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Pharmaceutical Validation: An Overview Of Concepts And Guidelines

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Abstract:
Validation has a very significant role in pharmaceutical sector. It ensures safe, effective and consistent processes and products. Validation helps to alleviate the risks linked with pharmaceutical processes and products which result in production of high-quality products that are manufactured using suitable processes and also meet the required specifications. Validation studies are considered to be a vital aspect of GMP. The studies should to be performed according to the predefined protocols and guidelines, which include validation of process, equipment, testing and cleaning. This review provides an understanding on the concepts of validation and the guidelines to be followed for it in the pharmaceutical industry.

Keywords: Validation, GMP, Pharmaceutical industry, Guidelines, ICH, WHO, Solid dosage form

Introduction

Major All the pharmaceutical manufacturing companies have to comply with the requirements of cGMP (current Good Manufacturing Practices). To validate and confirm that the quality standards are being met, there has to be an organized and efficient approach to collect data and study it to approve the equipment, process, procedure and the materials involved. This can be done by an approach called "Validation" which ensures that every process and equipment operates as per its intended use and the materials provide expected results.[5] Validation according to **World Health Organization (WHO)** is defined as the documented act of demonstrating that a procedure, process, or activity carried out in testing and then production maintains the desired level of compliance at all stages.[1] The U.S Food and Drug Administration (FDA) defines validation as the collection and evaluation of data which establishes scientific evidence that a process is capable of consistently delivering quality product throughout the product lifecycle.[2]

Need for validation:

Pharmaceutical industry use variety of costly materials, advanced equipment, multifaceted facilities, and highly skilled personnel. These resources need to be efficiently utilized for ensuring prolonged success of the pharmaceutical industry.
The expenditure of product rejects, failures, recalls and reworks are the major areas of the total production cost.
Comprehensive study and manufacturing process control. Validation is necessary to minimize failure and to improve productivity.
Following reasons for which the pharmaceutical industry should be concerned for validation are:
Quality assurance
Reduction in costs
Government regulation[3]

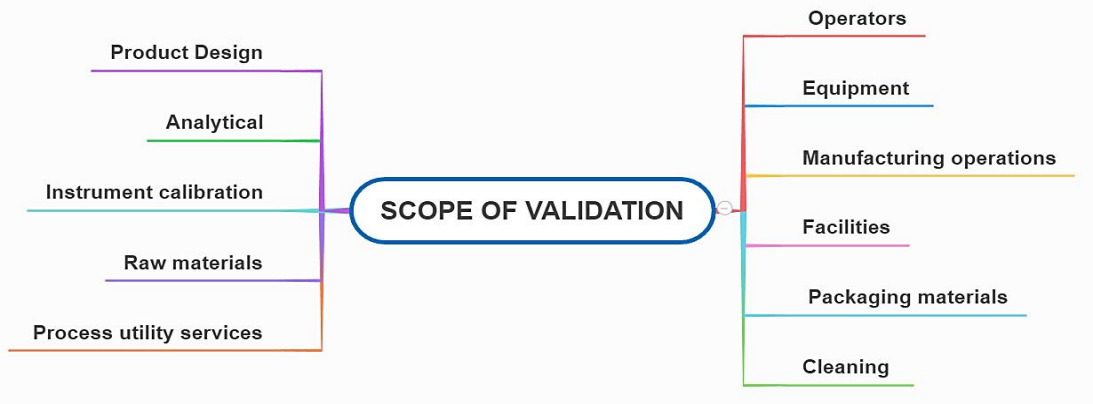
In summary, pharmaceutical validation is a critical process that makes sure that the pharmaceutical products are safe, effective, and meet the required standards for maintaining good quality. It is therefore, known as a key component of the pharmaceutical industry. It consists of a series of procedures and tests to ensure that the pharmaceutical product is manufactured in a consistent and reproducible manner.[4]

Scope of validation:

Finding the validation scope becomes a very challenging assignment because pharmaceutical validation is an extensive area of work that covers almost every component of the activities involved in pharmaceutical

manufacturing. But a careful review of the pharmaceutical processes will at the minimum will highlight the following areas involved in validation:

Fig.1: Scope of Validation



Pharmaceutical validation has to be carried out for any new equipment, utilities, premises, procedures, systems and processes. Also, when a major change occurs in these, validation should be performed then too. Validation differs from in-process testing as the latter only provides help in monitoring process runs as predicted, whereas the purpose of validation is to demonstrate the suitability of a given process is for routine and continuous use because it yields a product of desired quality consistently. [5, 6]

Merits of validation:

