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# AN OVERVIEW OF PHARMACEUTICAL PROCESS VALIDATION AND PROCESS CONTROL VARIABLES OF TABLETS MANUFACTURING PROCESSES IN INDUSTRY

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## ABSTRACT

Validation is an integral part of quality assurance; the product quality is derived from careful attention to a number of factors including selection of quality parts and materials, adequate product and manufacturing process design, control of the process variables, in-process and end-product testing. Recently validation has become one of the pharmaceutical industry's most recognized and discussed subjects. It is a critical success factor in product approval and ongoing commercialization, facilities and processes involved in pharmaceutical manufacturing process impact significantly on the quality of the products. Process controls are mandatory in good manufacturing practice (GMP). The purpose is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it.

**INTRODUCTION:** Pharmaceutical process validation is a key element in assuring that these quality assurance goals are met. It is through careful design and validation of both the process and process controls that a manufacturer can establish a high degree of confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing. It should be noted that in all most cases, end-product testing plays a major role in assuring that quality assurance goals are met; i.e., validation and end-product testing are not mutually exclusive.

The U.S. Food and Drug Administration (FDA) has proposed guidelines with the following definition for *process validation:* Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics [1].

**History of Validation:** The concept of validation was first proposed by two FDA officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals (Agalloco 1995). It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated process of pharmaceutical.

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U.S.F.D.A. was the pioneer in advocating the concept of process validation, but till 29th September 1978 the definition of process validation did not appear in any part of literature of U.S.F.D.A. no cGMP regulations talked anything about process validation.

Process validation and its role within a pharmaceutical organization have come a long way from its inception in the 1970s. At that time, the effort was primarily focused on sterilization validation and demonstrating that the conditions to achieve sterility were met. As a result, the mission was often managed from within the sterile manufacturing organization using a small team. In the 1980s validation organizations were created and began interacting with the other traditional groups such as Research, Engineering, Production, Manufacturing, and Quality Assurance [2].

The term process validation was first used is debatable, as the concepts underlying the term are quite old and the use of synonyms such as verification and confirmation appears to predict the use of validation.

The first edition of the Orange Guide the British version of GMPs, which was published in 1971 contains a section titled "Verification of Procedures" that states, "Procedures should undergo a regular critical appraisal to ensure that they are remain capable of achieving the results which they are intended to achieve". This term now here appeared in the U.S.F.D.A. documentation, this was not defined in law; it was only in a F.D.A. The compliance programmed entitled "Drug Process Inspections" issued in June 1978 (before publication of the revised cGMP Regulations) [3].

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and validation process as shown in **Figure 1**. This guidance describes process validation activities in three stages which discusses later.

