Writing Effective Validation Protocols and Validation Master Plans

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Outline
- Regulatory Basis
- Validation Lifecycle
- Validation Plan
- Protocols
- Task Reports
- Documentation
Process Validation

The collection and evaluation of data from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.


Why Validate?

Quality cannot be tested into a process or product. It must be designed and built in. Validation assures that quality is designed and built into the process.
Regulatory Basis

§211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

US Drug GMPs

211.110 (a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall 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.
Validation – EU GMPs

5.22 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

Canadian GMPs

The documented act of demonstrating that any procedure, process and activity will consistently lead to the expected results. It includes qualification of systems and equipment.

Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
ICH Q7A

Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

EU GMPs

1.3. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

i. all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

ii. critical steps of manufacturing processes and significant changes to the process are validated;
EU GMPs

5.23. Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

Canadian GMPs

C.02.011

(I 2) All critical production processes are validated.

(I 3) Validation studies are conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions is prepared, evaluated, approved and maintained.

(I4) Changes to production processes, equipment or materials that may affect product quality and/or process reproducibility are validated prior to implementation.
## Key Elements from Regulations

- Documented evidence
- Defined process (Development Reports, SOPs, Mfg. Instructions)
- Specifications and quality attributes (Design Specs, Material Specs, Equipment Specs, Product Specs)
- Change Control
- Reports
Quality System Elements

Management
- Validation Plans
- Validation Teams
- Procedures

Resources
- Equipment Commissioning/Qualification
- Training
- Control of Suppliers (FAT, Audits)

Manufacturing Operations
- Define critical parameters and attributes
- Data Collection
- Product lifecycle
- Conformance Batches

Evaluation
- Trends
- Risk Assessment
- CAPA

Stages of Process Validation

- Stage 1 – Process Design
  - Commercial process is defined based on knowledge gained through development and scale-up activities.

- Stage 2 – Process Qualification
  - Process design is confirmed as being capable of reproducible commercial manufacturing.

- Stage 3 Continued Process Verification
  - Ongoing assurance that the process remains in a state of control.

ICH Q10 Annex 2

Technology Transfer

- Scale up and confirm (conformance batches) critical process parameters and quality attributes.
- Approved materials
- Equipment and personnel qualification
- Confirm control strategy
- SOPs and batch records prepared
Stage 2 - Process Qualification

- Design of facilities, and qualification of equipment and utilities
- Performance Qualification (PQ)

Design of Facilities & Qualification of Utilities & Equipment

- Define requirements
- Specify & Design
- Verify
- Accept & release

ASTM Standard E2500-07
Define Requirements

- Based on product and process knowledge from Design Phase.
  - Critical Quality Attributes (CQA)
  - Critical Process Parameters (CPP)
  - Variability
  - Process Control Strategy
  - Prior production experience
- Regulatory Requirements
- Company requirements

Specify & Design

- Develop system for communicating requirements to those responsible for specifying and designing.
- Focus on aspects critical to product and patient safety (Risk Assessment)
- Supplier may help in the development of specifications and design.
Specify

- Equipment materials of construction (316L stainless steel, glass-lined)
- Capacity
- Functionality (blend, mix, stir)
- Controls (automated, manual)
- Performance requirements
  - Cleaning
  - Sterilization
  - Operating environment

Verification

- Verify that specifications were met.
  - Correct materials of construction
  - Correct capacity
  - Correct functionality
  - Properly connected
  - Calibrated
- Commissioning, IQ, OQ, PQ
A Validation Program

- Validation Plan(s)
- Validation SOPs
- Protocols
- Final Reports

Attribution to Rebecca Fuller

Verification Activities & Deliverables

- Define and document (e.g., validation plan, verification plan, approved procedure, or protocol).
- Base on potential impact on product quality or patient safety.
- Additional items for consideration
  - Level of standardization (e.g., standardized equipment),
  - Complexity,
  - Configuration,
  - Customization,
  - Intended use, and
  - Criticality of the system.
Validation Plan

All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

EU Guide Annex 15

Planning

- **Validation Master Plan (VMP)** - a brief, concise summary document that clearly defines validation activities.
- **Validation Project Plan (VPP)** - a comprehensive, project-oriented action plan that describes the purpose, scope and approach for the validation activities. The plan defines in order of execution the specific tasks, responsibilities, documentation requirements, and programs that are required to achieve validation.
VMP Contents – EU Annex 15

(a) Validation policy;
(b) Organisational structure of validation activities;
(c) Summary of facilities, systems, equipment and processes to be validated;
(d) Documentation format: the format to be used for protocols and reports;
(e) Planning and scheduling;
(f) Change control;
(g) Reference to existing documents.