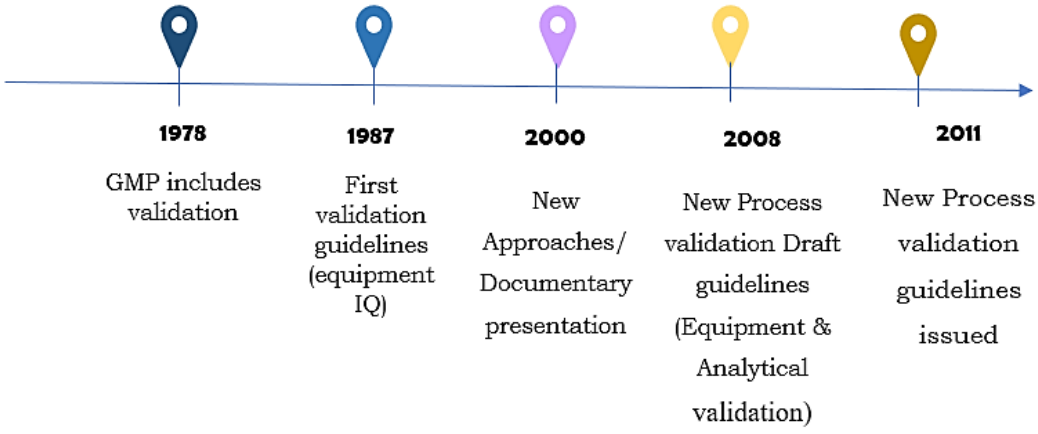
Processes that are consistently in control need less support for the process and also have shorter downtime.
Less batch failures and possibly increased productive operations.
Additionally, prompt and adequate validation studies demonstrate a dedication towards the quality of the product, that could speed up the marketing permission process and pre-approval inspection.
Validation is a smart business move.
Decrease in reworks and rejections
Reduced testing time and final products.
Faster and more precise process deviation analysis.[5]

History of validation:

In 1979, Ted Byers and Bud Loftus, two Food and Drug Administration (FDA) officials in the United States, introduced the concept of pharmaceutical validation. Due to multiple issues with the sterility of the large volume parenteral, validation became necessary. Failures in the early 1970s terminal sterilisation procedure are the source of validation in the pharmaceutical sector. One event, known as the "1971 Devonport incident," involved a batch of IV bottles containing 5% dextrose that were improperly sterilised and ended up on the market for sale. Following that, patients at the hospital in Devonport, England, were administered with these. Unfortunately, five patients lost their lives as a result of receiving treatment with the contaminated solution. Henceforth, everyone in the industry was made aware of how crucial it is to ensure the safety of drug manufacturing processes after this tragedy.

The first Orange Guide in the UK was issued in 1971 under the title "Guide to Good Pharmaceutical Manufacturing Practice." The term "validation" was used for the first time in the 1983 edition. Presently, EU GMP is covered by the UK Orange Guide but not British GMP. The standardisation of legislation has been aided by such multinational initiatives. In the US, the GMPs for pharmaceuticals (21 CFR Parts 210 and 211) and medical devices (21 CFR Part 820) were initially released in 1978. The term "validation" was later included to the Orange Guide in 1983. After the FDA realised in the 1980s that processes were not very effective, regulators looked at ways to force companies to validate their processes more successfully and economically. As a result, several formative guidance publications were published, including. As a result, a number of formative guidelines were published, including the 1983 guide on the inspection of computerised systems used in drug processing.[7]

Fig.1: Important years for pharmaceutical validation guidelines



Responsible authorities:

The working portion of validation is set up to define, examine, move forward, arrange, coordinate, and ultimately approve, taking into account all produced documentation. The following employees would typically be part of the working staff: manager in charge of quality control, production manager, executive in quality control, head of engineering, production executive validation executive, validation manager and head of quality assurance. [8]

Table 1: Responsibilities of validation authorities

DESIGNATION	FUNCTIONS
Production Manager	In charge of batch manufacturing, procedure and report review
QC Manager	In charge of sample collection
QC Executive	In charge of analysis samples submitted to QC
Maintenance Manager	Supplying engineering and utility support
Production Executive	In charge of creating the protocol and producing the validation batches
QA Manager	In charge of authorising the procedure and preparing the summary report

TYPES OF VALIDATION:

Given the numerous risks involved in the production of pharmaceutical products, validation is one of the most crucial tasks in the pharmaceutical sector. The various types of validation used in the pharmaceutical industry are listed below:

ANALYTICAL METHOD VALIDATION

The method used to carry out the analysis is referred to as the 'analytical procedure' or 'analytical method'. It should describe the steps in detail which are necessary to perform different analytical tests. This may include: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

Analytical method validation in the pharmaceutical industry verifies and offers proof of tthat the procedure chosen for a particular test is fit for the intended purpose and provides high quality, reliable and consistent results. So much so, the same method can be used in any other laboratory across the world and should be able to replicate the results, given they are performed under identical conditions and parameters.

