activities in testing and production consistently comply with predefined standards. It ensures not only the final product's quality and compliance but also the consistent production of expected results. The main goal of pharmaceutical plants is to consistently manufacture high-quality products at the lowest possible cost, making validation a key element in efficient production operations. Validation encompasses various activities, including analytical methods and computerized systems (1). It is a critical part of current good manufacturing practices (cGMP) and focuses on proving the effectiveness and validity of processes. Pharmaceutical validation is integral to ensuring product quality and is based on the principles of quality system regulations. Its objective is to consistently produce products fit for their intended use by maintaining criteria, quality attributes, and reproducibility. In the complex landscape of pharmaceuticals, end-product testing alone may not suffice for quality assurance, making in-process control and process validation essential. The core principle of quality assurance is producing a product fit for its intended use, which necessitates a deep understanding of processes and their performance. Quality should be built into manufacturing processes to meet all specifications, ensuring that the process is suitable and under control (2).

2. HISTORY OF VALIDATION

The concept of validation was initially introduced by Ted Byers and Bud Loftus, both FDA officials, during the 1970 (3).

Their aim was to enhance the quality standards within the pharmaceutical industry. This concept emerged in response to issues related to the sterility of large volume parenteral products. While the primary focus of validation activities was initially on the manufacturing processes of these products, it gradually extended to encompass various other processes associated with pharmaceutical production. In 1976, the FDA put forth a comprehensive set of regulations known as the current Good Manufacturing Practices (cGMP) regulations. These regulations were subjected to several amendments over time. The pharmaceutical industry adopts these regulations as a fundamental aspect of effective management and ethical business practices. The U.S. FDA played a pioneering role in promoting the concept of process validation. It wasn't until September 29th, 1978, that the formal definition of process validation was officially included in U.S. FDA literature (3).

1978 – GMP include validation.

1987 – First validation guidelines (equipment IQ).

2000 – New Approaches/Documentary presentation.

2008 – New Process validation Draft guidelines.

(Equipment & analytical validation)

2011– New Process validation guidelines issued (4).

3. DEFINITION

According to European commission

1991 – Validation – "Act of proving, in accordance of GMPs that Any…" process actually leads to expected results.

2000 – "Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes." (6)

US FDA Definition

"Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its predetermined specifications and quality characteristics." (6)

ICH Definition

"Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality." (6)

WHO Definition

"The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result." (6)

According to cGMP Academy

"pharmaceutical validation is a program that confirms processes, methods, equipment or systems as intended. It involves collecting and analyzing data to show that process can deliver the expected outcomes and quality attributes." (5)

Pharmaceutical validation is based on scientific evidence and rational design and it follow a systemic approach that includes planning, execution, documentation and review.

4. NEED OF VALIDATION

- The pharmaceutical sector extensively employs valuable materials, advanced facilities, sophisticated equipment, and highly skilled personnel.
- Thorough analysis and stringent control of the manufacturing processes through batch validation are imperative. This is vital not only to mitigate the impact of failure costs but also to enhance productivity.
- Employing equipment without certainty of its ability to yield the desired product or hiring personnel without assurance of their competence would be impractical. Likewise, neglecting process checks and assessments to verify product adherence to specifications is untenable.
- Optimizing the utilization of these resources is crucial for the industry's sustained prosperity. Expenses related to product failures, rejections, reworks, recalls, and customer complaints significantly contribute to the overall production expenses.
- This underscores the importance of quality assurance and the pursuit of cost reduction (7).

5. SCOPE OF VALIDATION

Pharmaceutical validation is a huge area of work and its practically covers every aspect of the pharmaceutical processing activity, hence explaining the scope of validation become a really hard task. However, an organized look at the pharmaceutical operation will point out at least following area for the pharmaceutical validation (6).

- Analytical
- Instrumental calibration
- Process utility services
- Raw materials
- Packaging materials
- Equipment

- Facilities
- Manufacturing operation
- Product design
- Cleaning
- Operators

6. THREE MAJOR PHASES OF VALIDATION

Fig. 1. Main Phases of Validation

6.1 PRE- VALIDATION QUALIFICATION PHASE

This phase encompasses all activities with product research and development, formulation pilot batch studies, scaling up processes, transferring technology to commercial-scale production, establishing stability conditions, and managing the storage and handling of in process and finished dosage forms. It also includes equipment qualification, installation qualification and Creation of master production documents, operational qualification, and assessing process capacity (8).

