SESSION 14

Documentation Requirements and Management for Validation

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Documentation Requirements and Management for Validation

I. Introduction
II. Documentation Requirements
III. Management for Validation
IV. Interactive Exercise
I. Introduction

- Regulations & Standards
- Documentation Requirements
- Management for Validation
# Regulation & standards

<table>
<thead>
<tr>
<th>Regulation &amp; Standards</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU GMP – Annex 15</td>
<td>Qualification and Validation</td>
</tr>
<tr>
<td>FDA – Guidance for Industry</td>
<td>Process Validation</td>
</tr>
<tr>
<td>GHTF Study Group 3</td>
<td>Quality Management Systems Process Validation Guidance</td>
</tr>
<tr>
<td>ISO 13485</td>
<td>Medical Devices - Quality Management Systems – Requirements for regulatory purposes</td>
</tr>
</tbody>
</table>
EU GMP Annex 15

2. DOCUMENTATION, INCLUDING VMP

2.1. **Good documentation practices** are important to support knowledge management throughout the product lifecycle.

2.2. All documents generated during qualification and validation should be **approved and authorized by appropriate personnel** as defined in the pharmaceutical quality system.

2.3. The inter-relationship between documents in **complex validation projects** should be clearly defined.

2.4. Validation protocols should be prepared which defines the **critical systems, attributes and parameters** and the **associated acceptance criteria**.

2.5. **Qualification documents** may be **combined** together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).
2.6. Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

2.7. Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.

2.8. Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report.
2.9. The review and conclusions of the validation should be reported and the results obtained summarized against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.

2.10. A formal release for the next stage in the qualification and validation process should be authorized by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.
Control of Documents

Documents required by the quality management system shall be controlled, which includes:

- Review, update and approval prior to issue
- Revision and change control
- Availability
- Prevent deterioration or loss
- Retention time
Control of Records

Records are a special type of document,

Additional requirements:

- Controls required by the quality management system must be defined, e.g. control for:
  - Identification
  - Storage,
  - Security and integrity
  - Retrieval
  - Retention time, e.g. lifetime of drug/device + 1 year
  - Disposition of records

- Protection of confidential health information

- Legible, readily identifiable (also after changes) and retrievable
Management for Validation
EU GMP Annex 15

1.1. All **qualification and validation** activities should be **planned** and take the **life cycle** of facilities, equipment, utilities, process and product into consideration.

1.2. Qualification and validation activities should only be performed by suitably **trained personnel** who follow **approved procedures**.

1.3. Qualification/validation personnel should report as defined in the **pharmaceutical quality system** although this may not necessarily be to a quality management or a quality assurance function. However, there should be appropriate quality oversight over the whole validation life cycle.

1.4. The key elements of the site qualification and validation programme should be clearly defined and documented in a **validation master plan (VMP)** or equivalent document.
Management for Validation
EU GMP Annex 15

1.5. The VMP or equivalent document should define the **qualification/validation system**

1.6. For **large and complex projects**, **planning** takes on added **importance** and separate validation plans may enhance clarity

1.7. A **quality risk management approach** should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the project phase or during commercial production, the risk assessments should be repeated, as required. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

1.8. Appropriate checks should be incorporated into qualification and validation work to ensure the **integrity of all data** obtained.
II. Documentation Requirements

- Validation documentation
- Good Documentation Practices
- Procedures, templates, plans/protocols, reports, raw data
- Paper documentation / Electronic documentation
- Validation Archive
Validation Documentation

The organization shall **document procedures for validation of processes**, including:

a) defined criteria for review and approval of the processes;
b) equipment qualification and qualification of personnel;
c) use of specific methods, procedures and acceptance criteria;
d) as appropriate, statistical techniques with rationale for sample sizes;
e) requirements for records;
f) revalidation, including criteria for revalidation;
g) approval of changes to the processes.
Validation documentation

The organization shall document procedures for the validation of the application of computer software used in production and service provision.

Such software applications shall be validated prior to initial use and, as appropriate, after changes to such software or its application.