The four most prevalent categories of analytical processes are the focus of the validation of analytical procedures:
Tests for identification.
Measuring the content of contaminants quantitatively.
Limit tests for impurity control.
Measuring the active moiety quantitatively in drug substance or drug product samples, or in other specific drug product component(s)

Factors considered during the analytical process validation process include-
Accuracy: The degree of agreement between the value found and the value acknowledged as a conventional true value or an accepted reference value indicates how accurate an analytical technique is. Stated differently, accuracy refers to how closely test findings match the actual or theoretical value.
Precision: An analytical procedure's precision can be defined as the degree of agreement (or scatter) between a set of measurements made from multiple samplings of the same homogenous material under specified conditions.
Specificity: The capacity of a method to test only the analyte of interest without interference from other components of the sample that may be present, such as matrix components, degradants, contaminants, etc., is known as specificity.
Linearity: The capacity of an analytical technique to produce test findings that are directly proportional to the concentration (amount) of analyte in the sample, within a specified range, is known as linearity.
Detection Limit: A single analytical procedure's detection limit is the lowest concentration of analyte in a sample that can be identified but may not always be quantified as a precise value.
Quantitation Limit: The quantitation limit of a certain analytical process refers to the smallest quantity of analyte in a sample that may be accurately and precisely determined using quantitative means. It is employed in the identification of degradation products and/or contaminants.
Reproducibility: The precision between laboratories is expressed by reproducibility (collaborative studies, usually used to standardisation of methodology). In other words, comparable results should be obtained by several analysts in various laboratories.
Repeatability: Repeatability is the ability to convey precision over a brief period of time under the same operational conditions. Another name for repeatability is intra-assay precision.
Range: The range of an analytical technique is the range of concentrations (amounts) of the analyte in the sample for which the analytical procedure has been shown to have the appropriate levels of linearity, accuracy, and precision.
Robustness: An analytical procedure's robustness indicates how reliable it is during typical use and is measured by its ability to withstand slight but intentional changes in method parameters.[9,10]

Table 2: Typical analytical performance characteristics (ICH)

ANALYTICAL PERFORMANCE CHARACTERISTIC	IDENTIFICATION	TESTING FOR IMPURITIES		ASSAY: CONTENT POTENCY
		QUANTITATION	LIMIT TEST	
Accuracy	–	+	–	+
Precision				
○ Repeatability	–	+	–	+
○ Intermediate precision	–	+	–	+
Specificity	–	+	+	–
Detection limit	–	+	+	+
Quantitation limit	–	+	–	+
Linearity	–	+	–	+
Range	–	+	–	+

+ *indicates this characteristic needs to be considered; – indicates this characteristic need not be considered*

CLEANING VALIDATION

In the pharmaceutical business, cleaning validation is a procedure that guarantees a system or specific equipment is cleaned to the highest possible standard. By doing this, pollutants such as microorganisms, residues, and airborne materials are ensured to be absent.

The goal of cleaning validation is to avoid cross-contamination and contamination, which can have a significant impact on test or product integrity or results in the laboratory. [10]

Fig.1: Types of Cleaning Validation

Swab sampling and rinse sampling are the two primary sampling methods used in the direct approach of sampling the equipment's surface:

Swab sampling: To evaluate the cleanliness of the product's surface, contact surfaces are swabbed following equipment cleaning. Swabs should not tamper with the assays or results; instead, they should be compatible with the active substances. The solvent or solvents used to swab the sample should be able to dissolve the substance well and should not degrade it in any way.

Rinse sampling: A widely recognised technique to assess cleanliness involves sampling and evaluating rinse samples for residual active component. In many situations, this is a rather convenient procedure, but it does require some control over the rinse solvent, the contact time, and the mixing. The active ingredient's solubility should determine the solvent to be utilised; it should either match a later batch of the product or at the very least offer sufficient solubility.[11]

