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AN OVERVIEW: VALIDATION AND ITS IMPLICATION IN PHARMACEUTICAL INDUSTRY

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ABSTRACT: In this review article, it has been tried to focus on familiarizing ideas of validation, its types and applications in different sectors of pharmaceutical industry. It has also been tried to integrate the information why and how validation has become integral and inseparable part of GMPs. Quality, identity, purity, stability, strength, safety and efficacy of the drug product are prime requirement of GMPs and cGMPs. These are the parameters that every drug should satisfy to ensure that they are consistently produced and controlled to quality standards, appropriate to their intended use as required by the product specification. Validation is the action of proving effectiveness by means of proper documentation, and accomplished through proper implementation of norms of GMP and cGMPs through mutual collaboration of each individuals involved in the manufacturing of medicinal products following a set of protocols. In order to build up quality in products, every pharmaceutical industry should put their prime focus in validation.

Keywords: Good Manufacturing Practices, Approaches in validation, Quality.

INTRODUCTION:

In this 21st century where science and technology is ever increasing its grasp all over the world, global health sector is also advancing in a day-to-day manner. New drugs are being discovered and marketed after years of research and clinical studies. In all these process, pharmaceutical industries are bound to follow specific procedures mentioned by the regulatory authorities. In this race of modern medical science, validation originated as a precaution to terminal sterilization process failures and now is so broad that no events/process carried in the pharmaceutical sectors escapes it. In a way, it has become very essential and integral part of regulatory requirements and everyday life in the pharmaceutical sector. Therefore, it is an important element of quality assurance with a product or process having principles such as:

- Quality, safety and efficacy must be designed and built in the product.
- Quality cannot be inspected or tested into the product.
- Each critical step of manufacturing processes must be valid [1].

Literally, validation in pharmaceuticals means to be valid or justifiable. Simply saying, validation means 'action of proving effectiveness."Validation is not a one-time event, rather an on-going process covering all the phases of a product. According to FDA 1987, "validation is a process of establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes". According to European Commission- 1991, "validation is an act of proving in accordance of GMPs that any process actually leads to expected results." According to European Commission-2000, "validation is 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 [2].

In general, validation covers the entire spectrum of cGMP concerns, which are essentially people, equipment, component, facility, methods and procedural qualification. Often we are confused of validation and process validation. But, validation has both a specific meaning and a general meaning, depending on the whether the term "process" is used.

Validation is not a new topic. Its origin can be traced back to terminal sterilization process failures in 1970s. This was the incident which awoke regulatory authorities about the need of validation. It was first applied in LVPs. Initially, pharmaceuticals felt that this is a new regulatory requirement to be added into the list of things they must do during manufacture, with little consideration. But, soon within 1980s, its importance was evident to all firms and ultimately they started integrating validation in real applications. Since then, validation has sustained [3].

Why validation?

One that comes first and foremost is to fulfill the regulatory requirement for virtually every process in the healthcare industry – for pharmaceuticals, biologics, and medical devices – continuing trend toward harmonization of requirements worldwide. Essentially, validation is done to ensure consistent product quality. A new product or an old product manufactured using a modified process or facility cannot be sold until the 'process' has been adequately validated. Some tangible and intangible benefits of validation are:[4]

- Increased throughput and improved production efficiency
- Reduce product recalls and troubleshooting in the manufacturing operations minimizing batch failures
- Fewer complaints about failures
- Reduced in-process and finished goods testing
- Easier maintenance and improved employee awareness
- More rapid and reliable startup
- Rapid automation
- Determine process parameters and necessary controls
- Compliance with government regulation
- Control point in the context of preventive maintenance

- Makes easy to investigate deviations, if any, from established parameters
- Risk/worst case assessment

When should validation be done?

Validation should be done prior to routine use, after repair and at regular time intervals. The decision of when, why and how has been easy with the help of validation decision tree. The model of decision tree [5] (in fig below) helps manufacturer to decide on whether a process needs to be validated or not. It is one of the easiest models under consideration.