The specific approach and activities associated with software (re)validation and shall be proportionate to the risk associated with the use of the software, including the effect on the ability of the product to conform to specifications.
FDA Process Validation Guidance

For purposes of this guidance, *process validation* is defined as the *collection and evaluation of data*, from the process design stage through commercial production, which establishes *scientific evidence* that a *process is capable* of *consistently delivering quality product*. Process validation involves a series of activities taking place over the lifecycle of the product and process.
FDA Process Validation Guidance

Stage 1: Process Development

- Defining the commercial manufacturing process based on knowledge gained through development and scale-up activities.

Stage 2: Process Qualification

- Confirming that the manufacturing process as designed 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.
Process Validation (FDA)

Stage 1
Process Design
- Product & Process Development
- FMEA, CPP/CQA DOE

Stage 2
Process Qualification
- Process monitoring
- Statistical trending
- Process Performance Qualification

Stage 3
Continued Process Verification
- Process Control
- IPC monitoring
- Batch records
- Design Facility Qualification
- Utilities/Equipment
Validation documentation

General:

– **Each stage** of Process Validation,
  • emphasis on stage 2: **Process Qualification**
– Effective **communication**
– Transparent, comprehensive and accessible
– **Scientific** (risk based and statistically sound)
– **Responsibilities** defined, e.g. **Quality** Unit
– **Deivation** reporting
– Change control
– Risk control
– Document control
Validation Lifecycle documents

Stage 1
Process Development
- Define Process:
  - URS
  - FS*, DS*
  - VMP
  - Traceability Matrix*
- Develop Process:
  - Risk Assessment
  - Engineering Study*

Stage 2
Process Qualification
- Verify Process
  - FAT*
  - SAT*
  - Supplier Assessment*
- Qualify Process
  - IQ, OQ
  - PQ, PPQ*
  - VSR*

Stage 3
Continued Process Verification
- Re-qualification
- Process Control
- Change Control

Note: Process Development activities and documents with an * are not mandatory.
Example of Validation documentation in a (Global) Organization

Corporate procedures

Divisional procedures

Divisional templates

Local site procedures (optional)

Plans/Protocols/Reports
Raw Data
Example of Validation templates and deliverables

- Validation of Processes: Company SOP
- Validation templates: electronically available (WORD)
  - Docno. Xxx-1: Validation Master Plan
  - Docno. Xxx-2: Validation Summary Report
  - Docno. Xxx-3: User Requirement Specification
  - N/A: FMEA (Equipment, Process)
  - N/A: Traceability Matrix
  - Docno. Xxx-4: IQ/OQ-protocol
  - Docno. Xxx-5: IQ/OQ-report, including raw data
  - Docno. Xxx-6: PQ protocol
  - Docno. Xxx-7: PQ Report, including raw data
Good Documentation Practices

Purpose of Documentation

- Provide detailed instructions to all personnel to insure that the product is made the same way every time.
- Record the exact conditions under which the product was manufactured
- Provide trace ability in the event of Quality problems and Recalls
Validation Documentation

- Validation provides assurance of Quality when testing 100% of the batch is not practical.
- Provides information that is supplied to the regulatory bodies in support of new product approval
Critical Concepts of Validation Documentation

- References
- Trace ability
- Identity of test the conditions
References

- SOP’s
- Batch Records
- Drawings
- Analytical Methods
- Microbiological Methods
- Compendial Methods
Trace Ability

- Manufacturing System
- Date and Time
- Reagents or test materials
- Personnel
- Measuring systems
- Raw Materials
Identity of test the conditions

- Those parameters that define the processing conditions
  - Time duration
  - Temperature
  - Pressure or Vacuum
  - Flow Rate
  - Agitator RPM
  - Differential Pressure
How to Document?