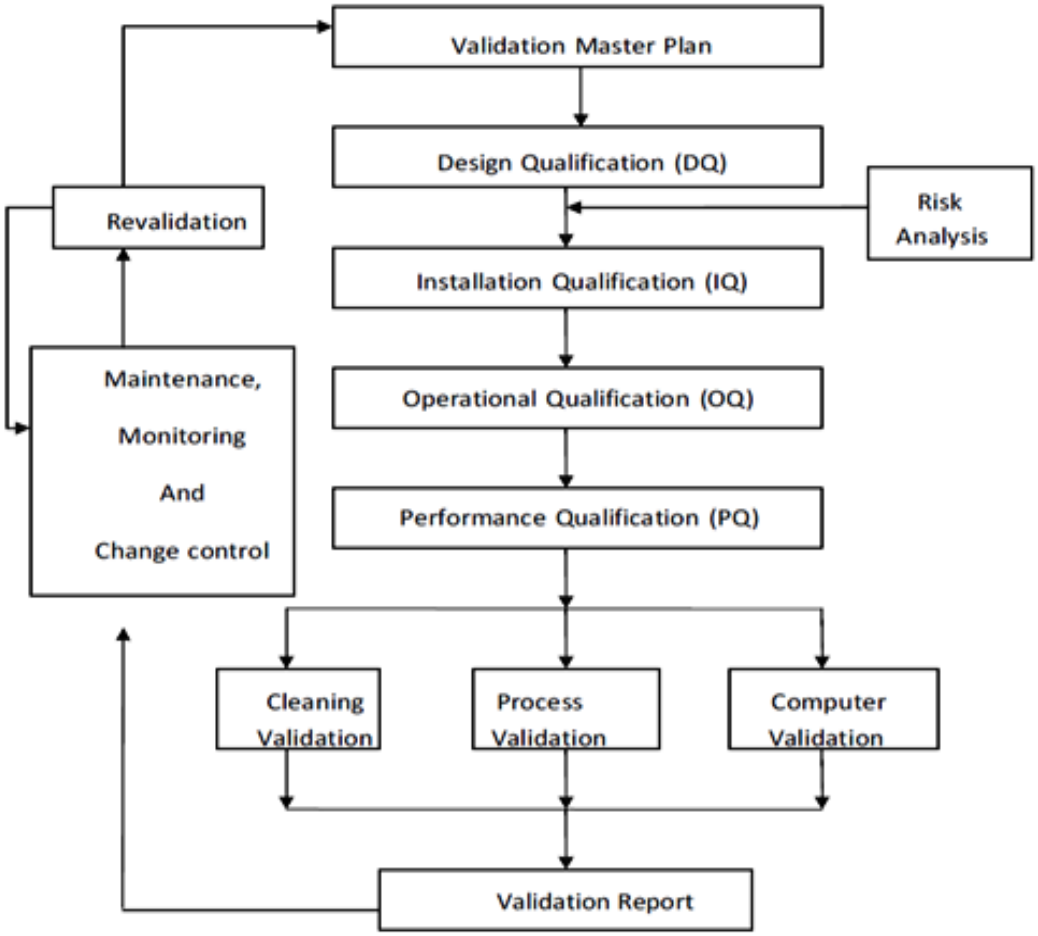


**FIGURE:** Error! No text of specified style in document.**. VALIDATION LIFE CYCLE**

This particular definition did not appear in any of the yearly revision of that particular compliance programmed but until March 29, 1983 it was the only official definition of process validation on March 29, 1983 draft on guidelines entitled "Guidelines on General Principles of Process Validation" was made available and the same was finalized in May, 1987 [4].

This guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonisation (ICH) guidance's for industry, Q8 (R2) Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality System [5].

Bernard T. Loftus was director of drug manufacturing in the Food and Drug Administration (FDA) in the 1970s, when the concept of process validation was first applied to the pharmaceutical industry and become an important part of current good manufacturing practices M (CGMPs).

"In process validation there's a lot common sense, you need to fully understand the process as you use it to make your product" (FDA) [6].

**What is process Validation:** The term process validation is not defined in the Food, Drug and Cosmetic Act (FD&C) Act or in FDA's CGMP regulations. Many definitions have been offered that in general express the same idea, that a process will do what it purports to do, or represent to do that the process works and the proof is documented.

Validation is defined as confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled. In contrast with verification, validation rather focuses on the question whether a system can perform its desired functions.

The word validation simply means assessment of validity or action of proving effectiveness. According to European community for medicinal products, validation is action of proving in accordance with the principals of good manufacturing practices that any procedure, process, equipment, material, activity or system actually leads to expected results.

This includes in particular, the manufacture of investigational products and the scaling up of processes from pilot plant to production unit. This is most important when processes go into routine full-scale production follows pharmaceutical development and pilot-plant operations. With a view to facilitating subsequent validation and its assessment in the course of quality audits or regulatory inspections, it is recommended that all documentation reflecting such transfers be kept together in a separate file (technology transfer document) [7].

**Scope of Validation:** Pharmaceutical Validation is a vast area of work and it practically covers every aspect of pharmaceutical processing activities, hence defining the Scope of Validation becomes a really difficult task. However, a systematic look at the pharmaceutical operations will point out at least the following areas for pharmaceutical validation;

1. Analytical
2. Instrument Calibration
3. Process Utility services
4. Raw materials
5. Packaging materials
6. Equipment
7. Facilities
8. Manufacturing operations
9. Product Design
10. Cleaning
11. Operators [8]

**The regulatory basis for Process Validation:** Once the concept of being able to pre-directs process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis of requiring process validation. The ultimate legal authority is in section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to bead ultimate differ the methods used in or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or administrated in conformity with CGMP. The CGMP regulations for finished pharmaceuticals 21CFR 210 and 211 were promulgated to enforce the requirements of the act,

which states that: There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality and purity they purport or are represented to possess [9].

**Need of Validation:** Quality is always an imperative prerequisite when we consider any product; it becomes primes when it relates to life saving products like pharmaceuticals. Although it is mandatory from the government and regulatory bodies but it is also a fact that quality of a pharmaceutical product can not be adequately controlled solely by pharmacopoeia analysis of the final product.

- Validation gives confident over the product manufacturing process.
- It's give assurance to the product quality as per customer requirements.
- Validation mandatory as per regulatory requirements[10].
  If we are not going for validation then following problems can be occur
- Low process capability
- Scrap, Rework
- Protracted production cycle times and low capacity utilization
- Resolution of process related problems slow and difficult
- High cost of compliance
  Risk of
- Drug shortages
- Releasing a poor quality product, Recalls
- Delay in approval of new drugs
- Quality problems confounding clinical trial data

So, as to minimize these problems we need to do validation [11].

**Importance of Validation:** Effective process validation contributes significantly to assuring drug quality, the basic principle of quality assurance is that a drug should be produced that is fit for its intended use. The most compelling reasons to optimize and validate pharmaceutical productions and supporting processes are quality assurance and cost reduction. The basic principles of quality assurance have as their goal and the production of articles that are fit for their intended use.

1. It deepens the understanding of processes, decreases the risks, processing problems.
2. It assures the smooth running of the process.
3. It decreases the risks of defect costs.
4. It decreases the risks of regulatory non-compliance.
5. A fully validated process may require less in-process control and end product testing.
6. It optimizes the process.
7. It gives assurance of quality and safety[12].
8. Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including in specifications.
9. Product selection
10. Process design
11. Process/ Product characterization
12. Process/ Product optimization
13. Process validation program
14. Product/process certification[13].

**Types of Validation:**

1. Process validation
2. Analytical method validation
3. Cleaning validation
4. Computer system validation

**Document regarding Validation:**

1. Getting started
2. Protocol development
3. User requirements specification (URS)
4. Design qualification (DQ)
5. Installation qualification (IQ)
6. Operational qualification (OQ)
7. Performance qualification (PQ) [14].