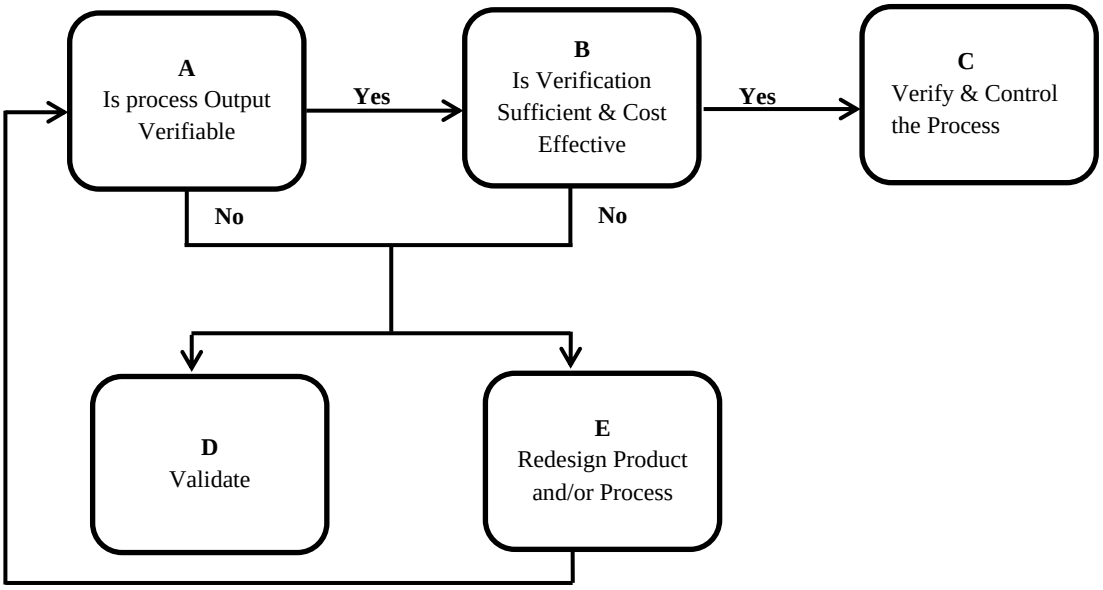

Fig.1. Validation Decision Tree

Each process should have a specification describing both the process parameters and the desired output. The tree is described below:

A. The manufacturer should consider whether the output can be verified by subsequent monitoring or measurement.
B. If the answer is positive, then the consideration should be made as to whether or not verification alone is sufficient to eliminate unacceptable risk and is a cost effective solution.
C. If yes, the output should be verified and the process should be appropriately controlled.
D. If the output of the process is not verifiable then the decision should be to validate the process.
E. The product or process should be redesigned to reduce variation, improve product or process and decrease risk or cost to a point where verification is acceptable decision.

For e.g. Computer systems should be validated during and at the end of the development process, during installation, prior and during routine use and after software updates. Analytical methods should be validated prior to routine use and after changing method parameters. Analytical systems should be tested for system suitability prior to and during routine use, practically on a day by day basis.

Scopes of validation:

Before manufacturing a product [6], all aspects of process need to be validated which includes bulk drugs, excipients, suppliers, analytical methods, computer systems, personnel, equipments as well as processes by which manufacturing is done. It must be ensured that the equipments comply with the specifications and all devices and recording equipment function correctly. As a result, the process must be robust and produce a product with consistent properties within the specifications. This is usually confirmed by manufacturing 3 full scale production batches under specified conditions. To minimize cross-contamination between batches, processes used to clean the equipments must also be validated.

Approaches for validation:

According to the guidelines of WHO [7], validation can be based on

a) Evidence obtained through testing process i.e. prospective and concurrent validation, and
b) Analysis of accumulated data i.e. retrospective validation.