6.2 PROCESS PHASE

The purpose of this is to confirm that the critical process parameter's established limits are reliable and that even under the most unfavorable conditions, acceptable products can be produced (9)

6.3 MAINTENANCE PHASE

The Maintenance Phase of pharmaceutical validation comes into play once the manufacturing process has achieved a consistent and trouble-free operation over a period. At this stage, the existing Standard Operating Procedures (SOPs) have proven their capability to produce a reliable product, and there are no apparent issues with the process. However, this isn't a time for complacency; it's a crucial phase for ongoing vigilance.

During this final stage, regular scrutiny of SOPs and meticulous documentation of any process changes are imperative. Scheduled audits must be carried out, and comprehensive audit reports must be documented. Consistent inspections and continuous process supervision are valuable practices. Additionally, providing refresher training to employees is essential to ensure that they maintain strict adherence to established protocols.

While any regulatory system involving documentation, inspections, training and protocol updates may become routine and cumbersome over time, it remains exceptionally vital. This holds particularly true for pharmaceutical validations, as the chemicals involved in pharmaceutical products are exceedingly sensitive to environmental conditions. It's the finer details, such as storage and packaging, that can significantly impact the safety and efficacy of the final therapeutic product (10).

7. TYPES OF VALIDATION

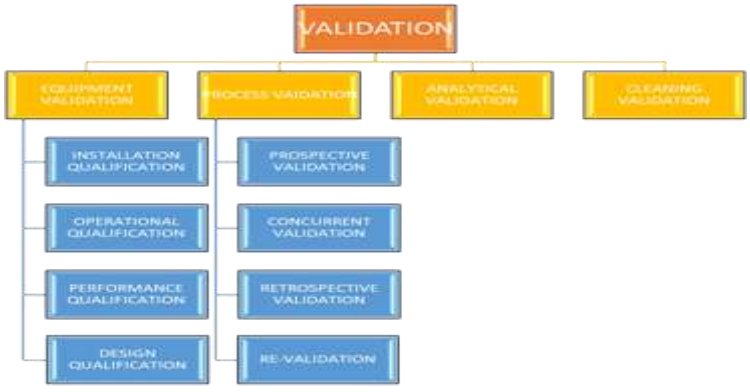

Fig. 2. Types of Validation

7.1 EQUIPMENT VALIDATION

Equipment validation in pharmaceutical industry tests various systems and processes against standard acceptance criteria. If equipment fulfills the acceptance criteria, validation becomes satisfactory, and equipment is allowed for production (12).

Equipment validation within the pharmaceutical industry holds a pivotal role as it verifies ongoing processes, equipment functionality, and the competency of personnel against established quality criteria. It serves as a proactive measure to identify and address any potential deviations that might arise during routine operations. Various regulatory bodies, including the FDA and the WHO, consider validation activity a mandatory prerequisite. Non-compliance with appropriate validation procedures can result in warnings or non-conformance notices (13).

The process of equipment validation encompasses the qualification of various aspects, Including equipment design, installation, operational functionality, instrumentation, control systems, and overall equipment performance. Pharmaceutical companies extend a wide array of equipment validation services, both within laboratory settings and manufacturing environments (13).

The primary objectives of equipment validation are to:

- Identify and evaluate risks associated with the entire process, the equipment used, and the materials involved.
- Gauge the potential impact of any equipment failure on the overall process and product quality.

In essence, equipment validation is a comprehensive procedure critical to maintaining the integrity and safety of pharmaceutical manufacturing processes [48].

Qualification is the term employed to describe the validation process of equipment. There are four distinct types of equipment validation,

Which are as follows:

A. Design Qualification (DQ)

B. Installation Qualification (IQ)

C. Performance Qualification (PQ)

D. Operational Qualification (OQ).

IQ entails the documentation of specific static characteristics related to the facility or product. It serves to confirm that the equipment has been correctly positioned and installed in accordance with the manufacturer's guidelines. Subsequently, the equipment should demonstrate the ability to operate within the specified limits outlined in the purchase agreement, which falls under the domain of OQ [12].

The primary objective of PQ is to demonstrate that the system or process being studied functions as intended and in alignment with the planned approach. These qualifications are integral to ensuring the effectiveness and reliability of equipment within various industries, particularly in pharmaceutical manufacturing (12).

A. Design qualification (DQ)

The documented confirmation that the planned design of facilities, systems, and equipment is appropriate for its intended use is essential. In this qualification process, it's crucial to showcase compliance with Good Manufacturing Practices (GMP). The design principles should align with GMP objectives related to equipment.