**Types of Process Validation:** Depending on when it is performed in relation to production, validation can be prospective, concurrent, retrospective and revalidation (Repeated Validation). It would normally be expected that process validation be completed prior to the distribution of a finished product that is intended for sale (Prospective Validation). Where this is not

possible, it may be necessary to validate processes during routine production (Concurrent Validation). Processes which have been in use for some time without any significant changes may also be validated according to an approved protocol (Retrospective Validation) [15].

**Prospective Validation:** Prospective Validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps; these are the evaluated on the basis of past experience to determine whether they might lead to critical situations.

It can be performed when a new formulation is developed or during critical changes like change in the batch size is done since here multiple parameters are changed like quantities of materials, equipment size, manufacturing process and parameters. The trials are then performed and evaluated and an overall assessment is made, if at the end the results are acceptable the process is satisfactory [16].

These experiments may incorporate a challenge element to determine the robustness of the process. Such a challenge is generally referred to as a worst case exercise. Each experiment should be planned and documented fully in an authorised protocol. This document will have the following elements;

- A description of the process / experiment
- Details of the equipment / facilities to be used (including measuring / recording equipment) together with its calibration status
- The variables to be monitored
- The samples to be taken -where, when, how and how many
- The product performance characteristics / attributes to be monitored, together with the test
- Methods
- The acceptable limits
- Time schedules
- Personnel responsibilities
- Details of methods for recording and evaluating results, including statistical analysis [17].

All equipment, the production environment and analytical testing methods to be used should have been fully validated (Installation/ Operational Qualification). Staff taking part in the validation work should have been appropriately trained, in practice, operational qualification may be carried out using batches of actual product. This work may also fulfil the requirements of prospective validation [18].

**Concurrent Validation:** Concurrent Validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The nature and specifications of sub sequent in-process and final tests are based on the evaluation of the results of such monitoring.

Concurrent validation carried out during normal production, it is together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product [19].

Concurrent validation may have the practical approach under certain circumstances. Examples of these may be:

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

It is important in these cases however, that the systems and equipment to be used have been fully validated previously. The justification for conducting concurrent validation must be documented and the protocol must be approved by the validation team.

A report should be prepared and approved prior to the sale of each batch and a final report should be prepared and approved after the completion of all concurrent batches. It is generally considered acceptable that a minimum of three consecutive batches within the finally agreed parameters giving the product the desired quality would constitute a proper validation of the process [20].

**Retrospective Validation:** Retrospective Validation involves the examination of past experience of production on the assumption that composition, procedures and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analyzed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.

Retrospective validation is obviously not a quality assurance measure in itself and should never be applied to new processes or products. It may be considered in special circumstances only e.g., when validation requirements are first introduced in a company, retrospective validation may then be useful in establishing the priorities for the validation programme [21].

Using either data-based computer systems or manual methods, retrospective validation may be conducted in the following manner:

- Gather the numerical data from the completed batch record and include assay values, end product test results and in-process data.
- Organize these data in a chronological sequence according to batch manufacturing data, using a spread sheet format.
- Include data from at least the last 20–30 manufactured batches for analysis. If the number of batches is less than 20, then include all manufactured batches and commit to obtain the required number for analysis.
- Trim the data by eliminating test results from noncritical processing steps and delete all gratuitous numerical information.
- Subject the resultant data to statistical analysis and evaluation.

Draw conclusions as to the state of control of the manufacturing process based on the analysis of retrospective validation data.

Issue a report of your findings (documented evidence) [22].

**Revalidation:** Revalidation is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional do not adversely affect process characteristics and product quality.

Revalidation may be divided into two broad categories: Revalidation after any change having a bearing on product quality.

Periodic revalidation carried out at scheduled intervals. Revalidation after changes may be based on the performance of the same tests and activities as those used during the original validation, including tests on sub processes and on the equipment concerned with validation.

Conditions requiring revalidation study and documentation are listed as follows:

1. Changes in the source of active raw material manufacturer.
2. Changes in packaging material (primary container/closure system).
3. Changes in raw materials (physical properties such as density, viscosity, particle size distribution, moisture etc. that may affect the process or product).
4. Changes in the process (e.g., mixing time, drying temperatures and batch size).
5. Changes in the equipment (e.g. addition of automatic detection system).
6. Changes of Equipment which involve the replacement of equipment on a “like for like” basis would not normally require a re-validation except that this new equipment must be qualified.
7. Changes in the plant/facility.
8. Variations revealed by trend analysis (e.g. process drifts).

**Periodic Revalidation:** The decision to introduce periodic revalidation should be based essentially on a review of historical data i.e., data generated during in-process and finished product testing after the latest validation, aimed at verifying that the process is under control.

During the review of such historical data, any trend in the data collected should be evaluated. In some processes such as sterilization, additional process testing is required to complement the historical data. Additionally, the following points should be checked at the time of a scheduled revalidation:

- Changes in master formula and methods, batch size, etc., if so, their impact on the product should be assessed.
- To check whether calibrations have been made in accordance with the established program and time schedule.
- Revalidation have the preventive maintenance been performed in accordance with the program and time schedule.
- To update the required standard operating procedures (SOPs).
- Checking the cleaning and hygiene program have been carried out.
- Any changes been made in the analytical control methods [23].