Retrospective validation is not used these in sterile products.

a) **Prospective validation** is carried out prior to the distribution of either a new product or a product made under revised manufacturing process. It's performed on at least 3 consecutive batches before the process is put into commercial scale.

b) **Concurrent validation** involves in-process monitoring of critical processing steps and product testing to generate evidence to show that the process is in a state of control. It's similar to prospective, except the firm sell product during qualification runs. It is carried under a protocol during the course of normal production.

c) **Retrospective validation** involves accumulated in-process production, final product testing and control (numerical) data to establish that the product and its manufacturing process are in a state of control. It is used for facilities, processes and process controls in operation that have not undergone formal validation. At this phase, batches selected should be representative of all batches, including any batch that failed to meet specifications, so it may be from 10 to 30 consecutive batches (minimum of 10 last consecutive batches).

d) **Revalidation** is applied to ensure that changes in process or the process environment, whether intentionally or unintentionally, do not affect product specifications and quality characteristics [8].There should be quality assurance program (change control) which requires revalidation whenever there is a significant change in formulation, equipment, process, and packaging that may impact product and manufacturing process performance[9]. Conditions that require revalidation study and documentation are as follows:

1. Change in critical component i.e. API, key excipients, or primary packaging.
2. Change in critical piece of equipment.
3. Significant change in processing conditions.
4. Change in facility or plant location, site or support systems.
5. Increase or decrease in batch size.
6. If sequential batches fail to meet product and in-process specifications.

Validation committee:

This committee is responsible to establish and operate the complete validation program for the manufacturing site [10].Specific validation assignments are done by those individuals with the necessary training, experience and expertise. The departments and their responsibility as validation task force are explained in table-1 below.

Table.1. Organization of Validation Committee

Representative of	Responsibility or function
Engineering	They install, qualify, and certify plant, facilities, equipment and support system.
Development	They design, optimize and qualify manufacturing process within design limits, specifications, or requirements for products.
Manufacturing	They operate and maintain plant, facilities, equipments, support systems, and various manufacturing process within its requirements and specifications.
Quality Assurance	They establish approvable validation protocols and conduct validation by monitoring, sampling, testing, challenging and auditing the plant, facilities, equipment, support systems, various manufacturing process and their products for compliance with design limits, specifications, and/or requirements.

Validation master plan and protocol:

Validation master plan is a concise and clear document that establishes an umbrella for entire project and summarizes manufacturer's overall philosophy and approach for establishing performance adequacy. It is a good practice to document all validation activities in a document. It provides an overview of entire operation, its organizational structure, its content and planning. It should give answer to what, where, why and how regarding the validation in pharmaceuticals. It permits the development of a logical overview of the validation effort. It lays out a logical sequence in the activities or key elements or both to be performed according to approximate time schedule in a Gantt or PERT chart format. This establishes critical path through which process can be monitored.

Validation protocol is a document describing activities to be performed in validation, including the acceptance criteria for the approval of manufacturing process for routine use. It is the step that comes after validation master plan. The validation protocol and format for completed validation report have been suggested in WHO Guidelines on Validation of Manufacturing Processes (TRS 823), which is as follows:

1. Objective and purpose (for the whole validation) and pre-requisites.
2. Presentation of the whole process and sub-processes including flow diagram and critical step analysis.
3. Validation Protocol approvals.
4. Installation and operational qualifications, including blueprints or drawings.
5. Qualification reports
    a. Sub-process 1
    b. Purpose
    c. Methods and procedures

d. Sampling and testing procedures, release criteria
e. Reporting function
f. Calibration of test equipment
g. Test data
h. Summary of results
i. Approval and requalification procedure
j. Sub-process 2 (repeat)

6. Product qualification, test data from pre-validation batches.
7. Product validation, test data from three formal validation batches.
8. Evaluation and recommendations (include revalidation and requalification requirements).
9. Certification (approval).
10. Summary report with conclusions.

Elements of validation:

Qualification is a pre-requisite of validation. Validation is used for processes while qualification is normally used for equipments, utilities and systems. So, in this sense, qualification is a part of validation. It has four phases or stages.