- The use of data collection forms and templates
- During Validation errors on the side of too much information
Manually Recorded Data
(written or using e.g. WORD)

- Start on a new page or form
- Identify what is being tested
- Name of the test
- Date and Time of test
- List all testing equipment
- All data collected
- Appropriate conclusions
- Signature at the end of the page or form
Electronically Recorded Data
(Recorder, paper or electronic data)

- Identity of equipment being tested
- Identity of run
- Notebook reference if applicable
- Date and time
- Identity of recording device
  - Traceable to the device calibration
- Rate at which the data was collected
- Signature and date
- Identification of various process phases
Supporting Documentation

- Batch Records
- Instrument records
- Calibration records
- Laboratory report forms
- Validation Notebooks
Paper Documentation

- **Procedures for:**
  - Document Control
  - Work flow for review and authorization
  - Authorization
  - Policies, Quality Manuals, Procedures, Work instructions
  - Documents, e.g. specifications, forms, etc.
  - Records, e.g.:
    - BMRs
    - Laboratory results
    - Qualification protocols and reports
Electronic Documentation

▪ Procedures for:
  – electronic Document Management System
  – Work flow for review and authorization
  – Electronic records
  – Electronic signatures
  – eDMS for the global organization

▪ Validation
  – eDMS must be validated
  – Validation procedures, work instructions
  – Validation protocols, reports, templates
    • Specifications, Risk Management Files, others ....
  – eDMS can be generic or dedicated to validation
III. Management for Validation

- Validation in a (Global) Organization
- Project management and Validation
- Validation in Operations
- Validation Master Plan
- Change Management and Validation
- Risk Management and Validation
- Case examples
Validation in a (global) organization

- Commitment upper management
  - Personnel Resources
    - Sufficient
    - Qualified
  - Equipment, instruments
    - Costs
- Project planning
- Organization:
  - Multidisciplinary:
  - Dedicated group
  - Subject Matter Experts
    - R&D, engineers, production, quality
Project management & Validation

- Projects
  - R&D project
  - New Facility, Utility, Equipment
  - Process
  - IT project
  - Changes

- Validation Master Plan
  - Design & Development
  - Quality by Design
  - GAMP
Validation in Operations

- Roles & Responsibilities
  - Management
  - Production
  - Engineers
  - Quality Control
  - Laboratories
  - Quality Assurance
- Site Validation Master Plan
  - Continued Process Verification
  - Requalifications
  - Changes
The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following:

1. Qualification and Validation policy;
2. The organisational structure including roles and responsibilities for qualification and validation activities;
3. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;
4. Change control and deviation management for qualification and validation;
5. Guidance on developing acceptance criteria;
6. References to existing documents;
7. The qualification and validation strategy, including requalification, where applicable.
Change Management & Validation

- Change Control Procedure

- Change Control Request
  - Description
  - Impact
  - Activities, including Validation
  - Responsibilities
  - Pre-approval
  - Quality Assurance
  - Final approval
Change Management

New process

Identify processes

Change Control

Complex process

VMP/VSRR

Specifications

Risk Assessment

Installation Operational Qualifications

Performance Qualifications

SVMP

Change

Retirement

Low impact process

High impact process

yes

no

Specification

Risk Assessment

Verification protocol/report

Medium impact process
Risk Management & Validation

- Risk Management Procedure

- Elements of risk management process:
  - Risk management plan
  - Risk analysis
  - Risk assessment
  - Risk control
  - Risk management report
  - Post production and post-market surveillance information.
Risk Management

**ICH Q9 Model**

**Initiate Risk Management Process**

**Risk Assessment**
- Risk Analysis
- Risk Evaluation

**Risk Control**
- Risk Mitigation
  - incl. elimination & avoidance
  - [Severity]
- Risk Reduction
  - [Probability]
- Risk Acceptance

**Risk Communication**

**Output/Results of the Risk Management Process**

**Review**
- (e.g. Inspections/Audits, Complaints)

- no additional risk
IV. Interactive Exercise

- Using real life examples for a project and regular production, participants will develop a Validation Master Plan.
Example: new sealer

- PQ protocol
  - Similar to Design Verification protocol
  - Risk Based Testing according to SOP

- PQ report
  - Similar to Design Verification protocol
  - Risk Based Testing according to SOP