**Major Phases in Validation:**

**Pre-validation Qualification Phase:** It covers all activities relating to product research and development, formulation pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions and storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production document, operational qualification and process capacity.

**Process Validation Phase:** It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory products can be produced even under the worst conditions.

**Validation Maintenance Phase:** It requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures have been followed.

It is assumed that throughout manufacturing and control operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture [24].

**Principles of Quality Assurance:** Assurance of product quality is derived from careful attention to a number of factors including selection of quality parts and materials, adequate product and process design, control of the process, in-process and end-product testing. The basic principles of quality assurance have as their goal the production of articles that are fit for their intended use.

These principles may be stated as follows:

1. Quality, safety and effectiveness must be designed and built into the product;
2. Quality cannot be inspected or tested into the finished product;
3. Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications.

Process validation is a key element in assuring that these quality assurance goals are meet. It is through careful design and validation of both the process and process controls that a manufacturer can establish a high degree of confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing [25].

**WHO Concept:** The "World Health Organization" (WHO) defines the validation in the same way but elaborates on the concept: "Validation studies are essential part of GMP and should be conducted according with predefined protocols. A written report

summarizing results and conclusions should be recorded, prepared and stored. Particular attention should be accorded to the validation of processing, testing and cleaning procedures. Critical processes should be validated with prospective and retrospective validation.

The cGMPs may also be viewed as consisting of the following four essential elements:

- Personnel: The people system and manpower required to carry out the various tasks within the manufacturing and control function.
- Parts: The raw materials and components used in connection with the manufacturing and packaging of the drug product as well as the materials used in association with its control.
- Process: The buildings, facilities, equipment, instrumentation and support system with the manufacturing process and its control.
- Procedures: The paper work, documentation and records used in connection with the manufacturing process and its control.

Thus, the four elements of cGMPs listed above may be combined with the four elements of pharmaceutical process validation (i.e., qualification, validation, control and revalidation) to form a 4×4 matrix with respect to the all the activities that may be considered in connection with the manufacturer and the control of the each drug product [26].

**Validation Master Plan (VMP):** All validation activities should be planned. The key elements of the validation program should be clearly defined and documented in validation master plan (VMP) or equivalent documents.

The VMP should have summary of document, which is brief, concise and clear. The VMP should contain data on at least the following:

- Validation policy
- Organizational structure of validation activities
- Summary of the facilities, systems, equipments and processes to be validated
- Documentation format: the format to be used for protocols and reports
- Planning and scheduling
- Change control
- Reference to the existing documents

In case of large projects, it may be necessary to create separate validation master plans [27].

**Pilot Scale-Up and Process Validation:** The following operations are normally carried out by the development function prior to the preparation of the first pilot-production batch. The development activities are listed as follows:

- Formulation design, selection, and optimization
- Preparation of the first pilot-laboratory batch
- Conduct initial accelerated stability testing

If the formulation is deemed stable, preparation of additional pilot laboratory batches of the drug product for expanded non-clinical and/or clinical use.

The pilot program is defined as the scale-up operations conducted subsequent to the product and its process leaving the development laboratory and prior to its acceptance by the full scale manufacturing unit.

Thus, product and process scale-up should proceed in graduated steps with elements of process validation (such as qualifications) incorporated at each stage of the piloting program.

**Laboratory Batch:** The first step in the scale-up process is the selection of a suitable preliminary formula for more critical study and testing based on certain agreed-upon initial design criteria, requirements and/or specifications. The work is performed in the development laboratory. The formula selected is designated as the (1 ×) laboratory batch. The size of the (1 ×) laboratory batch is usually 3–10 kg of a solid or semisolid, 3–10 litres of a liquid or 3000 to 10,000 units of a tablet or capsule.

**Laboratory Pilot Batch:** After the (1 ×) laboratory batch is determined to be both physically and chemically stable based on accelerated, elevated temperature testing (e.g., 1 month at 45°C or 3 months at 40°C or 40°C/80% RH), the next step in the scale-up process is the preparation of the (10 ×) laboratory pilot batch.

The (10 ×) laboratory pilot batch represents the first replicated scale-up of the designated formula. The size of the laboratory pilot batch is usually 30–100 kg, 30–100 litres, or 30,000 to 100,000 units. It is usually prepared in small pilot equipment within a designated cGMPs approved area of the development laboratory

**Pilot Production:** The pilot-production phase may be carried out either as a shared responsibility between the development laboratories and its appropriate manufacturing counter part or as a process demonstration by a separate, designated pilot-plant or process-development function.

The object of the pilot-production batch is to scale the product and process by another order of magnitude (100 ×) to, for example, 300–1,000 kg, 300–1,000 litres, or 300,000–1,000,000 dosage form units (tablets or capsules) in size. Usually large production batch scale-up is undertaken only after product introduction. Again, the actual size of the pilot-production (100 ×) batch may vary due to equipment and raw material availability [28].

**Prerequisites for Process Validation:** Before process validation can be started, the manufacturing equipment and control instruments, as well as the formulation, must be qualified. The formulation pharmaceutical product should be studied in detail and qualified at the development stage, i.e. before the application for the marketing authorization is submitted. This involves pre-formulation studies, studies on the compatibility of active ingredients and excipients of final drug product, packaging material, stability studies, etc.