1. **Design qualification:**
   Is documented verification of all key aspects of design, procurement and installation? It reviews design at an appropriate stages in the project for conformance to operational and regulatory expectations. It provides evidence that design specifications are met. The validation program starts from design qualification.
2. **Installation qualification:**
   It includes procedures and documentation to show that all important aspects of the installation of the facility, support system, or piece of modular equipment, having been properly calibrated, meet its design specifications and that he vendor's recommendations had been suitably considered.
3. **Operational qualification:**
   Following IQ, it includes procedures and documentation that facility, support system, or piece of modular equipment perform as intended throughout all anticipated operating ranges under a suitable load.
4. **Performance qualification:**
   Following IQ and OQ, actual demonstrations during the course of validation program show that the facility, support system, or piece of modular equipment perform according to a predefined protocol and achieve process reproducibility and product acceptability.

Moreover, in 2005, component qualification (CQ) has been developed. It refers to manufacturing of auxiliary components to ensure that they are manufactured to correct design criteria. This might involve packaging components like folding cartons, shipping cases, labels or phase change material.

Different types of validation:

Process Validation:

Process validation is a requirement of cGMP for finished pharmaceuticals (21 CFR 211) and of the GMP regulations for medical devices (21 CFR 820) and so applies to manufacture of both drug products and medical devices. According to FDA Guidelines, process validation is defined, "as establishing documented evidence, which provides a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics".

Stages of process validation:

Stage 1 – Process Design:

The commercial manufacturing process is defined during this stage. It is based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification:

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification:

Ongoing assurance is gained during routine production that the process remains in a state of control.

Typical content requirements for process validations:

- Production processes (fermentation, bulk production, purification, filling, lyophilization) must be run according to approved Master formula including all raw material, personnel, equipment, and facility preparations, in-process tests, processing, through to final testing of the batch lot.
- All facility systems must be monitored.
- Three consecutive lots must be produced and all facility support systems, product specifications, and process being validated must pass at all steps.

Analytical Method Validation:

According to ISO, "method validation is confirmation by examination and provision of evidences that the particular requirements for a specified intended use are fulfilled." The ultimate objective is to provide evidence that the method does what it is intended to do, accurately, reliably and reproducibly. It is the process which is established by laboratory studies that the performance characteristics of the method meet the requirement for the intended application. The methods adapted should be such that it should be able to detect the content, assay, purity or standard of pharmaceutical product without any error even if there is a change in chemicals, instrument, or person and this has to be validated by crosschecking separately and documented as evidence for efficacy and efficiency of method adapted. The methods needed to be validated or revalidated are as follows:

- Before the introduction into routine use.

- Whenever the conditions change for which the method has been validated (e.g. instrument with different characteristics).
- Whenever the method is changed, and the change is outside the original scope of the method.
- When quality control indicates an established method is changing with time.
- In order to demonstrate the equivalence between two methods (.e. a new method and a standard).

Typical tests to be validated:

- Identification tests
- Quantitative tests for impurities content
- Limit tests for the control of impurities
- Quantitative tests of the active moiety

Typical analytical performance characteristics to be considered in different types of procedures are as follows:[11,12]

1. **Accuracy:** Closeness of agreement between accepted reference values and the obtained value.
2. **Precision:** Expresses closeness of agreement (i.e. degree of scatter).
3. **Specificity:** Ability to clearly assess an analyte in presence of components expected.
4. **Detection limit (LOD):** Lowest amount of analyte in a sample that can be detected but not necessarily quantified.
5. **Quantitation limit (LOQ):** Lowest concentration of analyte in sample which can be quantitatively determined with suitable precision and accuracy.
6. **Linearity:** Ability to obtain test results which are proportional to concentration of the sample.
7. **Range:** Interval between the upper and lower concentration of analyte in sample.
8. **Robustness:** Measure of analytical method to remain unaffected by small but deliberate variations in parameters.
9. **Ruggedness:** Degree of reproducibility
10. **Stability and system suitability tests:** It depends on type of analytical procedure; and reference is given to pharmacopeias.