Validation Project Plan

Represents dynamic, project-specific validation information, often accompanied by several appendixes that change as the Project progresses.
Validation Project Plans - Contents

1. Specific purpose, size, and scope of the Project;
2. A list of all systems, processes, and/or methods to be included in the validation efforts;
3. Validation approach(es) to be followed;
4. A list of the primary and support departments expected to be involved;
5. List identifying all Project-related qualification and validation protocols;
6. List of SOPs required;
7. Training requirements;
8. Procedure for handling deviations;
9. Design Qualification, IQ, OQ, and/or PQ requirements;

Risk Management

- Use Risk Assessment to determine which systems require validation
- Use Risk Assessment to determine which systems (equipment) have direct impact on product quality.
- Define Risk Assessment process in the Validation Plan and document.
Design Qualification (DQ)

- The first element of the validation of new facilities, systems or equipment should be design qualification (DQ).

- The compliance of the design with GMP should be demonstrated and documented.

Design Qualification (DQ)/Design Reviews

- Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

- Conduct design reviews of specifications, designs, design development, and changes throughout the process lifecycle.
Design Reviews

- Verify that product and process requirements are satisfied by the design
- Verify that critical aspects of the equipment are appropriately addressed
- Verify that risks to product quality and patient safety have been identified
- Verify that unacceptable risks are mitigated by the design or other means

*Design reviews should be conducted by subject matter experts and documented.*

DQ Documentation

- A reference to all documents used to verify the design
- A description of the review process or reference to the procedure followed
- Personnel performing the review
- Conclusion
Install/Build
- Commissioning
- Factory Acceptance Testing (FAT)
- Site Acceptance Testing

Test
- **Qualify** Equipment;
- **Qualify** Personnel - Training, Practice;
- **Qualify/ Validate** Subsystems, Interconnected Systems
Protocol Requirements

A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

EU Guide Annex 15

Protocol

- Objective
- Responsibilities
- Scope (Identify the equipment, product, process, and product specifications)
- Specify the procedures and acceptance criteria for the tests to be conducted
  - Detailed, step-wise statement of actions to be taken in performing the study (or studies)
- Specify the data to be collected
- Sampling plans, relevant diagrams, or tests
Acceptance Criteria

- Qualification protocols define the specific acceptance criteria that must be met to demonstrate that the equipment or system was properly designed, installed, and operates. When commissioning activities are performed in lieu of qualification tasks, the commissioning activities should be verified during qualification rather than repeating the commissioning tasks.

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer’s recommendations.

EU Guide Annex 15
Verification/Commissioning/IQ

- Factory Acceptance Testing (FAT)
- Site Acceptance Testing (SAT)
- Verification of materials of construction
- System start-up and shakedown
- Electrical checks (voltage, resistance, continuity)
- Drawing verifications
- Code verifications
- Loop checks
- Pneumatic checks
- Calibration
- Preventative Maintenance Plans

SAT and FAT

- FAT/SAT generally consist of one or multiple checklists. Depending on the complexity of the equipment, may also include test data, measurements, etc.
- The same checklist may be used for both FAT and SAT. The only difference is WHEN and WHERE the testing is done.
- Once the equipment manufacturer has signed off on the SAT, the owner of the equipment can perform their own verification.
- Use data and information from SAT and FAT to support verification and minimize repeating tests during verification.
- FAT and SAT documents can be filed as part of the verification documentation.
Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

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Verification/Qualification (OQ)

- Verify that the equipment operates correctly through all anticipated operating ranges
- Interventions (stop, start)
- Alerts and Alarms
- Interlocks, recorders, indicators, controllers
- Power failure testing
- Sequence testing
- Challenge functions while under load comparable to routine production
- Operating ranges are capable of being held as long as would be necessary during production.
New vs. Existing Facilities & Equipment

- Equipment is independent of individual process but is important in controlling the final output.
- Verify existing facilities and equipment are qualified.
- Verify that qualified operating ranges are appropriate for new process.
- Verify that the method of operation is appropriate for new process.
- Verify that the calibration ranges encompass the new process critical process parameter ranges.
- Verify that the materials of construction for existing equipment is appropriate for new process.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.
Performance Qualification (PQ)