Other aspects of manufacture must be validated, including critical services (water, air, nitrogen, power supply, etc.) and supporting operations, such as equipment cleaning and sanitation of premises. Proper training and motivation of personnel are prerequisites to successful validation.

**Evaluation and Selection of Process Control Variables**

Following unit operations should be needed to determine during the manufacturing of the tablets and steps involved as shown in **fig. 2** [29].

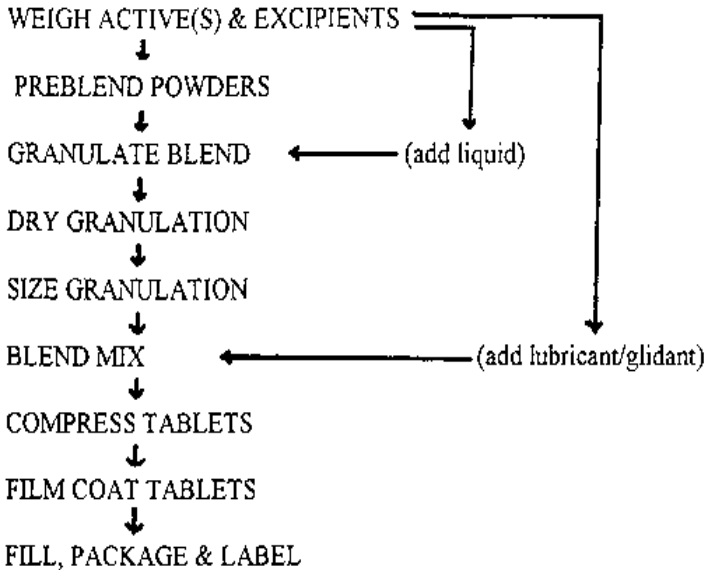


**FIGURE: 2. PROCESS FLOW STEPS**

**Process Description:** Manufacturing of Tablets includes the following processes;

1. Premixing & Sifting
2. Granulation
3. Drying
4. Sifting & Milling of Dried granules
5. Blending
6. Sifting of Lubricants & Lubrication
7. Compression
8. Film Coating Suspension Preparation
9. Film Coating

**Mixing or Blending:** The mixing or blending unit operation may occur once or several times during the tablets manufacture. For example, a direct compression formulation may involve one blending step in which the drug and the excipients are blending together prior to compression.

A wet granulation formulation may require two mixing/blending steps:

- Prior to granulating to have a uniform drug/excipient mixture
- After milling the dried granulation to add other excipients, such as the lubricant

The following physical properties of the drug and excipients are factors in creating a uniform mix or blend:

- Bulk density

- Particle size distribution
- Surface area

Mixing or blending operation parameters to be considered during development and validation are:

- Mixing or blending technique
- Mixing or blending speed/ time
- Drug uniformity
- Excipient uniformity
- Lubricants
- Distribution of Colorant(s)
- Equipment capacity/load[30]

**Wet Granulation:** The type of granulation technique to be used is to be decided, on the basis of low shear (e.g., Hobart), high shear (e.g., Diosna, GEI-Collette) or fluid bed (e.g., Glatt, Fluid Air). Each technique will produce granules with different physical properties and will require monitoring of different processing parameters as listed below:

**Wet massing:**

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

**Wet Milling:**

- Equipment size and capacity of mill
- Screen size
- Mill speed
- Feed rate

**Drying:**

- Inlet/Outlet temperature
- Air flow
- Moisture uniformity
- Equipment capability/capacity

**Dry Milling:**

- Mill type
- Screen size
- Mill speed
- Feed rate [31]

**Tablets Compression:** Compression is a critical step in the production of a tablets dosage form. The materials being compressed will need to have adequate flow and compression properties.

Compression process parameters to be considered during development and validation are:

- Tooling
- Compression speed
- Compression/ejection force

The following in-process tests (as discussed above) should be examined during the compression stage:

- Appearance
- Hardness
- Friability
- Disintegration
- Weight uniformity

**Tablet Coating:** A basic understanding of rheology and surface chemistry, two primary sciences of liquid flow and solid–liquid interaction is necessary for understanding coating and printing processes and materials. A generally qualitative treatment of these subjects will suffice to provide the insight needed to use and apply coatings and inks and to help solve the problems associated with their use, of pan coating.

Tablet coating process parameters to be considered during development and validation are:

- Pan load
- Inlet/exhaust temperature/ humidity
- Pan speed
- Spray nozzle size
- Atomizing pressure
- Spray rate
- Spray angle
- Gun to bed distance
- Tablets core characteristics [32, 33].

