



INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

PHARMACEUTICAL PROCESS VALIDATION: AN OVERVIEW

MAHAR P, VERMA A

Department of pharmacy, GRD (PG) IMT, Dehradun-248001, Uttarakhand.

Accepted Date: 30/06/2014; Published Date: 27/08/2014

Abstract: Drug must be manufactured to the highest quality levels. The validation study provides the accuracy, sensitivity, specificity and reproducibility of the test methods employed by the firms, shall be established and documented. Validation studies are conducted in accordance with pre-defined protocols. Written reports summarizing recorded results and conclusions are prepared, evaluated, approved and maintained. Validation is the mean of catering enormous benefits to even more than the acceptable quality level which in the global standard scale. Lending importance to validation is increasingly profound in recent years. Validation is the art of designing and practicing the designed steps alongside with the documentation.

Keywords: Process Validation, cGMP, Validation Protocol



PAPER-QR CODE

Corresponding Author: MS. PAWANA MAHAR

Access Online On:

www.ijprbs.com

How to Cite This Article:

Mahar P, Verma A; IJPRBS, 2014; Volume 3(4): 243-262

INTRODUCTION

Pharmaceutical Process Validation is the most important and recognized parameters of CGMPs. The requirement of process validation appears of the quality system (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goal are met. The process validation is standardization of the validation documents that must be submitted with the submission file for marketing authorization. The process validation is intended to assist manufacturers in understanding quality management system (QMS) requirements concerning process validation and has general applicability to manufacturing process. According to FDA, assurance of product quality is derived from careful and systemic attention to a number of importance factors, including: selection of quality process through in-process and end-product testing.

PROCESS VALIDATION DEFINITION

Validation means demonstration, by provision of objective evidence that consistently meets its predetermined requirements. It is, therefore, an element of the quality assurance program associated with a particular product or process. "Process validation is a documented program which provides a higher degree of assurance that a specific process will produce a product meeting its predetermined specifications & quality attributes."The basic principles of quality assurance have as their goal the production of products that are fit for their intended use.

- Drug Efficacy
- Computer system Output
- Safety of medical device
- Effectiveness of sterilizer
- Ability of manufacturing the acceptable product

BACKGROUND^[1]

In the *Federal Register* of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled *Guideline on General Principles of Process Validation* (the 1987 guidance). Since then, we have obtained additional experience through our regulatory oversight that allows us to update our recommendations to industry on this topic. This revised guidance conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entitled "Pharmaceutical

CGMPs for the 21st Century — A Risk-Based Approach,” particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts.⁸ This revised guidance replaces the 1987 guidance.

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).

PRINCIPLE FOR PROCESS VALIDATION

The basic principle for validation may be stated as follows:

1. **Installation Qualification (IQ):** The process or equipment meets all specifications, is installed correctly, and all required components and documentation needed for continued operation are installed and in place.

IQ considerations are:

- Design features of equipment (material of construction cleanability.)
 - Equipment Installation conditions (wiring, utility, functionality, etc.)
 - Calibration, preventative maintenance, cleaning schedules.
 - Safety features.
 - Supplier documentation, prints, drawings and manuals.
 - Documented Software.
 - Environmental conditions of the manufacturing area (such as clean room requirements, temperature, and humidity).
2. **Operational Qualification (OQ):** The process or equipment are operating correctly. Operational qualification (OQ) should follow Installation qualification.

OQ considerations include:

- Control limits of Process (time, temperature, pressure, line speed, setup conditions, etc.)
- Software parameters.
- Specifications of raw material.

- Operating procedures for the process.
 - Material handling requirements.
 - Process change control.
 - Training.
3. **Performance Qualification (PQ):** The process or equipment performs as intended in a consistent manner over time. It should follow successful completion of Installation qualification and Operational qualification.

PQ considerations include:

- Actual product and process parameters and procedures established in OQ.
 - Acceptability of the product.
 - Assurance of process capability as established in OQ.
 - Process repeatability, long term process stability.
4. **Re – Qualification:** This formal review should include consideration of re-qualification of the equipment. Minor changes or changes having no direct effect on final or in-process product quality should be handled through the documentation system of the preventive maintenance program.

