Qualification and Validation
- an Overview -
by Dr. Ingrid Walther

Definitions

“Qualification”
Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.”
EU-GMP-Guide, Glossary

qualification
Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word “validation” is sometimes extended to incorporate the concept of qualification.

Qualification is something that has to be done additionally to GEP. It is done for those systems that have a direct impact on product quality.
ISPE Baseline Volume 5
Definitions

Qualification provides documented evidence that equipment is designed and works as it should:

**Qualification**

\[ \Rightarrow \text{equipment-related} \]

Validation provides documented evidence that processes lead to product of the desired quality and safety:

**Validation**

\[ \Rightarrow \text{process-related} \]

Example: baking oven / car

Regulatory Background

- **EU Guide to Good Manufacturing Practice**
  - Part 1, Chapters 5 + 6
  - Annex 11: Computerised Systems
  - Part 2: GMP for Active Pharmaceutical Ingredients
- **US-FDA Regulations**
  - FDA 21 CFR Parts 210 and 211: CGMP-Regulations
  - Process Validation, General Principles and Practice, January 2011
  - Guides for Inspection
- **GAMP 5 (Computerised Systems)**
- ...further national regulations and laws
Regulatory Background

Guidelines (no legal obligation, but should be followed):

- **PIC-Document PI 006-3** (Title: „Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation“, 25 September 2007)

- **ISPE Baseline, Vol. 5, Commissioning and Qualification, 2001**
  January 2008 – Draft for comments – no new version published yet!

Common understanding in all Regulations and Guidelines:

→ Qualification and Validation activities are needed to achieve the target of reliable product quality and safe products!

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Regulatory Overview

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<th>VMP</th>
<th>RA</th>
<th>DQ</th>
<th>IQ</th>
<th>OQ</th>
<th>PQ</th>
<th>PV</th>
<th>CV</th>
<th>Comp. Val.</th>
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</table>

New: URS is expected in EU-GMP-Guide!
Different interest groups in Qualification

Qualification shall be done by interdisciplinary teams – team members have different attitudes!

Basic Idea of the Guideline: GEP $\Rightarrow$ GMP

“Engineers ./. Pharmacists”
Common understanding of the GEP and GMP Regulations

→ Qualification and Validation activities are needed to achieve the target of reliable product quality and safe products!

Qualification and Validation Overview
Separate responsibilities and target!

Why does the split between GEP and GMP make sense?

- Pharmaceutical responsibility lies with a pharmacist: He / she is obliged to ensure that all quality relevant process parameters and conditions are under control.

- Approval of Qualification documents → pharmacist / biotechnologist may not be able to evaluate ALL technical requirements.

- Technical equipment is often very complex → Focusing on GMP-aspects in Qualification allows the view on the essential.

- In case of authority inspections: → GMP requirements must be fulfilled and THIS must be documented (the amount of paper does NOT count!)

- In production routine: → Formal Change Control is only required for GMP-relevant aspects.

- Reduce documentation effort by separating GEP from GMP!
What is the basis of ASTM E2500-7?

- „Risk- und science-based approach“ – ICH Q9
  - Risk evaluations are based on technical expertise and always target at patient safety
  - Level of effort, formalty and documentation of the QR process must be commensurate with the risk for the patient
- critical / relevant aspects of a system must be understood
- „Quality by Design“
- GEP in this sense serves GMP
- Subject Matter Experts (SMEs) participate in the entire process
- Supplier documentation is available
- continuous improvement process
- reduced qualification effort without compromising patient safety!
1. Step in Risk Assessment: Impact Assessment = Separation into GEP and GMP

- identify critical systems
- explain, why non-critical systems have been identified as such
  - non-critical systems are under GEP-control
- for critical systems: explain the scope of qualification

"Impact Spectrum" (ISPE)

- Parking facilities
- Elevators
- Office Air Conditioner
- Chilled Water
- Production Air Conditioner
- Building Management System
- Autoclave
- Purified Water System

ISPE Baseline: Figure 2-1

May 2015, page 15
Complex structure of Qualification and Validation work and flow of information in projects!

Organization required

The Validation Master Plan

Validation work needs to be organised!
Implement a „Validation Project Manual“

⇒ the Validation Master Plan

VMP

WHO-Requirement
4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.
The Validation Master Plan Annex 15 EU-GMP-Guide

The VMP or equivalent document should define the qualification validation system and include or reference information on at least the following:

i. Qualification and Validation policy;

ii. The organisational structure including roles and responsibilities for qualification and validation activities;

iii. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;
   - equipment to be qualified
   - processes to be validated
   ⇒ summarised and compiled in a matrix format

iv. Change control and deviation management for qualification and validation;

v. Guidance on developing acceptance criteria;
   ⇒ will be presented in the presentation on Risk Analyses

vi. References to existing documents;

vii. The qualification and validation strategy, including requalification, where applicable.

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  ⇒ will be presented in the presentation on Risk Analyses
- References to existing documents;
- The qualification and validation strategy, including requalification, where applicable.