**TABLE: 1. PROCESS CONTROL VARIABLES AND METHOD RESPONSES**

| Process Step | Control Variables | Measured Responses |
|---|---|---|
| Dry Mixing | Load size, Impeller & Chopper Speed, Mixing Time | Motor Power Load (Amperage) |
| Wet Granulation | Load size, Binder Addition Time, Impeller & Chopper Speed, Quantity of purified Water, Total Granulation Time | Motor Power Load (Amperage) |
| Drying | Load Size, Inlet Air Temperature | Loss On Drying (LOD), Exhaust Air Temperature |
| Milling | Screen Size | ……. |
| Blending | Load Size, Pre blending Time, Final Blending Time | Description, Assay, Blend Uniformity, Tapped Density, Untapped Density, Particle Size Distribution, LOD |
| Compression | Compression speed, Compaction Force, Pre – Compression Force | Description, Average Weight, Individual Weight Variation, Thickness, Hardness, Friability, DT, CU & Dissolution test of 1st batch |
| Film Coating | Number of spray guns, Spray nozzle diameter, Gun to bed distance, Pan RPM, Product Temperature, Inlet air temperature, Spray rate, Atomization Air Pressure, Fan width air pressure | Description, Average Weight, Individual Weight Variation, Thickness, DT & Dissolution Profile of 1st batch |

**Definition and Control Variables of Process Validation:** Process validation can be defined a same as of challenging a process during development to determine variables that must be controlled to ensure the consistent production of a product or intermediate. It also provides the means for an ongoing quality audit of the process during the marketing phase of the product to ensure its compliance with these specifications.

The activity starts at the pharmaceutical development department. Pertinent data or information's are collected during the pre-formulation stage and additional inputs are generated during formulation development and evaluation, process development and full–scale manufacture [34].

**In-Process Test**

- **Moisture content of "dried granulation":** Loss on drying (LOD) can be used to determine whether or not the granulation solvent has been removed to sufficient level during the drying operation (usually less than 2 % moisture).
- **Granulation particle size distribution:** An extremely important parameter that can affect tablets compressibility, hardness, thickness and content uniformity. This parameter, which can be done by sieve analysis, which should be monitored throughout the tablets validation process.

**Blend uniformity:** Samples of the blend are taken and analysed to ensure that the drug is uniformly dispersed throughout the tablets blend. The proper blend time must be established so that the blend is not under or over mixed. The sampling technique is critical for this test to be valid.

**Individual tablets weight:** the weight of individual tablets is determined throughout compression to ensure the material is flowing properly and the equipment is working consistently. The individual weight should be within 5% of the nominal weight.

**Tablets hardness:** Tablets hardness is determined periodically throughout the batch to ensure that the tablets are robust enough for coating, packing and shipping and not too hard to affect dissolution

**Tablets thickness:** Tablets thickness is also determined periodically throughout the batch and is indirectly related to the hardness. It is another indication of whether or not the formulation has proper flow and compression properties.

- **Disintegration:** Disintegration is determined during the manufacture as a predictor of tablets performance (e.g., dissolution).

**Finished product tests:**

- **Appearance:** The tablets should be examined for such problems as tablets mottling, picking of the monogram, tablets filming, and capping of the tablets. If the tablets are colored, the color quality needs to be examined.
- **Assay:** This test will determine whether or not the product contains the labeled amount of drug.
- **Content Uniformity:** Samples are taken across the batch profile (beginning, middle and end) and analyzed to ensure that the dosage form comply with compendia standards (±15% of the labeled amount) or more stringent internal limits. It will indicate whether there is improper mixing during the manufacturing operation (i.e., segregation during flow of granulation from a storage bin).
- **Tablets hardness:** A critical parameter for dosage form handling and performance.
- **Tablets friability:** Friability is an important characteristic on the tablets ability to withstand chipping, cracking or "dusting" during the packaging operations and shipping.
- **Dissolution:** Dissolution is important to ensure proper drug release characteristics (in vitro availability) and batch to batch uniformity.

These key test parameters are the yardsticks by which the major processing variables in solid dosage form are evaluated [35].

**Guidelines for Process Validation of Solid dosage form**

Numerous factors should be considered when developing and validating solid dosage form. **Figures 2 and 3** are flowcharts for the validation of new and existing processes. As a means of providing a broad overview of these validation criteria, the following checklist/ guideline is provided for tablets for inclusion in a depth validation program.

- **Tablets composition:** Identify the key physiological properties of the drug substances that need to be considered in developing the formulation such as the following:

- **Solubility of the drug substance throughout the physiological pH range:** Depending on the solubility of the drug, a surfactant may be needed to enhance dissolution.

- **Particle size distribution and surface area:** The particle size distribution of the drug may determine grade of an excipients (e.g., microcrystalline cellulose) to use.

- **True and bulk density:** An excipients (e.g., diluents) that has a similar bulk density as the drug may be selected to minimize segregation, especially with a direct compression formulation.

- **Material flow and compressibility:** A free flowing, highly compressible material such as microcrystalline cellulose may be used for drugs with poor flow or compressibility properties.

- **Hygroscopicity:** Special environmental working conditions may be required to ensure that moisture is not picked up during material storage or handling and during the manufacture of the tablets dosage form.

- **Melting point:** If the drug has a low melting point, a direct compression formulation may need to be developed instead of a wet granulation formulation to avoid drying the material and potentially melting or degrading the drug.

Reasons should be provided for the presence of each ingredient in the formula. Justification of the level or range of each ingredients especially the binder, disintegrant and lubricant. The requirement of the unit operations in the tablets formulation should be defined like the use of high shear wet granulation instead of dry granulation or the coating step [36].