Approach to Process Validation^[9]

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which include scientific evidence that a process is capable of consistently delivering quality product. Process This guidance describes process validation activities in three stages.

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage 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.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that result in products with the desired quality attributes. Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process

Stage 1 — Process Design

Process design is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

A. Building and Capturing Process Knowledge and Understanding^[1]

Generally, early process design experiments do not need to be performed under the CGMP conditions required for drugs intended for commercial distribution that are manufactured during Stage 2 (process qualification) and Stage 3 (continued process verification). They should, however, be conducted in accordance with sound scientific methods and principles, including good documentation practices. Decisions and justification of the controls should be sufficiently documented and internally reviewed to verify and preserve their value for use or adaptation later in the lifecycle of the process and product.

Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes, and a general manufacturing pathway. Process information available from product development activities can be leveraged in the process

design stage. The functionality and limitations of commercial manufacturing equipment should be considered in the process design, as well as predicted contributions to variability posed by different component lots, production operators, environmental conditions, and measurement systems in the production setting. However, the full spectrum of input variability typical of commercial production is not generally known at this stage. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

Designing an efficient process with an effective process control approach is dependent on the process knowledge and understanding obtained. Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs (e.g., component characteristics or process parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product).

B. Establishing a Strategy for Process Control

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches. FDA expects controls to include both examination of material quality and equipment monitoring. Special attention to control the process through operational limits and in-process monitoring is essential in two possible scenarios:

1. When the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination)
2. When intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified.

The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation.

Stage 2 — Process Qualification

During the process qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This stage has two elements: design of the facility and qualification of the equipment and utilities and process performance qualification (PPQ). During Stage 2, CGMP-compliant procedures must be followed. Successful completion of Stage 2 is necessary before commercial distribution.¹⁵ Products manufactured during this stage, if acceptable, can be released for distribution.

A. Design of a Facility and Qualification of Utilities and Equipment

Proper design of a manufacturing facility is required under part 211, subpart C, of the CGMP regulations on *Buildings and Facilities*. It is essential that activities performed to assure proper facility design and commissioning precede PPQ. Here, the term *qualification* refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. These activities necessarily precede manufacturing products at the commercial scale.

Qualification of utilities and equipment generally includes the following activities:

Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific uses.

Verifying that utility systems and equipment are built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).

Verifying that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production^[13].

Qualification of utilities and equipment can be covered under individual plans or as part of an overall project plan. The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify the following items:

- The studies or tests to use,
- The criteria appropriate to assess outcomes,
- The timing of qualification activities,
- The responsibilities of relevant departments and the quality unit, and
- The procedures for documenting and approving the qualification.

B. Process Performance Qualification^[1,12]

The process performance qualification (PPQ) is the second element of Stage 2, process qualification. The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Success at this stage signals an important milestone in the product lifecycle. A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product.¹⁶ The decision to begin commercial distribution should be supported by data from commercial-scale batches. Data from laboratory and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected.

The approach to PPQ should be based on sound science and the manufacturer's overall level of product and process understanding and demonstrable control. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PPQ. To understand the commercial process sufficiently, the manufacturer will need to consider the effects of scale. However, it is not typically necessary to explore the entire operating range at commercial scale if assurance can also be helpful. In addition, we strongly recommend firms employ objective measures (e.g., statistical metrics) wherever feasible and meaningful to achieve adequate assurance.

1. PPQ Protocol

A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation. We recommend that the protocol discuss the following elements:

- The manufacturing conditions, including operating parameters, processing limits, and component (raw material) inputs.
- The data to be collected and when and how it will be evaluated.
- Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.
- The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.

- Criteria and process performance indicators that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products. The criteria should include:
- A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
- Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PPQ without a documented, science-based justification.¹⁷
- Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources (components and container/closures), if not previously accomplished.
- Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.

Review and approval of the protocol by appropriate departments and the quality unit.