Everything described in the VMP / QP / VP must be done!
The Validation Master Plan

i. Qualification and Validation policy (firm’s policy, general description), e.g.:
   - Targets
   - Validity (for which Project - how long?)
   - Basic Guidelines
     (WHO, EU- and US-FDA-cGMP-Guidelines)
   - Information about general GMP-interpretation
   - GEP issues

The Validation Master Plan

ii. organisational structure of validation activities
   - Organisational structure / organisational charts
   - Tasks in the project: approve, check or prepare the documents
   - Names of responsible personnel
   - CVs / background
   - Matrix of responsibility (Task, function: responsible, carry out the work, support the work)
   - Description of the relationship between commissioning and qualification
   - project schedule / reference to the project schedule
   - capacities / staffing
   - training needs
The Validation Master Plan

iii. **Summary of the facilities, equipment, systems, processes on site and the qualification and validation status**

- Building
- Rooms
- Production equipment
- Media supply
- Processes
- Methods

Detailed description provides good overview  
⇒ High effort for changes during the project!  
Impact Assessment process has to be described!

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1. Step in Risk Assessment:  
**Impact Assessment = Separation into GEP and GMP**

```
identify systems

develop system boundaries

Impact on product qualify?
  yes
  no

Link to DI-System?
  yes
  no

„No Impact“ System

Commissioning

„Direct Impact“ System

„Indirect Impact“ System

develop supporting rationale

GEP

GEP and GMP

```

according to: ISPE Baseline Guide on Commissioning and Qualification, 2000
iii. summary of facilities, systems, equipment and processed to be validated

Example for “supporting rationale” for indirect and no impact systems

<table>
<thead>
<tr>
<th>Equipment System</th>
<th>Explanation</th>
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</thead>
<tbody>
<tr>
<td>City water</td>
<td>Only raw material for pharmaceutical water; quality defined according to national regulations</td>
</tr>
<tr>
<td>Chilled water</td>
<td>Only for indirect cooling; no direct contact with product or product contacts parts; direct measurement of product temperature where necessary</td>
</tr>
<tr>
<td>Iced water</td>
<td>Only for indirect cooling; no direct contact with product or product contacts parts; direct measurement of product temperature where necessary</td>
</tr>
<tr>
<td>Plant steam</td>
<td>Only for indirect heating; no direct contact with product or product contacts parts; direct measurement of product temperature where necessary</td>
</tr>
<tr>
<td>Humidification for HVAC system</td>
<td>Requirements of steam to be specified during RA ‘HVAC system’</td>
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<tr>
<td>Waste water system</td>
<td>Not in contact with production equipment; risk for contamination of equipment will be covered during qualification of production equipment and rooms</td>
</tr>
<tr>
<td>Electrical power supply / UPS - system</td>
<td>No direct influence on product quality; reaction on failure of power supply will be checked during qualification of equipment</td>
</tr>
<tr>
<td>Building Management System; IT – systems and telecommunication</td>
<td>GMP relevant data will not be handled by these systems, only for system controls; GMP relevant data will be covered by separate systems</td>
</tr>
<tr>
<td>HVAC system for packaging area</td>
<td>To be decided during Risk analysis ‘HVAC system’</td>
</tr>
</tbody>
</table>

The Validation Master Plan

iii. List of systems and processes, e.g.:

Description of Validation Activities during the Phases:
- Process transfer (from existing to new plant)
- Process Optimisation
- Cleaning Validation
- Process Validation

Similar to Qualification:
- Operational Organisation (Organisational charts, tasks…)
- Processes to be validated (Matrix)
- Document format
## The Validation Master Plan

### Qualification Matrix – Result of the Impact Assessment

<table>
<thead>
<tr>
<th>System / Equipment</th>
<th>RA</th>
<th>DQ</th>
<th>IQ</th>
<th>IOQ</th>
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<td>Diluent tank</td>
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</tbody>
</table>

**Example to show possible structure!**

## The Validation Master Plan

### v. Change control and deviation management for qualification and validation:

- Reference to existing procedure (SOP?)
- Definition of new and project specific process
  - Define project stage for start of CC
  - Who has to inform about changes?
  - Who has to approve the changes?
- Deviation management may be different from routine process because deviations during qualification and validation do not impact on patient safety!

⇒ **Simple process for quick decisions!**
vi. Reference to existing documents

- SOPs
- List of abbreviations
- Definitions
- Literature, Codes and Standards, Guidelines
- Attachments (Layouts, P&IDs)

vi. The qualification and validation strategy, including requalification, where applicable.

- frequency of requalification
- when to revalidate

Further possible and common subjects:

- general acceptance criteria
- how to choose and involve suppliers
- training of personnel
- how to carry out Risk Analyses
- documentation format
  - document structure
  - numbering system
  - example document
  - way from protocol → report
The Validation Master Plan

The VMP

• overview
• official GMP-document
• is required due to regulations
• available to all project team members
• read and recognised by all project team members
• importance for equipment suppliers

The VMP is a summary document:

⇒ brief, concise and clear!

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