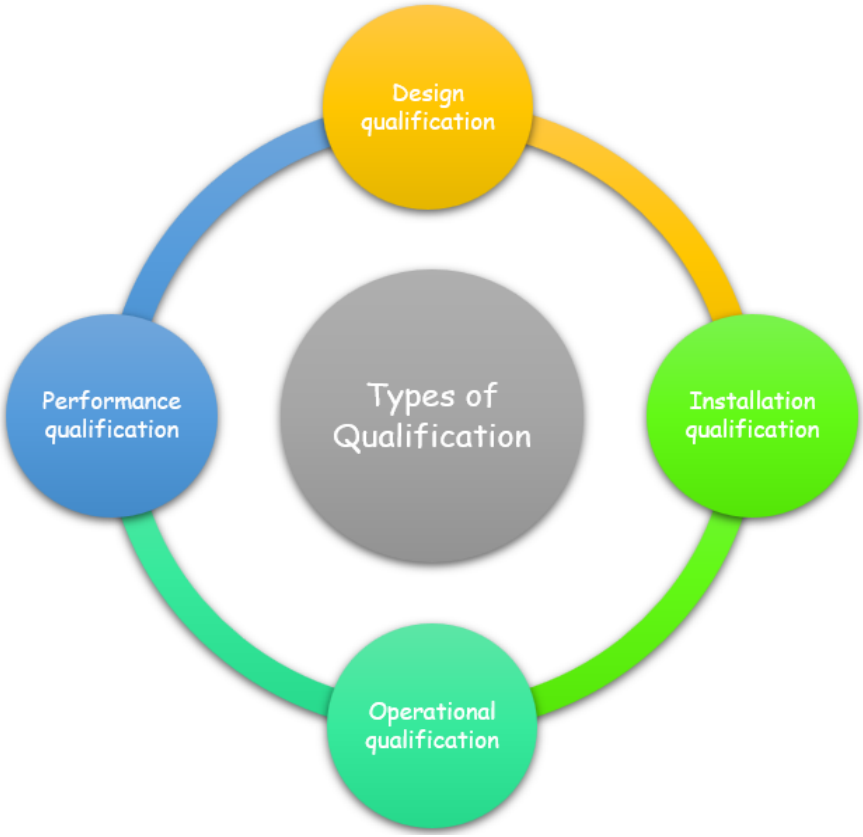
Fig.2: Acceptance criteria for Cleaning Validation

EVALUATION CRITERIA	ACCEPTANCE CRITERIA
Physical determination	The apparatus must have a tidy appearance. That is, after cleaning there should be no trace of residue on the equipment.
Chemical determination	a) NMT 0.1% of the typical therapeutic dose of any substance that will be included in the next product's maximum daily dose. b) NMT 10 ppm of any product (the starting material's heavy metal content) to be included in the subsequent product. c) The limit should be lower than the limit of detection by the most advanced analytical techniques for specific allergic ingredients, penicillin, cephalosporins, strong steroids, and cytotoxins.
Microbial contamination	Total number of aerobics a) NMT 10 cfu/100 ml using the rinse approach. b) NMT 5 cfu/25 cm2 by swab technique.

EQUIPMENT VALIDATION

Equipment validation checks that all equipment used within the production process operate as per their intended uses. Equipment validation makes sure that the equipment is installed and operates correctly. It should perform and also produce for its intended purpose correctly. For example, Computer System Validation (CSV)[12]

Fig.3: Types of Qualification



Phases/ Stages involved in validating equipment: The process of validating equipment is generally separated into three stages:
Phase – 1: PRE-VALIDATION PHASE
Phase – 2: PROCESS VALIDATION PHASE
Phase – 3: VALIDATION MAINTENANCE PHASE

Pre-Validation (Qualification) Phase:
Design Qualification (DQ): It is a methodical approach of verifying the production facilities' and equipment's designs. Making sure that every requirement for the systems is specified explicitly from the beginning is the primary goal of DQ. It outlines the functional and operational specifications of an instrument with all necessary requirements in accordance with the cGMP guidelines and the user requirement specification (URS). When the documented qualification can confirm that the specified design will adhere to:
Functional specification
Tender specification
Purchase specification
Vendor qualification
User requirement specification (URS): It is the client's list of specifications and expectations for the equipment.

Typical demands from clients consist of:
Dimensions of the apparatus and the area it takes up.
The equipment's robustness and efficiency.
Working speed of the equipment.
Equipment should operate with minimal to no air pollution and noise.
The availability of spare parts
Offering services at a reasonable price.
Overall excellent build quality.

Installation Qualifications (IQ): An IQ verifies that the equipment has been delivered and installed in accordance with the agreement and target in a precise format or design, undamaged, with all necessary parts, spares, gauges, and other components. IQ's goal is to guarantee that every piece of equipment is installed accurately and in accordance with the URS design. The working ambient conditions of the work site are recorded and examined to determine whether or not they are appropriate for the operation of the instrument, in accordance with the manufacturer's installation instructions. The installation paperwork ought to contain the following:

Manufacturer and supplier details
Equipment name, colour, model, and serial number
Installation and calibration dates.[13]

Process Qualification Phase:
Operational Qualification: Operational Qualification: This process verifies that, under the specified environmental circumstances, installed equipment and instruments will operate exactly as intended and in accordance with their operating specifications. Additionally, it guarantees that the apparatus operates in accordance with the predetermined performance standards. The operational qualification's goal is to confirm that every dynamic circumstance closely adheres to the URS design. The following should be included in the documentation for operational validation:
Completed and authorised operations (functions testing)
Certified calibrations
Results of system stability tests
Applications of SOPs.

Performance Qualification: This process verifies that the machinery operates consistently in accordance with the specified specifications and is appropriate for daily or routine use. Documentation exists for the equipment's performance verification. It confirms whether every element of the equipment's functionality, performance, and facility satisfies the predetermined acceptance criteria derived from the manufacturer's specifications and the user requirement specification (URS). When equipment is utilised or functioning, performance qualification is carried out under particular circumstances that are comparable to normal sample analysis. It is done every day (or at least once every week). The documentation includes:
Report on performance qualification.
Reports on process stability testing (long-term productivity
Acceptance of the product record (customers reviews)
Actual documentation of the product and process characteristics.
Documentation of test results that are done routinely.

