Process Validation

Concept of Process Validation

- Process validation is a documented activity that proves a manufacturing process can consistently produce a product of the required quality.
- It shows that the process works properly when it is operated within approved conditions.
- Process validation is not based on testing only the final product. It also involves controlling each important step of manufacturing.

Main Purpose

- Process validation ensures that every batch has the same quality, strength, purity, safety, and effectiveness.
- It reduces the possibility of manufacturing defects and batch failure.
- It helps the manufacturer identify and control sources of variation.
- It provides confidence that the process is reliable and reproducible.

Important Elements

1. **Critical Quality Attributes**
   - Critical quality attributes are the physical, chemical, biological, or microbiological properties that must remain within specified limits.
   - Examples include tablet hardness, drug content, dissolution, sterility, viscosity, and pH.
2. **Critical Process Parameters**
   - Critical process parameters are operating conditions that can affect product quality.
   - Examples include mixing time, drying temperature, compression force, filling speed, and sterilization time.
3. **In-Process Controls**
   - In-process controls are tests performed during manufacturing.
   - They help detect problems before the product reaches the final stage.
4. **Acceptance Criteria**
   - Acceptance criteria are the approved limits that results must meet.
   - The batch is considered acceptable only when the required criteria are satisfied.

Importance

- Process validation improves consistency between batches.
- It supports compliance with Good Manufacturing Practices.
- It reduces product recalls, complaints, and wastage.

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- It protects patients by ensuring that medicines are produced safely and correctly.

Process of Process Validation

- Process validation is performed through a planned series of activities.
- Each activity must be scientifically justified and properly documented.

Main Steps

1. **Process Design**
   - The manufacturing process is developed during research and product development.
   - The formulation, equipment, manufacturing method, and operating conditions are selected.
   - Possible sources of variation are identified.
2. **Identification of Critical Parameters**
   - Parameters that may affect product quality are identified.
   - These parameters are studied to understand their effect on the finished product.
3. **Preparation of Validation Protocol**
   - A written validation protocol is prepared before validation begins.
   - The protocol explains how the validation study will be performed.
4. **Qualification of Equipment and Utilities**
   - Equipment, rooms, water systems, air systems, and other utilities are qualified.
   - Qualification confirms that they are installed correctly and operate properly.
5. **Manufacture of Validation Batches**
   - Validation batches are manufactured under normal production conditions.
   - Usually, sufficient batches are studied to demonstrate process consistency.
6. **Sampling and Testing**
   - Samples are collected from different stages and locations.
   - The samples are tested according to the approved protocol.
7. **Evaluation of Results**
   - Test results are compared with the acceptance criteria.
   - Any variation, deviation, or unusual observation is investigated.
8. **Preparation of Validation Report**
   - A final report is prepared after completion of the study.

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- The report states whether the process is validated or requires further action.

9. Continuous Monitoring

- The validated process is monitored during routine production.
- Ongoing monitoring ensures that the process remains under control.

Personnel Involved

- Production personnel perform the manufacturing activities.
- Quality control personnel perform sampling and testing.
- Quality assurance personnel review and approve the protocol and report.
- Engineering personnel support equipment and utility qualification.
- Research and development personnel provide process knowledge.

Documentation of Process Validation

- Documentation provides written evidence that process validation was properly planned, performed, reviewed, and approved.
- All records must be clear, accurate, complete, and traceable.

Validation Master Plan

- The validation master plan is a high-level document that describes the overall validation program of the manufacturing facility.
- It includes the validation policy, responsibilities, schedule, systems to be validated, and documentation requirements.

Validation Protocol

- The validation protocol is an approved written plan for conducting the validation study.
- It should be prepared before the validation work begins.

Contents of a Validation Protocol

1. Title and Identification Number

- The protocol should have a clear title and a unique identification number.

2. Objective

- The objective should explain what the validation study is intended to demonstrate.

3. Scope

- The scope should describe the product, process, equipment, and manufacturing area covered by the study.

4. Responsibilities

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- The duties of production, quality control, quality assurance, and engineering departments should be stated.

5. Process Description

- The protocol should describe each important manufacturing step.

6. Critical Process Parameters

- Important parameters and their approved ranges should be listed.

7. Sampling Plan

- The sampling locations, sample quantities, sampling frequency, and sampling method should be stated.

8. Test Methods

- The tests to be performed and the approved analytical methods should be described.

9. Acceptance Criteria

- The required limits for each test and process parameter should be clearly mentioned.

10. Deviation Handling

- The procedure for recording and investigating deviations should be included.

11. Approval

- The protocol should be reviewed and approved by authorized personnel before execution.

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Validation Report

- The validation report presents the results and conclusions of the validation study.
- It should include all observations, test results, deviations, investigations, and corrective actions.

Contents of a Validation Report

- The report should contain a summary of the activities performed.
- It should include the actual results obtained during manufacturing and testing.
- It should compare the results with the approved acceptance criteria.
- It should explain all deviations and their impact on product quality.
- It should provide a clear conclusion about the validated status of the process.
- It should be signed and approved by responsible departments.

Other Supporting Documents

- Batch manufacturing records provide details of each manufacturing operation.
- Standard operating procedures explain how routine activities must be performed.

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- Equipment qualification records show that equipment is suitable for use.
- Calibration records confirm that measuring instruments are accurate.
- Analytical test reports provide laboratory results.
- Change control records document approved changes in the process.
- Deviation reports record unexpected events.
- Training records confirm that personnel are qualified to perform their duties.

Prospective Validation

- Prospective validation is performed before a new product or a modified process is used for routine commercial production.
- It is the preferred type of validation for newly developed manufacturing processes.

When Prospective Validation Is Used

- It is used when a new product is introduced.
- It is used when a new manufacturing process is developed.
- It is used when major changes are made to the formulation, equipment, process, batch size, or manufacturing site.
- It is used before routine production and market distribution begin.

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Procedure

1. **Preparation of Protocol**
   - A detailed protocol is prepared and approved before manufacturing starts.
2. **Selection of Batches**
   - Validation batches are selected to represent the proposed commercial process.
   - These batches are manufactured using approved materials, equipment, and procedures.
3. **Control of Manufacturing Conditions**
   - All important process parameters are carefully controlled.
   - Actual operating conditions are recorded throughout manufacturing.
4. **Extensive Sampling**
   - Samples are collected from different stages and locations.
   - More samples may be taken than during routine production.
5. **Testing**
   - Raw materials, in-process materials, bulk products, and finished products are tested.

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