This involves a comprehensive examination of mechanical drawings and design features provided by the equipment manufacturer. The aim is to ensure that the proposed design, or in the case of an off-the-shelf item, the existing design, aligns with all the requirements outlined in the User Requirements Specification (URS).

Successful completion of the Design Qualification (DQ) is an obligatory prerequisite before authorizing the construction or procurement of the new design. This process ensures that the design meets the necessary criteria for safe and compliant operation, emphasizing the importance of GMP principles in pharmaceutical operations (1).

B. Installation qualification (IQ)

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendation of the supplier of the equipment are suitably considered.

Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. (FDA) The documented verification that the facilities, systems and equipment as installed or modified complies with the approved design and the manufacturer's recommendations (10).

IQ considerations are:

- Equipment design features (i.e. material of construction clean ability, etc.)

- Installation conditions (wiring, utility, functionality, etc.)
- Calibration, preventative maintenance, cleaning schedules.
- Safety features.
- Supplier documentation, prints, drawings and manuals.
- Software documented.
- Spare parts list.
- Environmental conditions (such as clean room requirements, temperature, and humidity).

C. Performance qualification (PQ)

"It is a documented verification that the equipment and ancillary systems as compared together can perform effectively and reproducibly based an approved method and specification."

Performance qualification is the process of ensuring that the equipment works as expected in the actual operating conditions and for the intended purpose (e.g., meeting safety standards, transmitting data reliably). Performance qualification tests the critical parameters of the equipment using appropriate test methods, which are documented in test specifications. Performance qualification is not required for all equipment or instruments, but only for those that are essential for the process. The decision to perform performance qualification depends on the specific situation.

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 considerations include:

- Actual product and process parameters and procedures established in OQ.
- Acceptability of the product.
- Assurance of process capability as established in OQ.
- Process repeatability, long term process stability (1).

D. Operational qualification (OQ)

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

OQ considerations include:

- Limits of process control (time, temperature, pressure, line speed, and setup conditions).
- 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 (10).

7.2 PROCESS VALIDATION

"Process Validation is 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."

Pharmaceutical process validation is a cornerstone of cGMP, crucial for ensuring product quality. It aligns with the quality system (QS) regulations, aiming to consistently produce safe and effective products. Process validation standardizes the required documents for marketing authorization submissions, fostering compliance with quality management system (QMS) requirements.

According to the FDA, product quality assurance depends on various factors, including the selection of quality processes through in-process and end-product testing. Validation, a concept that originated in the United States in 1978, has since expanded to encompass activities ranging from analytical methods for quality control to computerized systems. It's not mandated by regulations but is a vital part of cGMP, aimed at assessing effectiveness.

Process Validation is a collaborative effort, involving professionals from diverse disciplines within the organization (7).

Types of process validation

I. **Prospective Validation**

II. **Retrospective Validation**

III. **Concurrent validation**

IV. **Re – validation**

Fig. 3. Types of Process Validation

I. Prospective Validation

Prospective validation is the process of ensuring a system functions as intended through a predefined protocol. It typically occurs before the distribution of a new product or one produced under a revised manufacturing process (6).

Key points:

- Performed on at least three consecutive production-size batches.
- Protocols executed before commercial use.
- Production steps analysed during product development.
- Critical parameters identified, and experiments conducted.
- Equipment, environment, and analytical methods fully validated.
- Master batch documents prepared after parameter determination.
- Multiple batches produced, usually three, within agreed parameters for validation.
- Extensive sampling and testing throughout, from various stages to final product.
- Recommendations for routine production controls and in-process monitoring.
- Detailed limits, frequencies, and actions defined for exceeding limits.

- Comprehensive elements of prospective validation, including process description, critical steps, equipment, and more.
- Validation batches match intended industrial scale batches.
- Compliance with Good Manufacturing Practice required for selling or supplying validation batches after successful completion.

Validation batches must match the size of intended industrial-scale batches. If these validation batches are meant for sale or supply, their production conditions must fully adhere to Good Manufacturing Practice standards.

This includes ensuring a successful validation process and obtaining the necessary marketing authorization.

II. Retrospective Validation

It is involves establishing documented evidence through the review of historical data to confirm that a system performs as intended. This validation method is applicable for well -established processes with no recent changes in product composition, procedures, or equipment. It requires a specific protocol, data review, and reporting to draw conclusions and make recommendations.

Data sources for this validation encompass batch processing records, packaging records, process control charts, maintenance logs, personnel change records, process capability studies, finished product data (including trend cards), and storage stability results.