Re-validation: Re-validation is carried out when a system or piece of functioning equipment has undergone minor modifications for any reason. Maintaining the equipment's and the system's overall validation status greatly benefits from revalidation. In accordance with the regulations established by the government, the revalidation procedure is also utilised for the regular verification of the present validation. Re-validation is separated out further into:

Regular/planned re-validation
Revalidation following adjustments or changes [13]

PROCESS VALIDATION
Process validation is defined by the FDA as the gathering and assessment of information that proves, via scientific evidence, that a particular process can reliably produce high-quality products, from the process design phase through commercial production.
Activities aimed at validating pharmaceutical processes confirm that manufacturing processes are as protected against interfering deviations as possible. If these variations are not thoroughly examined, they may impair the effectiveness and quality of the finished pharmaceutical product, disrupting the supply chain and eventually having a severe impact on public health. As a result, it's critical to follow process validation methods in order to guarantee the efficacy and safety of pharmaceutical goods as well as high-quality patient care.

Process validation verifies the integrity and efficacy of a product's design and manufacturing processes. Four different forms of process validation do this:

Prospective Validation
Another name for prospective validation is "premarket validation." It is done in the course of developing a product. Finding the risk analysis for the manufacturing process is made easier by the outcomes of the prospective validation. Analysis of crucial aspects in the product manufacturing process, such as mixing time, temperature, and relative humidity, is carried out on several stages.
When new products are brought into the manufacturing facility or when there is a significant change or alteration in the manufacturing process and its impact (e.g., leak test failing due to blister sealing issues), prospective validation of the manufacturing process is conducted.
The following criteria need to be met for prospective validation:
Three batches of prospective validation should have identical parameters.
All three batches should have identical process parameters.
Out of the three, the first batch is only shipped once the third batch has finished being manufactured, tested, and the results have been reviewed. [1,14]

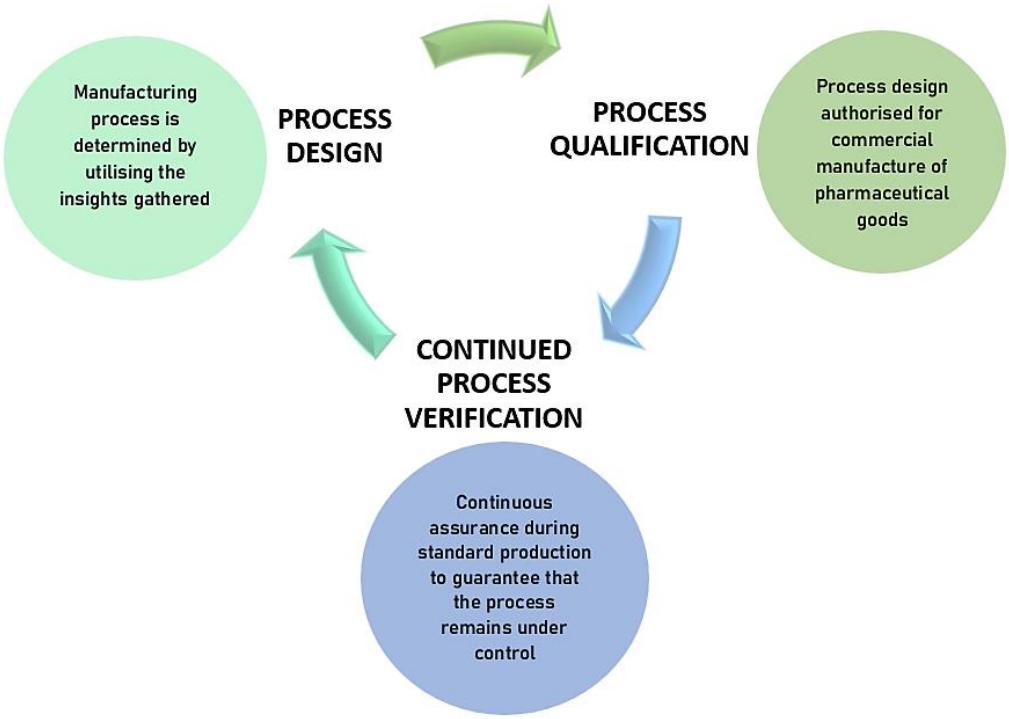
Concurrent Validation
Concurrent validation entails closely monitoring the product both throughout manufacture and at the critical points that have been predetermined. Based on data produced during the actual process verification, concurrent validation is utilised to develop written proof that procedures and the facility function as intended.
This stage will require numerous in-process tests, including measurements of the product's weight, density, clarity, viscosity, and pH.
Concurrent validation is performed in the following situations:
A new product has completed prospective validation at the manufacturing facility
No changes have been made to the manufacturing process, or if they have, the changes have not had a substantial impact.
The raw material supplier for the ongoing production process has changed. [14,15]