Computer System Validation:

Computer systems in pharmaceuticals is expected to support the fundamental requirement of minimizing risk to product identity, purity, strength, and efficacy by providing consistent and secure operation and reducing the potential of human error. Computer validation encompasses all computers which directly controls processes or systems or collects analytical data. It includes qualification of all software and hardware, which has direct or indirect impact on the quality of a product. The validation approach to programmable logic controller (PLC) hardware and PCs is similar, both to one another and to the general overall approach top validation, in that the end user should define each requirement [13].

It ensures that the computerized operation maintains its validated status throughout its operational life and that GMP-specific records are readily available for a stipulated period after the system has been decommissioned or retired.

The computerized system which are adapted in manufacturing of pharmaceuticals is tested for their worthiness, if the actual readings obtained from system, and those obtained manually in process are both matching and are accurate and satisfactory so as to rely completely on the computer systems adapted in the process of pharmaceutical manufacturing and quality control, and quality assurance, and stores activity, rules governing computerized system validation, electronic signature and document generated through computerized systems are included in 21 cfr Part 11 of the US code of federal regulations. It requires that all software or programs which are utilized by pharmaceutical companies in manufacturing should work without error. For e.g. dispensing of raw material using computerized system or process control using a computerized system[14].

Cleaning Validation:

Cleaning is a process of removing undesirable substances such as dust, drug, excipients, etc. from equipment or premises so that they will not contaminate or cross-contaminate the product [15].Cleaning validation is a methodology of providing documented evidence to ensure and assure that the cleaning process being performed removes residues to the predetermined levels of acceptability, taking into consideration of batch size, dosing, toxicology, and equipment size. This methodology assures that cleaning performed removes residues of the active pharmaceutical ingredients of the product manufactured in a piece of equipment, the cleaning aids utilized in the cleaning process and the microbial attributes. All residues are removed to predetermined levels to ensure the quality of next product manufactured is not compromised by waste from previous product and the quality of future products using the same equipment, to prevent cross-contamination and as a GMP requirement. The FDA has strict regulations about the cleaning validation. It requires manufacturers to conduct the validation studies in accordance with the protocols and to document the results of studies. The evaluation is also strictly regulated, which usually mainly covers the aspects of equipment design, cleaning process written, analytical methods and sampling. It is usually ascertained by carrying out trace analysis of active ingredient of previous products, doing rinse water analysis or swab test, etc.

Facilities Validation:

It includes planning, documentation, construction and testing to design specifications and cGMP requirements. It's a tool for enhancing reliability, cost and quality. Often it involves qualification activities like: environmental control system (HVAC, AHU); water storage and distribution system, compressed air system, steam distribution system, etc.

Equipment Validation:

Equipment validation comprehensively establishes in a documented way that the instrument is working accurately. It offers evidence that the components critically contributing to accurate functioning of the equipment consistently meet the predefined specifications and operational attributes [16]. Equipments must be located, designed, constructed, adapted and maintained to suit the operations to be carried out successfully. It involves qualifying the design, installation, operation, instrumentation, control system and performance of the equipment. The layout and design must aim to minimize risks of error to permit effective cleaning and maintenance and avoid cross-contamination, dust and dirt buildup on the quality of products. The pharmaceutical companies offer a wide range of equipment validation services whether it is in laboratory or in manufacturing area. It helps us to identify the risks associated with the process, equipment, and materials; and assesses the impact of failure [17].

Vendor Validation:

Also popularly known as source validation is "the collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes – including equipment, buildings, personnel and materials - are capable of achieving the intended results on a consistent and continuous basis" [18]. It involves qualification of the supplies who provides the active material, excipients and the instruments required for the manufacturing. It's usually done conducting audits.

Personnel Validation:

Personnel validation act as validating something, such as a certificate, that validates something; attestation, authentication, confirmation, proof or verification. Establishment and maintenance of satisfactory system of QA of products relies on people. So, sufficiently qualified personnel should carry out the tasks and they should be aware of the principles of GMP that affect them [19].