To perform retrospective validation, representative batches from a defined period (at least the last 10 consecutive batches) are selected. The number of lots released annually, batch size, strength, manufacturer, and year must be considered. Additionally, master manufacturing and packaging documents, current specifications for active materials and finished products, a list of process deviations, corrective actions, and changes to manufacturing documents, as well as stability testing data for several batches, are essential elements to include in the validation process (10).

III. Concurrent validation

Shares similarities with both prospective and retrospective validation approaches. It differs in that the operating company sells the product to the public during qualification runs at market prices (6).

Key points:

- Involves in-process monitoring and product testing to provide documented evidence of a controlled production process.
- In exceptional cases, validation may not be completed before routine production starts.
- Justification, documentation, and approval by authorized personnel are necessary for the decision to proceed with concurrent validation.
- Documentation requirements for concurrent validation mirror those specified for prospective validation.

IV. Revalidation

Revalidation is serves as the means to provide evidence that alterations in a process or its environmental conditions do not negatively impact the process's characteristics or the quality of the product. The documentation requirements for revalidation mirror those of the initial validation process.

Routine assessments of facilities, systems, equipment, and processes, including cleaning procedures, are necessary to confirm their ongoing validity. In cases where the validated status remains unchanged, a review backed by evidence demonstrating that these components comply with the prescribed requirements suffices for revalidation (10).

Revalidation becomes imperative under specific circumstances, such as:

- Alterations in raw materials, encompassing changes in physical properties like density, viscosity, particle size distribution, and moisture, which may affect the process or product.
- Modifications in the source of active raw material suppliers.
- Adjustments in packaging materials, including primary containers and closure systems.
- Changes in the process, such as variations in mixing times, drying temperatures, or batch sizes.
- Adjustments to equipment, for instance, the introduction of automatic detection systems. It's important to note that equipment replacements on a "like for like" basis typically don't mandate revalidation, but the new equipment must undergo qualification.
- Modifications to the plant or facility (3).

❖ **Process Validation comprises three key stages:**

Stage 1 – Process Design:

- Focuses on understanding the manufacturing process.
- Involves product research, development, formulation, pilot batches, scale-up, and technology transfer.

- Addresses stability conditions, storage, and equipment qualification.
- Strategy for process control is established based on knowledge gained.

Stage 2 – Process Qualification:

- Evaluates the process design's capability for reproducible commercial manufacturing.
- Validates Critical Process Parameters and ensures products can be produced even under challenging conditions.
- Complies with GMP procedures.
- Two aspects: Design of Facilities and Qualification of Equipment/Utilities, and Process Performance Qualification.
- Performance criteria are defined, data collection plans developed, and analysis conducted.

Stage 3 – Continued Process Verification:

- Ensures ongoing process control during routine production.
- Requires frequent review of process-related documents, including validation audit reports.
- Monitors for changes, deviations, failures, or modifications to the production process.
- Validates adherence to SOPs, including change control procedures.

A successful validation program relies on understanding manufacturing processes, including variation sources, detection limits, and susceptible attributes (14).

7.3 ANALYTICAL METHODS VALIDATION

Analytical method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytic. The main objective of the validation of an analytical method is to demonstrate that it is suitable for its intended purpose.

Method validation provides an assurance of reliability during normal use, and is sometime referred to as "the process for providing documented evidence that the method does what it is intended to do." The main objective of the validation is to demonstrate that the analytical method is suitable for its intended purpose, is accurate, specific and precise over the specified range that an analyte will be analysed. Analytical Method Validation is to be performed for new analysis methods or for current methods when any changes are made to the procedure, composition of the drug product and synthesis of the drugs substances (15).

Definitions

The performance characteristics required to validate various methods by using various guidelines such as USP, ICH, FDA, European guidelines etc.

According to USP:

The analytical parameters can be validated are accuracy, precision, specificity, detection of limit, quantitation limit, linearity, range, ruggedness and robustness (15).

According to ICH:

The analytical parameters can be validated are accuracy, precision, specificity, detection of limit, quantitation limit, linearity, range, system suitability and robustness (15).

According to FDA:

The analytical parameters can be validated are accuracy, precision, specificity/selectivity, detection of limit, quantitation limit, linearity, range, system suitability, reproducibility, sample solution stability and robustness (15).

According to European guidelines:

The analytical parameters can be validated are accuracy, precision, specificity, detection of limit, quantitation limit, linearity and range (15).