Retrospective Validation
Retrospective validation is closely examining a system or piece of equipment that has been in use for a while to ensure that it continues to adhere to the rules and specifications that were originally established.
For facilities, procedures, and process controls that are being used in operations but have not completed a formal validation process, retrospective validation is carried out. Historical data that has all the necessary documentation proof to demonstrate that the process is carrying out its intended functions can be used to validate these. This makes this kind of validation appropriate only for processes that are well-established.
These days, this method is rarely employed as it is quite unlikely that any product that is already in use will not undergo prospective validation.[1,15]

Revalidation
The final step in the process validation exercise is revalidation. It offers the chance to check if a system is still functioning even after a sizable change in circumstances.
Revalidation is required to ensure that modifications made to manufacturing process environments, whether deliberate or accidental, do not negatively impact the process or the quality of the final product.
Revalidation processes can be carried out for a variety of reasons, some of which are as follows:
Product transfers between plants
Modifications made to the product, the plant, the manufacturing process, the cleaning process, or any other change that may have an impact on the product's quality.
Regular verification of the validation results is carried out.
Significant variation in the number of batches produced.
Batches that are successive and don't match the requirements for the product and procedure.
The size of the modifications and their impact on the finished product determine how far revalidation procedures need to go.[1,13,14]

A series of actions in the product and process lifecycle are involved in process validation as shown in Fig.4:

Fig.4: Process Validation Lifecycle



VALIDATION MASTER PLAN:

The management has agreed upon a document called a Validation Master Plan that outlines the company's whole philosophy, aims, and operational strategies for performance competency verification.
A summary of the scheduled validation activities can be found in the Validation Master Plan (VMP). It enumerates the tasks and significant papers that must be completed, along with the staff members' duties. Although it can also be used in unlicensed units, a VMP is necessary for all validation actions carried out in licenced facilities.

A VMP ought to include:
An overview of the entire validation process
The organization's structure, content, and planning
The primary components of the inventory list containing the things that require validation and the timeline for planning.
It should include all types of validations, including retrospective, concurrent, and prospective validations as well as, in certain situations, re-validation.
Since the VMP is a summary, it should be concise, straightforward, and to the point.
It should not repeat material that is already documented elsewhere; instead, it should make reference to the policy documents, SOPs, validation methods, and reports that are already in existence.[16]

VALIDATION PROTOCOL:

A written plan of action outlining the procedures to be followed for process validation is called a validation protocol. It identifies who is in charge of carrying out certain duties and defines the parameters, sampling plans, testing procedures and requirements, product attributes, and equipment that will be utilised.

VALIDATION REPORT:

After the validation process is completed, a final report needs to be organised. The protocols and outcomes are fully compiled in this paper, together with references. It should draw conclusions about the process's validation state and offer any essential advice for using the procedure on a regular basis. After a final written report has been evaluated and determined to be acceptable, the validation team and relevant management should authorise and approve it. [15]

ICH AND WHO GUIDELINES: CALIBRATION AND QUALIFICATION OF EQUIPMENT:

Calibration- This process compares findings obtained over an appropriate range of measurements with those obtained using a reference or traceable standard in order to show that a certain device or equipment yields adequate results within the designated limitations.

Qualification- Qualification is the process of verifying and recording that a piece of equipment or an accessory system is installed correctly, functions as intended, and yields the desired outcomes. Although qualification procedures by themselves do not equal validation, they are a necessary component of it.

ICH GUIDELINES FOR CALIBRATION OF EQUIPMENT

The equipment should be calibrated using standards traceable to certified standards, if available, and covering the whole working range of the device, according to the ICH Q7 Chapter 5 guideline;

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

ICH GUIDELINES FOR QUALIFICATION OF EQUIPMENT

ICH Q7 Chapter 12.30 guideline, describes the equipment validation or qualification;

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.

Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.[18]

WHO GUIDELINES FOR CALIBRATION OF EQUIPMENT

The calibration and verification of equipment is described in WHO Annex 3, 15.0 guideline;

15.1 Calibration and verification of equipment, instruments and other devices, as applicable, should be initiated during installation qualification, to ensure that the system operates according to the described specifications and because the calibration status could have been affected during transport and installation.

15.2 Thereafter, it should be performed at regular intervals in accordance with a calibration programme and SOPs.

15.3 Personnel who carry out calibration and preventive maintenance should have appropriate qualification and training.

15.4 A calibration programme should be available and should provide information such as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.

15.5 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration. A valid certificate of calibration should be maintained, which is dated and includes reference to and traceability to, for example, standards used, acceptance limits, uncertainty where applicable, range, calibration due date.