Cold Chain Validation:

Cold chain is a temperature-controlled supply chain, an uninterrupted system of transporting and storing vaccines within a recommended temperature range of +2°C to +8°C. This temperature range has been selected by WHO [20,21]. It is used to store vaccines, and certain injectable preparations. Cold chain validation involves both tests in an environmental chamber and actual shipping of packages by commercial overnight delivery service. It is useful to help extend and ensure shelf-life of products and protect heat-sensitive medicines such as insulin, vaccine, interferon, etc.

Environment Validation:

Pharmaceutical manufacturing facilities are required to comply with numerous environmental regulations promulgated by the U.S. Environmental Protection Agency (EPA), State environmental regulatory agencies, and local environmental ordinances. They regulate air emissions, wastewater discharges, and waste streams generated by pharmaceutical manufacturing facilities prior to initiating construction activities. So, it is suggested that an evaluation of environmental requirements be performed during very early stages of the project.

Packaging Validation:

According to WHO, packaging is a process that bulk material must undergo to be a finished product. The basic need for packaging validation is, it enables packaging process to meet the product and market requirements i.e. quality attributes and consumer needs in a cost effective and consistency efficient process with minimum down time, rejects and errors. It's crucial to guarantee that the integrity of the packaging system is always assured and maintained during transport and storage until the time of use. Some tests that can be performed for validating packaging are: microbial barrier test, toluidine blue test, visual inspection test, immersion test, pealability test (manual and with tensile strength equipment), sealing strength test, vacuum test, and accelerated aging test [22].

Validation life cycle:

Whenever any system is set for its validation to verify that it meets the required criteria of operation and quality, a comprehensive validation life cycle is formed to keep the integrity of the systems validity. A pharmaceutical validation process must consider lifecycle of development of a product right from research and development activities selection of dosage form, formulation and procedures for manufacturing and testing, to production of scale-up batches and exhibit batches as well. The figure-2 below indicates the total stages of validation life cycle.

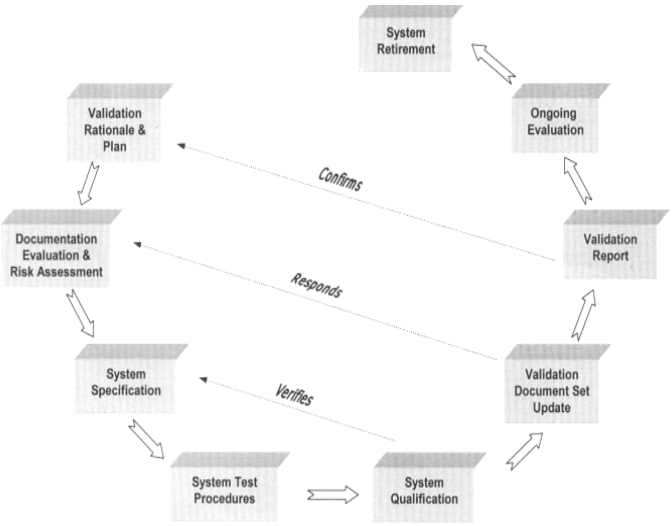

Fig.2. Validation Lifecycle

Change Control:

Procedures with respect to establishing change control should be in place before, during, and after the completion of formal validation program. It maintains a sense of functionality as the process

evolves and provides the necessary documentation trail that ensures that the process continues in a validated, operational state, even when small non-critical adjustments and changes have been made.

CONCLUSION:

The prime requirement of all the pharmaceuticals in every regulatory body, be it FDA, MHRA, TGA, or EU, is identity, strength, quality, purity, stability, safety and efficacy. In order to ensure all requirements as per their specifications, validation is the integral part. Quality cannot be inserted into the product; it should be built with the product. Every tasks accomplished in validation requires planning, rationale, risk assessment, evaluation, documentation and proper implementation of protocol. From this review, we conclude that every pharmaceutical industry should put their prime focus in validation to produce and assure quality products.

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