- ***Parameters of Analytical Method Validation***

Analytical methods have been validated in pursuance of ICH guidelines of Q2 (R1) Validation parameters are:

1) System suitability
2) Specificity

3) Linearity
4) Range
5) Precision
    - Repeatability
    - Intermediate Precision
    - Reproducibility
6) Accuracy
7) LOD (Limit of detection)
8) LOQ (Limit of quantitation)
9) Robustness

Parameters of analytical method validation as per USP guidelines (19)

1. Accuracy
2. Precision
3. Specificity
4. Detection limit
5. Quantitation limit
6. Linearity
7. Range
8. Ruggedness

i. Accuracy

Accuracy pertains to how closely a measured value aligns with the true value. In methods characterized by high accuracy, the measured value closely matches the true value, which can be determined through recovery studies.

Three common methods for assessing accuracy are:

1. Comparing the measurement to a reference standard.
2. Determining the recovery of the analyte when spiked into a blank matrix.
3. Employing standard addition of the analyte.

It is essential to have a clear procedure for determining individual or total impurities (20).

ii. Precision

Precision in an analytical method refers to how closely repeated measurements of the same analyte align with each other. This precision is typically expressed as the standard deviation or relative standard deviation (coefficient of variation) within a series of measurements.

Precision is often indicated by the Relative Standard Deviation (RSD).

Precision is classified as follow:

a) Repeatability

Repeatability involves employing the same analytical procedure within a laboratory over a brief timeframe, utilizing the same analyst and equipment. To assess repeatability, a minimum of nine determinations should be conducted, encompassing the defined range for the procedure. (i.e., three concentrations and three replicates of each concentration or using a minimum of six determinations at 100% of the test concentration) (21).

b) Reproducibility

Reproducibility pertains to the consistency observed between different laboratories, often examined through collaborative studies aimed at standardizing methodologies. Typically, reproducibility is demonstrated through inter-laboratory trials (21).

c) Intermediate Precision

Intermediate precision refers to the variability observed within a single laboratory, stemming from random occurrences like different days, distinct analysts, diverse equipment, and so forth.

It is essential to include the reporting of standard deviation, relative standard deviation (coefficient of variation), and confidence intervals for each type of precision investigated (21).

iii. Specificity:

Specificity denotes the capacity to conclusively evaluate the analyte's presence, even when other anticipated substances like excipients, impurities, and components of the mobile phase are present.

This encompasses:

- **Identification**: Ensuring the confident identification of the ingredient.
- **Purity Tests**: Acknowledging the practical impossibility of complete impurity removal, specific limits are established for impurities. These impurities can manifest as residual solvent content, heavy metals, related substances, etc. Purity tests are employed to assess these substances.
- **Assay (Content or Potency)**: This entails quantitatively determining the Active Pharmaceutical Ingredient (API). The API's potency serves as an indicator of the drug's effectiveness (18).

iv. Linearity:

Linearity denotes the capacity to generate results that exhibit a direct correlation with the concentration of the analyte in the sample, covering the specified range – the region between the upper and lower analyte levels.

This is initially determined through a visual examination of a signal-versus-analyte concentration plot. If a linear relationship is evident, the test results are subsequently substantiated via appropriate statistical techniques. The data derived from the regression line yields mathematical estimations of linearity. The correlation coefficient, y-intercept, and slope of the regression line are included in the submission (22).

v. Range:

The range in an analytical procedure signifies the span from the lowest to the highest analyte levels, which encompasses these levels. It has been proven to be determinable with a satisfactory degree of precision, accuracy, and linearity when adhering to the procedure as outlined. This range is typically expressed in the identical units as the test results derived from the analytical process (21).

vi. Robustness:

Robustness in an analytical procedure refers to its ability to withstand minor, intentional variations in the procedural parameters outlined in the procedure documentation. It offers insight into its suitability for regular use. Robustness assessments are typically conducted during the development of the analytical procedure (21).

vii. Limit of detection

LOD is determined by the analysis of samples with known concentration of analyte and by establishing that minimum level at which the analyte can reliably detected, but not necessarily quantitated as precise value, under the stated experimental conditions. The detection limit is generally expressed in the concentration of analyte (ppm) in the sample.

A number of approaches are recommended by the ICH for determining the detection limit of sample depending on instrument used for analysis, nature of analyte and suitability of the method. The acceptable approaches are

• Visual evaluation.

• Signal-to-noise ratio.

• Standard deviation of the response.

• Standard deviation of the slope of linearity plot (20).

viii. Limit of quantitation

Limit of quantitation is the least concentration of drug in a sample which is estimated with appropriate precision and accuracy under the affirmed experimental conditions similar to LOD, ICH recommends the following four methods for estimation of LOQ. The acceptable approaches are

• Visual evaluation.

• Signal-to-noise ratio.

