M.Pharm II (MIP202T) unit -3 PROCESS VALIDATION

Process Validation is the most important and recognised 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

FDA issued a notice announcing the availability of a guidance entitled Guideline on General Principles of Process Validation (the1987 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 "Pharmaceuticals. 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. 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 produce with a high degree of assurance of meeting all the attributes they are intended to possess.

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.
•Specificationsof 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 ofInstallation 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 effecting final or in-process product quality should be handled through the documentation system of the preventive maintenance program.

Approach to Process Validation

Process validation 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–ProcessQualification:

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 UnderstandingGenerally, 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. Thefunctionality 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 13 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 tolimitations 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 theequipment 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 productionQualification 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: 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. The decision to begin commercial distribution should be supported by data fromcommercial-scalebatches. 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 ofsamples, 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 science-and risk-based decision about the ability of 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 non conforming data. Data should not be excluded from further consideration in terms of PPQ without a documented, science-based justification. .
- 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.

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.
An ongoing program to collect and analyse product and process data that relate to product quality must be established . 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. 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.

STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION

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. Stage 2
ProcessQualification(PQ)Evaluate/ConfirmChangesProcess Performance Qualification (PPQ)Design offacilities &Qualificationof equipmentand UtilitiesChangesDistributeStage 3 Continued Process.