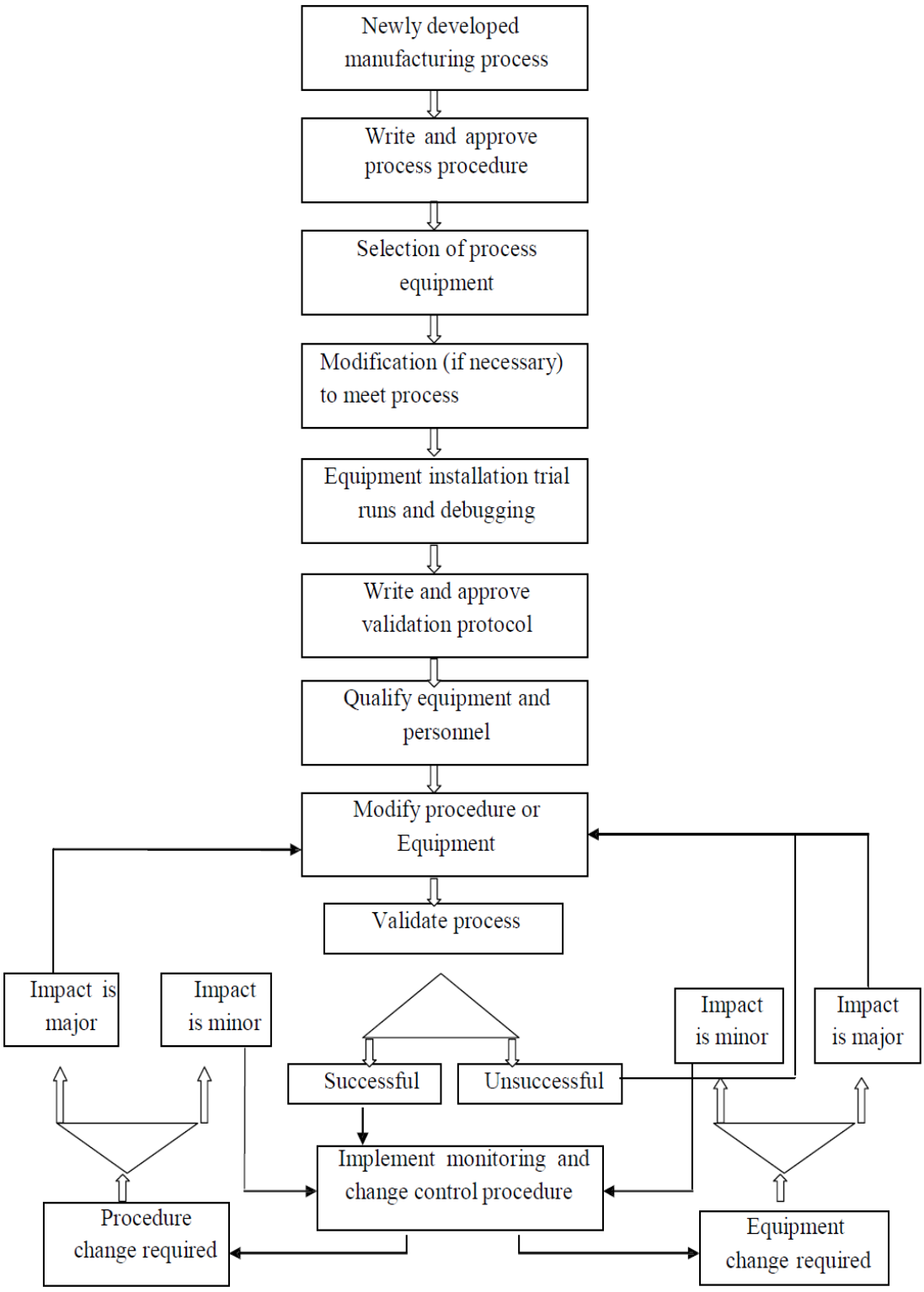


**FIGURE: 3. VALIDATION OF NEW PROCESSES**

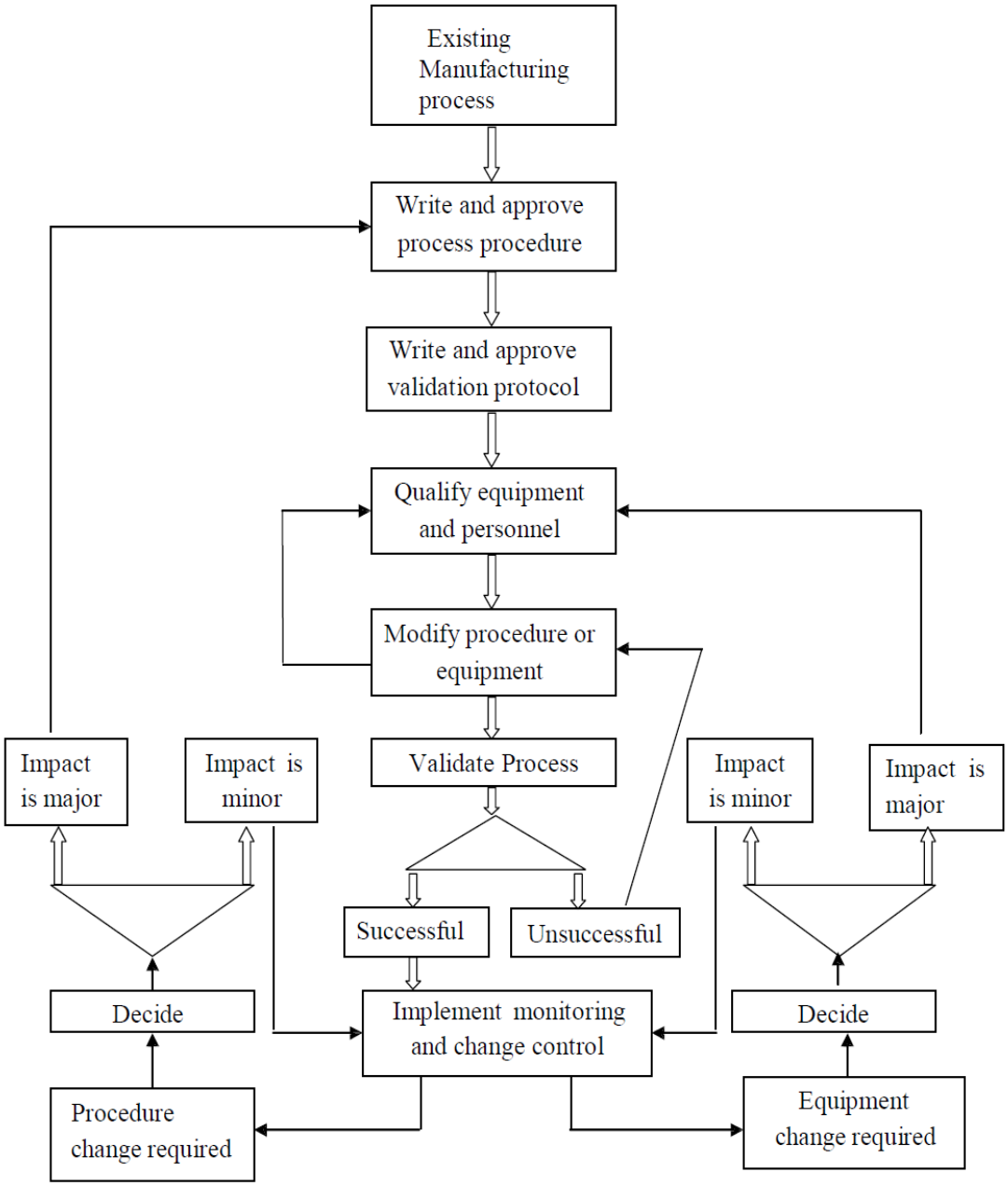


**FIGURE: 4. VALIDATION OF EXISTING PROCESSES**

**Strategy for Validation of Methods:** The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol preferably written in a step-by-step instruction format as follows:

- Develop a validation protocol or operating procedure for the validation;
- Define the application purpose and scope of the method;
- Define the performance parameters and acceptance criteria;
- Define validation experiments;
- Verify relevant performance characteristics of the equipment;
- Select quality materials, e.g., standards and reagents;
- Perform pre-validation experiments;
- Adjust method parameters and/or acceptance criteria, if necessary;
- Perform full internal (and external) validation experiments;

- Develop SOPs for executing the method routinely;
- Define criteria for revalidation;
- Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine; and
- Document validation experiments and results in the validation report [37].

**Approaches to Validation Process:**

There are two basic approaches to the validation of the process itself (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors, etc). These are the experimental approach and the approach based on the analysis of historical data. The experimental approach, which is applicable to both prospective and concurrent validation, may involve;

- Extensive product testing,
- Simulation process trials,
- Challenge/worst case trials, and
- Control of process parameters (mostly physical) [38]

**Expert Evaluation:** This is an evaluation of the entire study against the protocol requirements as outlined above. It should be prepared and the conclusion drawn at each stage stated. The final conclusions should reflect whether the protocol requirements were met. The evaluation should include an assessment of the planned calibration and maintenance programmes for the equipment and instrumentation to maintain the validated conditions. In addition, all process monitoring and control procedures required to routinely ensure that the validated conditions are maintained should be reported.