• Standard deviation of the response.

• Standard deviation of the slope of linearity plot (20).

ix. Ruggedness

Ruggedness is measure of reproducibility test results under the variation in conditions normally expected from laboratory to laboratory and from analyst to analyst. The Ruggedness of an analytical method is degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, such as; different laboratories, analysts, instruments, reagents, temperature, time etc. (22).

7.4 CLEANING VALIDATION

Cleaning validation is a critical methodology ensuring the removal of residues, including active pharmaceutical ingredients, cleaning aids, and microbial attributes from equipment and areas within the pharmaceutical industry. The goal is to maintain the quality of subsequent products and prevent contamination (23).

Cleaning validation is a documented process that establishes the effectiveness and consistency of equipment cleaning in pharmaceutical production. It plays a pivotal role in preventing cross-contamination and adhering to regulatory standards. The primary benefit lies in identifying and addressing potential issues that could jeopardize the safety, efficacy, or quality of future drug batches (24).

In the pharmaceutical context, cleaning is essential to remove dirt, marks, and unwanted matter from equipment and processing areas. Inadequate cleaning can lead to contamination, including residue from previous ingredients, cleaning agents, or dust particles. Good Manufacturing Practices (GMP) prioritize contamination prevention and control, making thorough cleaning and cleaning validation vital for ensuring product safety and quality (24).

Cleaning validation provides documented evidence that equipment and systems can consistently achieve predetermined and acceptable cleanliness levels, safeguarding product integrity and consumer safety (23).

Cleaning and cleaning validation within an Active Pharmaceutical Ingredient (API) area play a crucial role in preventing contamination of future batches with residues from previous batches. Ensuring the effectiveness of the cleaning process is of utmost importance, often requiring at least three successful applications of the cleaning procedure to validate its efficacy (23).

Objectives:

The need for cleaning validation stems from several key reasons:

1. **Customer Requirement**: Customers demand clean and safe products, and cleaning validation ensures product quality and safety.
2. **Regulatory Requirement**: Regulatory bodies mandate cleaning validation in the manufacturing of Active Pharmaceutical Ingredients (APIs) to maintain product integrity.
3. **Quality Assurance**: It serves as an internal control mechanism to uphold the quality of the manufacturing process.

The primary objective of cleaning validation is to consistently clean equipment, removing product, detergent, and microbial residues to an acceptable level, thereby preventing contamination and cross-contamination.

The primary objective of cleaning validation is to consistently clean equipment, removing product, detergent, and microbial residues to an acceptable level, thereby preventing contamination and cross-contamination

Efforts to prevent contamination in both API and pharmaceutical production areas share common objectives. Addressing challenging-to-reach surfaces is a critical aspect of equipment cleaning validation, especially in the API context, where cross-contamination can have significant consequences (25,26).

Cleaning Agents in Cleaning Validation:

Cleaning agents can be categorized into several broad categories, including:

1) **Water**: Water is a universal solvent and is ideal for cleaning when it effectively removes residues without excessive time or physical effort.
2) **Solvents**: Solvents are used when the manufacturing process already involves their use, such as mother liquors for cleaning Active Pharmaceutical Ingredients (APIs).
3) **Commodity Chemicals**: Chemicals like NaOH may be used for cleaning but can pose hazard and effluent issues. They are often used for inactivation processes but are less efficient in detergency and rinsing compared to formulated cleaning agents.
4) **Formulated Cleaning Agents**: This is the largest category of cleaners, including solvent-based and aqueous formulations. They typically contain alkalinity or acidity sources, sequestrants, surfactants, builders, chelants, and either a solvent or water. They are designed for industrial use, low foaming, easy rinsing, and are suitable for high turbulence cleaning (27).

Degree of Cleaning:

Level 1 Cleaning: Used between manufacturing batches of the same product within a campaign.

Level 2 Cleaning: Employed between manufacturing different batches of different products or at the end of a manufacturing operation, even if the same product is planned for the next operation.

These levels differ in terms of risk, acceptance limits, degree of cleaning, and verification methods. Additionally, CEFIC-APIC recommends three levels of cleaning, which can be adapted based on process requirements (27).

Sampling Techniques in Cleaning Validation:

In cleaning validation, various sampling techniques are employed to assess the cleanliness of equipment. Three main types of sampling techniques are commonly used, with the most preferred being direct surface sampling. The other methods include swab sampling and rinse sampling.

1. **Direct Surface Sampling:**

This technique involves determining the sampling material used and its impact on test data to ensure it doesn't interfere with the results.