- Combines actual facility, utilities, equipment, and personnel with commercial manufacturing process, control procedures, and components to produce a commercial batch.
- Conformance batches

Prerequisites for PQ (1)

- Approved Master Manufacturing Instructions and applicable SOPs
- Critical Process Parameters and Critical Quality Attributes identified
- Equipment, facilities, utilities, and computerized Systems qualified
- Supporting processes that may affect process validation (e.g., cleaning, filtration, sterilization) are qualified or validated
- Compatibility studies with product-contact equipment for leachables and extractables
Prerequisites for PQ (2)

- Critical instruments calibrated
- Approved specifications for finished product and components
- In-Process Controls established and decision criteria for them documented
- Test Methods required for release of products validated
- Personnel trained and qualified

Reproducibility

- The number of PQ conformance batches prepared and data collected shall be sufficient to provide enough data for the evaluation of process reproducibility
- The number of PQ conformance batches selected must be documented and justified, based on process knowledge.
- Each batch shall meet all acceptance criteria identified in the PQ protocol
PQ Protocol (1)
- Manufacturing conditions
  - Critical process operating parameters
  - Critical process operating parameter ranges
  - Components inputs
- Data to be collected & how evaluated
- Test to be conducted & Acceptance Criteria
  - Statistical methods used to analyze data
- Sampling plan
- Confidence level based on risk analysis

PQ Protocol (2)
- Deviations & non-conforming data
  - Data should not be excluded from the PQ without documented scientific rationale
- Change management
- Status of validation of analytical methods used to measure the process including in-process and final product.
- Review and approval by appropriate departments including quality unit.
Sampling

- Number of samples taken should be adequate to provide statistical confidence of quality within and between batches.
- Sampling should be more extensive than routine production.
- Sampling Plan
  - Sampling points
  - Number of samples
  - Frequency of sampling
  - Rationale

Protocol Execution & Follow-up

- Approve protocol before execution
- Use the commercial process and SOPs under normal conditions with normal operating personnel
- Prepare a final report
Documenting Results

- Record all observations made during qualification or validation activities
- Document results so that objective pass/fail decisions can be made
- Pass/Fail check boxes alone are not acceptable; actual results should be recorded
- Expected results and acceptance criteria should be clearly defined in the protocol.

Documentation

A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies.

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Validation Task Reports

- Used for documenting and summarizing results of validation studies.
- Should use definitive statements, especially in describing objectives, conclusions, and product or process definitions.
- Collectively, project validation task reports are to support acceptability of all critical process operating parameter ranges, corresponding acceptance limits, and evidence of process robustness and reproducibility.

Task Reports - Contents

- Cross reference to protocols or other related documents
- Summary of results
- Analysis of results
- Summary and discussion of any deviations observed
- Conclusions
- Recommendations or corrective actions needed
- Attachments (e.g., raw data)
- Approved by quality unit
Release for Use

- Approved SOPs are available for the use, control, and maintenance of systems and processes
- Critical system instruments are calibrated and entered into the calibration program
- Critical system components must be entered into the Site Preventive Maintenance program
- Training requirements must be established for personnel

Key Process Validation Documents

2. Equipment Design Requirements and Specifications
3. Operators Manual, drawings, schematics, etc.
4. Risk Analyses
5. Calibration Records
6. SOP for Equipment Use, Operation, cleaning
7. Training Records
8. FAT and SAT documentation from equipment manufacturer
9. Verification Protocol(s) (DQ, IQ, OQ) and Associated Data and Reports
10. PQ protocol
11. Final Report
12. Process Monitoring Procedures (may be part of batch record, or in an SOP)
13. Change Management
Maintenance

- On-Going monitoring of Process (trends)
- Deviations
- Rejects
- Reprocess or rework
- Complaints
- Returned Products
- Annual Product Review

Document Review, Approval & Retention

- Define Purpose of Signature
  - Technically correct
  - Compliance with regulations and company policies/procedures
  - Authorization to proceed
- Quality Unit Approval
- Establish Document Management
Document Management

- Numbering
- Format
- Tracking
- Change control
- Retention
- Retrievability

Group Project
Develop a Validation Plan

- Solid oral dosage form (dry granulation)
- Process includes:
  - Blending
  - Tabletting
  - Coating
- Identify at least 3 pieces of equipment requiring verification (IQ, OQ, PQ)
- Identify the types of validation required (e.g., sterilization, cleaning, process)
- List at least 5 SOPs supporting the Process Validation

Thank you

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