The evaluation should be signed by authorized officers of the organization who were members of the team establishing the protocol and who have appropriate expertise in the area assigned to them. Overall approval of the study should be authorized by the head of the validation team and the head of the quality control department [39].

**The Validation Report:** A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated), the report should include at least the following:

1. Title and objective of study;
2. Reference to protocol;
3. Details of material;
4. Equipment;
5. Programmes and cycles used;
6. Details of procedures and test methods;
7. Results (compared with acceptance criteria); and
8. Recommendations on the limit and criteria to be applied on future basis [40].

**CONCLUSION:** From the review validation data on pharmaceutical process validation and process control variables of tablets manufacturing processes in industry, it can be stated that process validation is major requirement of cGMPs regulation for the process efficiency and sturdiness and it is the full fledged quality attributing tool for the pharmaceutical industries.

Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing. Apart from all the consistency and reliability of a validated process to produce a quality product is the very important for an industry. For the tableting procedure, the steps that have been studied include powder blending, granulation, particle size, and lubrication with compression, coating and drug release studies. Such step-wise studies have brought light into the impact of the parameters and their interactions and increased the understanding of the respective processes and also to collect a complete and rational database for the building of validation evidence.

From the review study it is concluded that pharmaceutical validation and process controls are important to assure that the drug product can meet standards for the identity, strength, quality, purity and stability.

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