Advantages:

- Effective for evaluating areas that are challenging to clean but reasonably accessible.
- Helps establish contamination or residue levels per a given surface area.
- Suitable for sampling residues that are dried out or insoluble through physical removal.

Disadvantages:

- It does not physically remove contaminants.
- Rinsing solvent may not reach inaccessible or occluded equipment parts.
- Organic solvents may be needed for water-insoluble materials (23).

2. **Swab Sampling in Cleaning Validation:**

Swab sampling is another technique used to assess surface cleanliness after equipment cleaning. When employing swab sampling, it's crucial to use swabs that are compatible with the active ingredients and won't interfere with assays or results. They should also not cause degradation of the compounds being tested. The solvent(s) used for swabbing should effectively dissolve the compound and avoid degradation.

Advantages:

- Dissolves and physically removes samples.
- Suitable for a wide variety of surfaces.
- Economical and readily available.
- Allows for sampling of specific areas.
- Applicable to active, microbial, and cleaning agent residues.

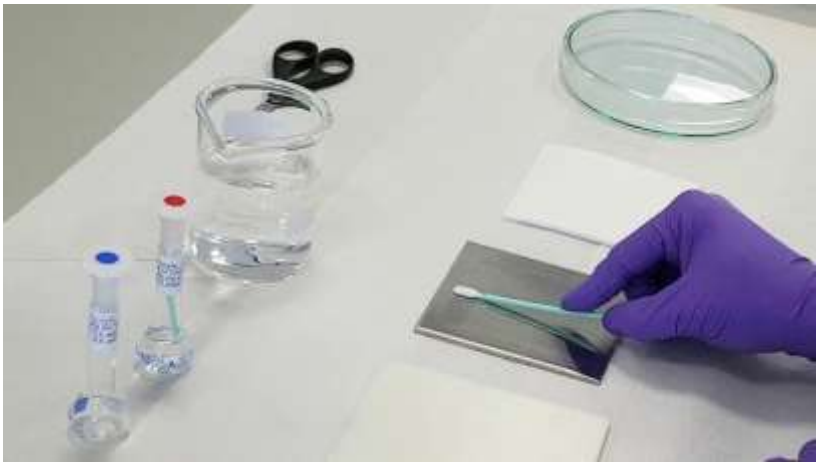

Fig. 4. Swab Sampling Technique

Limitations:

- An invasive technique that may introduce fibers.
- Results can depend on the sampling technique.
- Swab material and design may hinder recovery and method specificity.

- Evaluating complex, hard-to-reach areas can be challenging (27).

3. Rinse Sampling in Cleaning Validation:

Rinse sampling Is a widely accepted method for assessing cleanliness by sampling and testing residual active ingredients. This method is often convenient and requires control over the rinsing solvent, contact time, and mixing process. The choice of solvent should be based on the active ingredient's solubility, ideally mimicking a subsequent batch of the product or ensuring sufficient solubility.

Advantages:

- Ease of sampling.
- Evaluation of the entire product contact surface.
- Suitable for sealed or large-scale equipment and equipment that isn't easily disassembled.
- Convenience of exposing all equipment parts to the rinsing solvent.

Fig. 5. Rinse Sampling Technique

Limitations:

- Limited information about actual surface cleanliness in some cases.
- Potential reduction in test sensitivity.
- Residues may not be evenly distributed.
- Inability to pinpoint residue locations.
- Rinse volume critical for accurate interpretation.
- Difficulty defining and controlling sampled areas, often used for rinsing entire equipment pieces like vessels (27).

Advantages of Cleaning Validation:

- Quality and Safety Assurance: Ensures product quality and safety, meeting regulatory standards.
- Regulatory Compliance: Complies with government regulations, preventing legal issues.
- Product Integrity: Preserves the integrity of the product by removing contaminants.
- Microbial Integrity: Prevents microbial contamination, crucial for pharmaceutical products.
- Cross-Contamination Integrity: Minimizes the risk of cross-contamination between different products.

- Batch Integrity: Safeguards batch consistency and quality.
- Business Sense: Demonstrates good business sense by upholding product quality.
- Fewer Batch Failures: Reduces the likelihood of batch failures, saving time and resources.
- Utility Cost Reduction: Lowers utility costs associated with cleaning processes.
- Recall Prevention: Avoids costly market recalls.
- Equipment Maintenance: Simplifies equipment maintenance.
- Cost Avoidance: Prevents the need for significant capital expenditures.
- Reduction in Rejections: Reduces product rejections and reworks.
- Enhanced Operator Safety: Increases operator safety through validated instruments and equipment.
- Efficiency Improvement: Enhances efficiency in safety practices.