15.6 Calibrated equipment, instruments and other devices should be labelled, coded or otherwise identified, to indicate the status of calibration and the date on which recalibration is due.

15.7 When the equipment, instruments and other devices have not been used for a certain period of time, their function and calibration status should be verified and shown to be satisfactory before use.

15.8 Equipment, instruments and other devices should be calibrated before or on the due date for calibration, to ensure that they are used in a calibrated state.
15.9 Where instruments and devices are identified as critical or non-critical, or impacting and non-impacting for the purpose of calibration, documented evidence of the decision-making process should be available. This should include impact and/or risk assessment.

WHO GUIDELINES FOR QUALIFICATION OF EQUIPMENT
WHO Annex 3, 10.0 guideline describes the qualification of equipment;
10.1 There are different approaches in qualification. The manufacturer should select an appropriate approach for the conduct thereof.
10.2 All relevant SOPs for operation, maintenance and calibration should be prepared during qualification.
10.3 Training should be provided to operators, and training records should be maintained.
10.4 Normally, qualification should be completed before process validation is performed.
10.5 The process of qualification should be a logical, systematic process and follow a logical flow from the premises, followed by utilities, equipment to procedures and processes.
10.6 Stages of qualification should normally start with the preparation of user requirement specifications (URS). Depending on the function and operation of the utility, equipment or system, this is followed by, as appropriate, different stages in qualification such as design qualification (DQ), a factory acceptance test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).
10.7 One stage of qualification should be successfully completed before the next stage is initiated. For example, OQ normally follows IQ but, depending on the complexity of the equipment, it may be performed as a combined installation/operation qualification (IOQ). Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.
10.8 In some cases, only IQ and OQ may be required, as the correct operation of the equipment, utility or system could be considered to be a sufficient indicator of its performance.
10.9 Major equipment and critical utilities and systems, however, may require URS, DQ, IQ, OQ and PQ.
10.10 Computerized systems, including equipment with software component(s), should be appropriately qualified and validated. [16]

GUIDELINES FOR PROCESS VALIDATION OF TABLETS:
A solid dosage form must be developed and validated taking into account a number of criteria. The following checklist/guideline is presented in Table 7 for tablets and dry-filled capsules for inclusion in a comprehensive validation programme, in order to give a general overview of these validation criteria. Nevertheless, some of these unit operations—such as uncoated and direct compression tablets—won't work with every solid dosage form.

Table 3: Check list of Validation and Control Documentation

S. No.	*SELECTION OF cGMP*	*VALIDATION AND CONTROL DOCUMENTATION*
1.	Introduction	Determining the roles of PV and QA
2.	Personnel and Organisation	Establishment, installation, and qualification of facilities
3.	Buildings and facilities	Qualification for plant and facility installation; upkeep and sanitation; control of microbes and pests
4.	Equipment	Cleaning techniques for qualification and installation.
5.	Air and water quality	Steam systems, air, heat and hoover handling; water treatment.
6.	Raw material, in-process material, and product controls	Arriving parts Producing non-sterile goods
7.	Production and process controls	Computers and instrumentation in process control systems
8.	Packing and labelling controls	Sterile packaging, filling, closure, Depyrogenation, and labelling regulations.
9.	Holding and distribution	Facilities
10.	Laboratory controls	Analytical methods
11.	Records and reports	Computer systems
12.	Returned and salvaged pharmaceutical products	Processing in batches

VALIDATION STEPS AND ACCEPTANCE CRITERIA:
In the industry, tablets through the wet granulation process are validated using the processes outlined in Table 4:

Table 4: Validation steps and acceptance criteria for wet granulation

S. No.	STEPS	CONTROLLABLE VARIABLES	CRITICAL PARAMETERS	ACCEPTANCE CRITERIA
1.	Dry mixing	Time	Mixing time	Mixing time: ____min
		Impeller speed	Mixing speed	Impeller speed: ____slow/medium/high) ±5RPM. Content uniformity: 90%-110% RSD: ±5%
2.	Adding binders	Time	Mode and time of addition	Depending up on the formulation.
		Temperature, solvent		
3.	Drying	Inlet/outlet temperature	Initial drying: ____°C Drying time: ____ min.	Final drying: ____ °C±5°C Loss on drying: ____ % below 3% or depending on formulation
		Drying time		
4.	Lubrication	Time	Mixing time	Mixing time: ____min.
		Blender/granulator speed	Mixing speed	Speed slow: ____ rpm. Content uniformity: Physical parameters
5.	Compression	Pressure and turret speed	Machine speed and compression pressure	Average weight: ___mg±5%,7.5%,10%. Uniformity of weight mg: Thickness: ____mm Hardness: ____KN or Kg/cm2 Disintegration time: NMT ____min. Friability: NMT ____%w/w Assay: As per the label claim Dissolution: ____%
6.	Coating	Pan speed and spray rate	Pan speed Inlet and outlet temperature Spray rate	Average weight: ____mg±5% Weight of 20 tablets: ____mg Thickness: ____mm Disintegration time: NMT ____min. Assay: As per the label claim Dissolution: ____%