Stage 3 — Continued Process Verification^[3,7,10]

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control (§ 211.180(e)).

An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability.¹⁸ Procedures should

describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements.

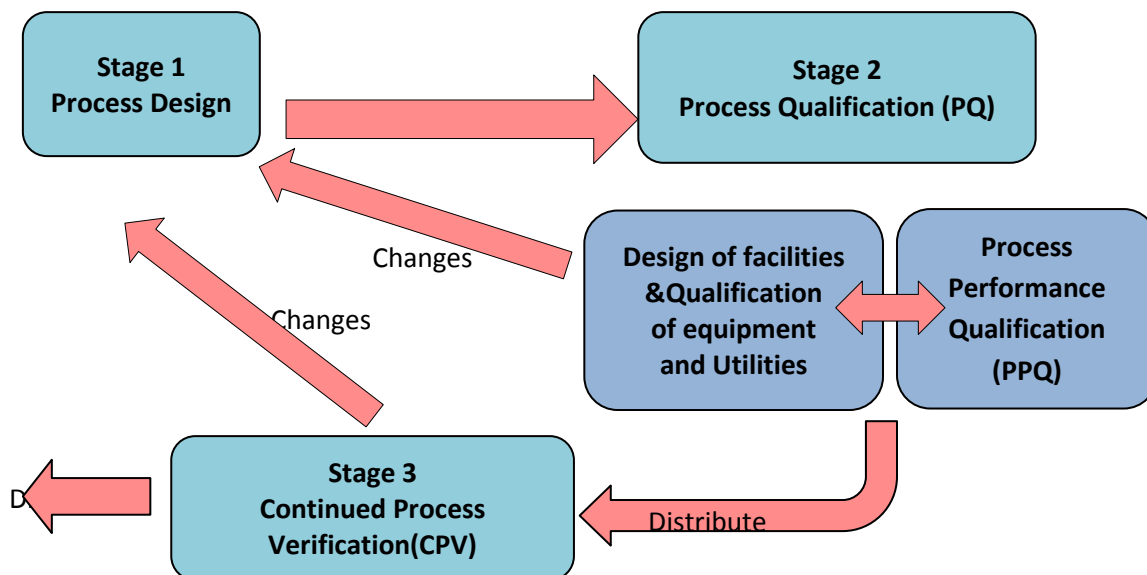


Figure 1: Three model of process validation according to FDA Guidance for Industry – Process Validation

STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION ^[1,13]

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a) (2)(B) of the Act (21 U.S.C. 351(a) (2)(B)), which states the following:

A drug shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

FDA regulations describing current good manufacturing practice (CGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211.

The CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that “[t]here 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...”(emphasis added). This regulation requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes.

Other CGMP regulations define the various aspects of validation. For example, § 211.110(a), *Sampling and testing of in-process materials and drug products*, requires that control procedures “be established to monitor the output and *to validate* the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product” (emphasis added). Under this regulation, even well-designed processes must include in-process control procedures to assure final product quality. In addition, the CGMP regulations regarding sampling set forth a number of requirements for validation: samples must represent the batch under analysis (§ 211.160(b)(3)); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)).

In addition to sampling requirements, the CGMP regulations also provide norms for establishing in-process specifications as an aspect of process validation. Section 211.110(b) establishes two principles to follow when establishing in-process specifications. The first principle is that “in-process specifications for such characteristics [of in-process material and the drug product] shall be consistent with drug product final specifications.” Accordingly, in-process material should be controlled to assure that the final drug product will meet its quality requirements. The second principle in this regulation further requires that in-process specifications “Shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.” This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability.

In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably^[1,13].

General Considerations for Process Validation

In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient. The following practices should ensure uniform collection and assessment of information about the process and enhance the accessibility of such information later in the product lifecycle.

We recommend an integrated team approach to process validation that includes expertise from a variety of disciplines (e.g., process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance). Project plans, along with the full support of senior management, are essential elements for success.

Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. All studies should be planned and conducted according to sound scientific principles, appropriately documented, and approved in accordance with the established procedure appropriate for the stage of the lifecycle.

Many products are single-source or involve complicated manufacturing processes. Homogeneity within a batch and consistency between batches are goals of process validation activities. Validation offers assurance that a process is reasonably protected against sources of variability that could affect production output, cause supply problems, and negatively affect public health^[3].

Types of Process Validation^[7,1]

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).

A. Prospective Validation

In prospective validation, the validation protocol is executed before the process is put into commercial use. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorised protocol.

All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. In practice, it may take some considerable time to accumulate these data.

Some considerations should be exercised when selecting the process validation strategy. Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the process data in case of requalification and revalidation.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production. These should be incorporated into the batch manufacturing and packaging record or into appropriate standard operating procedures. Limits, frequencies and actions to be taken in the event of the limits being exceeded should be specified.

Matrix or "Family" approaches to prospective process validation^[8]

The matrix approach generally means a plan to conduct process validation on different strengths of the same product. However, discrete manufacturing steps such as compression and coating that involve different tools, equipment, and process conditions for the different dosage strengths cannot be generally validated using the matrix approach. It should be recognized that the matrix approach has limitations when there are concerns with respect to physical characteristics such as flow properties, particle size distribution, homogeneity.

The "family" approach means a plan to conduct process validation on different products manufactured with the same processes using the same equipment.

The validation process using these approaches must include batches of different strengths or products which should be selected to represent the worst case conditions or scenarios to demonstrate that the process is consistent for all strengths or products involved.

B. Concurrent Validation^[7,1]

Unconditional use of this approach is not encouraged by the Inspectorate and is not acceptable as being the "norm". In using this approach there is always the risk of having to modify process parameters or specifications over a period of time. This situation often leads to questions regarding disposition of the batches that had already been released for sale, subsequently known to have undesired quality characteristics.

Concurrent validation may be 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 number 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.

C. Retrospective Validation^[7,1]

In many establishment, processes that are stable and in routine use have not undergone a formally documented validation process. Historical data may be utilized to provide necessary documentary evidence that the processes are validated.

The steps involved in this type of validation still require the preparation of a protocol, the reporting of the results of the data review, leading to a conclusion and recommendation.

Retrospective validation is only acceptable for well established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there have been recent changes in the formulation of the product, operating procedures, equipment and facility.

The source of data for retrospective validation should include amongst others, batch documents, process control charts, annual product quality review reports, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results.

For the purpose of retrospective validation studies, it is considered acceptable that data from a minimum of ten consecutive batches produced be utilized. When less than ten batches are available, it is considered that the data are not sufficient to demonstrate retrospectively that the process is fully under control. In such cases the study should be supplemented with data generated with concurrent or prospective validation.

Some of the essential elements for retrospective validation are:

- Batches manufactured for a defined period (minimum of 10 last consecutive batches)
- Number of lots released per year
- Batch size/strength/manufacturer/year/period
- Master manufacturing/packaging documents
- Current specifications for active materials/finished products
- List of process deviations, corrective actions and changes to manufacturing documents
- Data for stability testing for several batches
- Trend analyses including those for quality related complaints

D. Process Re-Validation

Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process^[7,1].

Periodic review and trend analysis should be carried out at scheduled intervals. Re-validation becomes necessary in certain situations. The following are examples of some of the planned or unplanned changes that may require re-validation:

- Changes in raw materials (physical properties such as density, viscosity, particle size distribution, and moisture, etc., that may affect the process or product).
- Changes in the source of active raw material manufacturer
- Changes in packaging material (primary container/closure system).
- Changes in the process (e.g., mixing time, drying temperatures and batch size)
- Changes in the equipment (e.g. addition of automatic detection system). 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.
- Changes in the plant/facility.
- Variations revealed by trend analysis (e.g. process drifts)

A decision not to perform re-validation studies must be fully justified and documented.

Change Control^[8]

Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment, processing site, method of production or testing or any other change that may affect product quality or support system operations.