Disadvantages of Cleaning Validation:

- Time-Consuming: Cleaning validation can be a time-consuming process.
- Complex and Costly: The manufacturing process for validation can be complex and costly.

8. VALIDATION MASTER PLAN (VMP):

Master planning employs project management tools to aid in validation project development and execution, covering aspects like project definition, coordination, administration, scheduling, and budgeting. While some in the industry advocate for it to be a cGMP (Current Good Manufacturing Practice) requirement for healthcare capital projects, this perspective might be overly stringent.

A Validation Master Plan (VMP) serves as a comprehensive document outlining a company's philosophy, intentions, and methods to ensure performance adequacy. Management's agreement is essential.

Validation requires meticulous preparation and adherence to approved standard operating procedures. Documentation is key, preferably with numerical results for observations.

The VMP provides an overview of the entire validation operation, including organizational structure, content, and scheduling. It covers all validation activities related to critical technical operations, including prospective, concurrent, retrospective validations, and re-validation.

The Validation Master Plan should be concise and clear, avoiding redundancy by referring to existing documentation such as policy documents, SOPs, and validation protocols and reports (28).

The format and content should comprise:

- **introduction:** Covering validation policy, scope, location, and schedule.
- **Organizational structure:** Defining personnel responsibilities, along with plant/process/product descriptions. Provide rationale for inclusions/exclusions and specify the extent of validation.
- **Specific process considerations:** Highlight critical aspects and areas needing special attention.
- **Matrix-format list:** Summarize products/processes/systems to be validated and outline the validation approach.
- **Re-validation:** Include ongoing and future planning, along with current status.
- Key acceptance criteria.
- Documentation format.
- Reference to required SOPs (Standard Operating Procedures).
- Time plans for each validation project and sub-project (29).

The Validation Master Plan (VMP) serves several crucial functions:

1. **Management Education:** Often, upper management might not fully grasp the importance of validations and qualifications, as their primary focus tends to be on the company's finances and business processes. The VMP serves as an educational tool, enlightening management about the potential impact of manufacturing processes on product quality.

2. **Project Monitoring and Management:** Within the VMP, you'll find validation schedules and timelines essential for effectively monitoring and managing the project's progress and completion.
3. **Auditing the Validation Program:** The VMP comprehensively outlines all activities related to process validation and manufacturing equipment and utilities qualification. It provides insights into the facility's approach and strategy for validations, along with a timeline that aligns with criticality.
4. **Planning Purposes:** The VMP plays a pivotal role in identifying expected resource requirements and offers crucial input for scheduling project timelines.
5. **Documenting the Scope of Validation Effort:** This encompasses a range of elements, including impacted products, processes, procedures, facilities, equipment, and utilities (29).

9. Conclusions:

One of the key aspects of cGMP is validation. Validation confirms that the product meets the quality, safety, efficacy, purity, and effectiveness standards of cGMP. Validation is often applied in the stages of drug development, manufacturing, and final product specification. Validation helps to reduce the cost of quality and achieve the highest level of product quality. When a product is made following cGMP guidelines, the consistency and integrity of each batch are guaranteed by pharmaceutical validation. Pharmaceutical validation is considered as the most important and widely accepted requirement for cGMP in the current literature review. Pharmaceutical companies should have a general validation policy that explains how validation will be performed. This policy should include the validation of the production process, cleaning methods, analytical techniques, and in-process control test methods. In summary, we can conclude that the purpose of validation is to show that processes such as production, cleaning, and analytical testing are essential for the research and manufacture of pharmaceuticals.

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Appendix A: List of Abbreviations

cGMP	Current Good Manufacturing Practices
FDA	Food and Drug Administration
ICH	International Council for Harmonization
WHO	World Health Organization
USP	United States Pharmacopeia
SOP	Standard Operating Procedure
IQ	Installation Qualification
DQ	Design Qualification
PQ	Performance Qualification
OQ	Operational Qualification
RQ	Re – Qualification
CQ	Component Qualification
URS	User Requirements Specification
QS	Quality System
QMS	Quality Management System
LOD	Limit of Detection
LOQ	Limit of Qualification
RSD	Relative Standard Deviations
API	Active Pharmaceutical Ingredients
CEFIC	European Chemical Industry Council
APIC	Active Pharmaceutical Ingredients Committee
VMP	Validation Master Plan
AIQ	Analytical Instrument Qualification
GLP	Good Laboratory Practice
HPLC	High Performance Liquid Chromatography