EVALUATION OF INDUSTRIAL PROCESS AND TABLET SELECTION:
During the tablet manufacturing process, the following unit operations must be identified-

Mixing or Blending:
This unit operation ensures a consistent blend so that the mixture of active pharmaceutical ingredients and excipients does not separate after blending. This procedure is therefore carefully examined and verified.
Factors to take into account include:

- Mixing or blending method
- Drug uniformity
- Excipient uniformity
- Speed of mixing or blending
- Duration of mixing or blending
- Equipment capacity/load

2. Wet Granulation:

A variety of processes, such as fluid bed (e.g., Fluid Air), high shear (e.g., GEI-Collette), and low shear (e.g., Hobart), can be employed in wet granulation. Every method yields granules with various physical characteristics, although numerous processing factors will need to be watched.
The following wet granulation parameters should be taken into account for development and validation:

- Binder addition
- Amount of binder solution/granulating solvent
- Binder concentration
- Mixing time
- Granulation end point
- Binder solution/granulating solvent addition

3. Wet Milling:
It may be necessary to mill the granules that are produced following the wet granulation process in order to break up lumps and accelerate granulation drying. Wide-ranging aggregates in wet granules can lead to ineffective drying, which might result in prolonged drying times or partially dried big granules or lumps.
Considerations include:

- Size and capacity of equipment
- Mill speed
- Screen size
- Feed rate

Drying:
Different drying methods exist, including tray, fluid bed, and microwave drying. Any technique used in the formulation must have a valid reason.
The kind of technique may vary depending on elements including equipment availability, medication qualities, and formulation properties. During this phase, changing the dryer methods could have an impact on the stability, disintegration, hardness, and dissolving of the tablets.
It is necessary to ascertain the dried granulation's ideal moisture content. Due to the possibility of tablet picking or sticking to tablet punch surfaces caused by a high moisture content. Hydrolysis may also result in low chemical stability.
An overly dry granulation may have low hardness and friability. Near infrared (NIR) spectroscopy or traditional loss-on-drying methods can be used to analyse the moisture content.
Factors to be considered are-

- Inlet and outlet temperature
- Moisture content
- Equipment working/capacity
- Airflow

Milling:
The grinding process aids in the dried granulation's particle size reduction. Properties including flow property, compressibility index, disintegration, and dissolution are impacted by the distribution of particle sizes.
It is necessary to ascertain the ideal particle size or size distribution for the formulation.
Considerations for milling include:

- Mill type
- Screen size
- Mill speed
- Feed rate

Lubrication:
During tablet ejection, lubricants are required to reduce friction between the tablet's walls and the die cavity.
Considerations include:

- Quantity of lubrication supplied
- Type of lubricant used
- Compatibility with other components
- Mixing time.

Tablet Compression:
One of the most important steps in the making of a tablet dosage form is compression.
The mixture being compressed needs to have sufficient flow and compression properties. The mixture needs to flow easily from the hopper to the feed frame and, ultimately, into the dies. The mix may segregate in the hopper or feed frame due to inadequate flow, which can cause "rat-holing" in the hopper. This may result in issues with content uniformity and tablet weight.
Things to think about while compressing are:

- Tooling
- Speed of compression
- Compression and ejection forces

The in-process tests that need to be evaluated at the compression step are as follows:

- Appearance
- Hardness
- Tablet weight
- Weight uniformity
- Friability
- Disintegration

Tablet Coating:
There are several ways to coat tablets (e.g., sugar, film, or compression). In recent times, film coating has become the most often employed approach.
When coating tablets, the following are crucial factors to keep in mind:

- Tablet property
- Type of equipment
- Inet/outlet temperature and airflow
- Spray gun
- Tablet flow
- Residual solvent level
- Coating solution
- Coating weight/load
- Pan speed

In-process tests:

- Moisture content of "dried granulation"
- Blend uniformity
- Granulation particle size distribution
- Tablet hardness
- Tablet thickness
- Impurity content
- Disintegration

10. Finished product tests:

- Appearance
- Assay
- Content uniformity
- Tablet hardness
- Tablet friability
- Impurity content
- Dissolution

The primary processing factors in solid dosage forms are assessed using these crucial test parameters as benchmarks. Among the processing factors are:
Blender and granulator mixing time and speed
Rates of solvent addition in the granulator
Time, temperature, and airflow conditions in dryers and coaters
Screen size, feed rate, and milling speed in mills
Machine speed and compression force in tablet presses.
Testing for process validation should ideally be carried out on the first three product batches produced using production-scale machinery. Revalidation testing is only carried out following a significant modification.[19]

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