All changes must be formally requested, documented and accepted by the validation team. The likely impact / risk of the change on the product must be assessed and the need for the extent of re-validation should be determined.

Commitment of the company to control all changes to premises, supporting utilities, systems, materials, equipment and processes used in the fabrication/packaging of pharmaceutical dosage forms is essential to ensure a continued validation status of the systems concerned.

The change control system should ensure that all notified or requested changes are satisfactorily investigated, documented and authorised. Products made by processes subjected to changes should not be released for sale without full awareness and consideration of the change by the validation team. The team should decide if a re-validation must be conducted prior to implementing the proposed change.

Validation protocol^[6]

A written plan stating how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested.

The validation protocol provides a synopsis of what is hoped to be accomplished. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance. The date of approval by the validation team should also be noted.

In the case where a protocol is altered or modified after its approval, appropriate reasoning for such a change must be documented.

The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information:

- objectives, scope of coverage of the validation study
- validation team membership, their qualifications and responsibilities
- type of validation: prospective, concurrent, retrospective, re-validation
- number and selection of batches to be on the validation study
- a list of all equipment to be used; their normal and worst case operating parameters
- outcome of IQ, OQ for critical equipment
- requirements for calibration of all measuring devices
- critical process parameters and their respective tolerances
- description of the processing steps: copy of the master documents for the product
- sampling points, stages of sampling, methods of sampling, sampling plans
- statistical tools to be used in the analysis of data
- training requirements for the processing operators
- validated test methods to be used in in-process testing and for the finished product

- specifications for raw and packaging materials and test methods
- forms and charts to be used for documenting results

Validation Master Plan

A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon by management.

Validation in general requires meticulous preparation and careful planning of the various steps in the process. In addition, all work should be carried out in a structured way according to formally authorized standard operating procedures. All observations must be documented and where possible must be recorded as actual numerical results.

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of it being the list inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation.

The validation master plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports^[4,5].

The format and content should include:

- Introduction: validation policy, scope, location and schedule
- Organizational structure: personnel responsibilities
- Plant/ process /product description: rational for inclusions or exclusions and extent of validation
- Specific process considerations that are critical and those requiring extra attention
- List of products/ processes/ systems to be validated, summarised in a matrix format, validation approach
- Re-validation activities, actual status and future planning
- Key acceptance criteria

- Documentation format
- Reference to the required sop's

CONCLUSION

From the study it can be stated that pharmaceutical Process Validation is the most important and recognized parameters of cGMP. The cGMP regulation require that manufacturing processes be designed and controlled to assure that in-process materials and finished product meet predetermined quality requirements and do so consistently and reliably. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Process validation involves a series of activities taking place over the lifecycle of the product and process.

REFERENCES

1. Guidance for Industry: Process Validation: General Principles and Practices. U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Biologics Evaluation and Research (CBER), Centre for Veterinary Medicine (CVM), January 2011.
2. Nash R. A and Wachter A. H, Pharmaceutical Process Validation an International Third Edition. Revised and Expanded, Marcel Dekkar, Inc., New York, 2003; 17 – 40.
3. FDA's guidance for industry, *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*,
4. Health Canada / Health Products and Food Branch Inspectorate Validation Guidelines for Pharmaceutical Dosage Forms (GUI – 0029) /December, 2009.
5. Note for Guidance on Process Validation – The Europe Agency for Evaluation of Medicinal Products; CPMP/QWP/848/96; EMEA/CVMP/598/99;
6. Guide to Inspections of Oral Solid Dosage Forms pre/post Approval Issue for Development and Validation; issue (1/94); January, 2010
7. Guidelines for Process Validation of Pharmaceutical Dosage Form – Saudi Food & Drug Authority; Version 2; February, 1992.
8. Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PIC/S September, 2007.

9. ASTM E2476-09 Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture.
10. ASTM E2281-03 Standard Practice for Process and Measurement Capability Indices.
11. ASTM E2500-07 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.
12. ASTM E2709-10 Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.
13. ASTM E2474-06 Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology.