Supplementary Training Modules on Good Manufacturing Practice

Validation

WHO Technical Report Series, No. 937, 2006. Annex 4.

World Health Organization

Validation

- **Part 1. General overview on qualification and validation**
- Part 2. Qualification of HVAC and water systems
- Part 3. Cleaning validation
- Part 4. Analytical method validation
- Part 5. Computerized system validation
- Part 6. Qualification of systems and equipment
- Part 7. Non sterile product process validation

Supplementary Training Modules on Good Manufacturing Practice

Qualification and Validation

Part 1

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Validation

Objectives

- Introduction and scope: Qualification and validation
- Associated activities including:
  - *calibration and change control*
- Documentation
  - *Validation Master Plan; Protocols and reports*
- Personnel

Validation

Introduction

- Validation is an essential part of GMP, and an element of QA
- Basic principles include:
  - *Safety, quality and efficacy of products*
  - *Built into the product – as it cannot be "inspected or tested into a product"*
  - *Critical steps in the process need to be validated*
- Need for confidence that the product will consistently meet predetermined specifications and attributes

1.

Introduction (2)

Documentation associated with validation:

- SOPs
- Specifications
- Validation Master Plan (VMP)
- Qualification protocols and reports
- Validation protocols and reports

These will be discussed later

1.

Validation

Introduction (3)

Validation work requires considerable resources such as:

- Time:
  - *work is subject to rigorous time schedules*
- Money:
  - *may need specialized personnel and expensive technology*
- People:
  - *collaboration of experts from various disciplines*
  - *a multidisciplinary team, comprising quality assurance, engineering, production, quality control (other disciplines, depending on the product and process to be validated)*

1.

Validation

Scope

- WHO guideline focuses mainly on the overall concept of validation
- It serves as general guidance only
- Principles may be useful:
  - *in production and control of active pharmaceutical ingredients (APIs) and finished pharmaceutical products*
- Validation of specific processes and products (e.g. sterile product manufacture) requires much more consideration and a detailed approach beyond the scope of the guideline

2.1

Validation

Scope

- Many factors affecting the different types of validation
- Manufacturers should plan validation to ensure
  - *regulatory compliance and*
  - *product quality, safety and consistency*
- The general text in the guideline (part 1 of presentation) may be applied to validation and qualification of:
  - *premises, equipment, utilities and systems*
  - *processes and procedures*
- More specific principles addressed in the appendices (parts 2 to 7)
- Semi-automatic or fully automatic clean-in-place (CIP) systems and other special cases should be treated separately.

2.2 – 2.4

Validation

Glossary…

See definitions in the guideline, e.g.

- *Calibration:* The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (for example, weight, temperature and pH), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

3.

Validation

Qualification and Validation

- Qualification and validation are essentially components of the same concept
- The term *qualification* is normally used for equipment, utilities and systems
- The term *validation* is normally used for processes
- In this sense, qualification is part of validation

4.

Validation

Validation: Approaches to validation

- Two basic approaches:
  1. Evidence obtained through testing (prospective and concurrent validation), and
  2. Analysis of accumulated (historical) data (retrospective validation)
- Whenever possible, prospective validation is preferred.
- Retrospective validation is no longer encouraged
- Retrospective validation is not applicable to sterile products

5.1.1

Validation

Validation: Approaches to validation (2)

- Both prospective and concurrent validation, may include:
  - *extensive product testing, which may involve extensive sample testing (with the estimation of confidence limits for individual results) and the demonstration of intra- and inter-batch homogeneity;*
  - *simulation process trials;*
  - *challenge/worst case tests, which determine the robustness of the process; and*
  - *control of process parameters being monitored during normal production runs to obtain additional information on the reliability of the process.*

5.1.2

Validation

Scope of validation

- Validation requires an appropriate and sufficient infrastructure including:
  - *organization, documentation, personnel and finances*
- Involvement of management and quality assurance personnel
- Personnel with appropriate qualifications and experience
- Extensive preparation and planning before validation is performed
- A specific programme for validation activities in place
- Validation done in a structured way according to documentation including procedures and protocols.

5.2.1 – 5.2.4

Validation

Scope of validation (2)

- Validation should be performed:
  - *for new premises, equipment, utilities and systems, and processes and procedures;*
  - *at periodic intervals; and*
  - *when major changes have been made.*
- Can periodic revalidation/requalification be substituted?
- Validation in accordance with written protocols.
- A written report on the outcome to be produced.
- Validation over a period of time, e.g.
  - *at least three consecutive batches (full production scale) to demonstrate consistency. (Worst case situations should be considered.)*

5.2.5 – 5.2.7

Validation

Scope of validation (3)

- Distinction between in-process controls and validation
  - *In-process tests (performed during the manufacture of each batch; their objective is to monitor the process continuously)*
- Demonstrate suitability for new manufacturing formula or method
- Process, materials and equipment to prove consistent yield of a product of the required quality
- Manufacturers to identify what validation work is needed
- Significant changes (facilities, equipment, processes) - should be validated
- Risk assessment approach used to determine the scope and extent of validation needed

5.2.8 – 5.2.10

Validation

Qualification

- Qualification should be completed before process validation is performed
- A logical, systematic process followed
- Start from the design phase of the premises, equipment, utilities and equipment
- Major equipment and critical utilities and systems normally require IQ, OQ and PQ

6.1, 6.3

Validation

Qualification (2)

- Some equipment, utilities and systems require only IQ and OQ as the correct operation could be considered to be a sufficient indicator of its performance
- The equipment, utility and system should then be maintained, monitored and calibrated according to a regular schedule

6.2

Validation

Calibration and verification

- Performed at regular intervals
- Responsible personnel with appropriate qualifications and training
- Calibration programme available including information, e.g.
  - *calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when necessary*

7.1–7.3

Validation

Calibration and verification (2)

- Traceability to standards used
  - *(e.g. national, regional or international standards)*
- Calibrated equipment, instruments and other devices to be labelled, coded or otherwise identified
  - *indicate status of calibration and recalibration due date*
- If not used for a certain period of time
  - *function and calibration status to be verified*
  - *shown to be satisfactory before use*

7.4 – 7.6

Validation

- Suitable labels indicate calibration status
- Traceability, e.g.
  - *Instrument*
  - *Date*
  - *Personnel*
  - *Standard*
  - *Range and conditions as appropriate*

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Validation

Documentation

- Validation Master Plan (VMP)
- Protocols
- Reports
- SOPs
- Others?

Validation

Validation Master Plan (VMP)

- Contains key elements of the validation programme.
- Concise, clear, contain at least:
  - *a validation policy*
  - *organizational structure of validation activities*
  - *summary of facilities, systems, equipment and processes validated (and to be validated)*
  - *documentation format (e.g. protocol and report)*
  - *planning and scheduling*
  - *change control and references to existing documents*

8.

Validation

Qualification and validation protocols

- Describe the study to be performed and include as a minimum:
  - *the objectives of the study*
  - *the site of the study*
  - *the responsible personnel*
  - *description of SOPs to be followed*
  - *equipment to be used*
  - *standards and criteria for the products and processes*
  - *the type of validation*

9.1 – 9.2

Validation

Qualification and validation protocols (2)

- Protocol contents (2):
  - *the processes and/or parameters*
  - *sampling, testing and monitoring requirements*
  - *predetermined acceptance criteria for drawing conclusions*
- Description (how results will be analysed)
- Protocol approved prior to use - changes approved prior to implementation of the change

9.2 – 9.4

Validation

Qualification and validation reports

- Written reports on the qualification and validation performed
- Reflect protocols followed and include at least:
  - *title and objective of the study; reference to the protocol; details of material*
  - *equipment, programmes and cycles used; procedures and test methods*
- Results evaluated, analysed and compared against the pre-determined acceptance criteria

10.1 – 10.3

Validation

Qualification and validation reports (2)

- The results should meet the acceptance criteria
- Deviations and out-of-limit results should be investigated. If these are accepted, this should be justified. Where necessary further studies should be performed
- Responsible departments and QA to approve completed report, including the conclusion

10.3 – 10.7

Validation

Qualification stages

- There are four stages of qualification:
  - *design qualification (DQ);*
  - *installation qualification (IQ);*
  - *operational qualification (OQ); and*
  - *performance qualification (PQ).*
- All SOPs for operation, maintenance and calibration should be prepared during qualification
- Training provided and records maintained

11.1 – 11.3

Validation

Design qualification: Provides documented evidence that the design specifications were met

Installation qualification: Provides documented evidence that the installation was complete and satisfactory

- During IQ:
  - *Purchase specifications, drawings, manuals, spare parts lists and vendor details should be verified*
  - *Control and measuring devices should be calibrated*

11.4 – 11.7

Validation

Operational qualification: Provides documented evidence that utilities, systems or equipment and all its components operate in accordance with operational specifications

- Demonstrate satisfactory operation over the normal operating range as well as at the limits of its operating conditions (including worst case conditions)
- Operation controls, alarms, switches, displays and other operational components should be tested

11.8 – 11.11

Validation

Performance qualification: Provides documented evidence that utilities, systems or equipment and all its components can consistently perform in accordance with the specifications under routine use

- Test results collected over a suitable period of time to prove consistency

11.12 – 11.13

Validation

Requalification

- In accordance with a defined schedule
- Frequency to be determined (e.g. on the basis of factors such as the analysis of results relating to calibration, verification and maintenance)
- Periodic and after changes
  - *e.g. changes to utilities, systems, equipment; maintenance work; and movement*
- Part of change control procedure

11.14 – 11. 16

Validation

Revalidation

- Processes and procedures - to ensure that they remain capable of achieving the intended results
- Periodic revalidation, as well as revalidation after changes
- In accordance with a defined schedule
- Frequency and extent determined using a risk-based approach together with a review of historical data

11.17 – 11.20

Validation

Periodic revalidation

- To assess process changes that may occur gradually over a period of time, or because of wear of equipment
- Consideration given to:
  - *master formulae and specifications*
  - *SOPs*
  - *records (e.g. of calibration, maintenance and cleaning)*
  - *analytical methods*

11.21 – 11.22

Validation

Revalidation after change

- After change that could have an effect on the process, procedure, quality of the product and/or the product characteristics. (Considered as part of the change control procedure.)
- Extent depends on the nature and significance of the change(s)
- Changes should not adversely affect product quality or process characteristics

11.23 – 11.25

Validation

Changes requiring revalidation should be defined in the validation plan and may include:

- changes in starting materials
- change of starting material manufacturer
- transfer of processes to a different site
- changes of primary packaging material
- changes in the manufacturing process
- changes in the equipment
- production area and support system changes
- appearance of negative quality trends
- appearance of new findings based on current knowledge
- support system changes

- e.g. including physical properties, such as density, viscosity or particle size distribution that may affect the process or product
- e.g. change of facilities and installations which influence the process
- e.g. substituting plastic for glass
- e.g. mixing times or drying temperatures
- e.g. addition of automatic detection systems, installation of new equipment, major revisions to machinery or apparatus and breakdowns
- e.g. rearrangement of areas, or a new water treatment method
- e.g. new technology

11.26

Validation

Revalidation after change (continuation)

- Changes of equipment which involve the replacement of equipment on a “like-for-like” basis would not normally require a revalidation
- For example, installation of a new centrifugal pump to replace an older model would not necessarily require revalidation

11.26

Validation

Change control

- SOP followed - as changes may have an impact on a qualified utility, system or piece of equipment, and a validated process and/or procedure
- Describe the actions to be taken, including the need for and extent of qualification or validation
- Changes should be formally requested, documented and approved before implementation
- Records should be maintained

12.1 – 12.3

Validation

Personnel

- Demonstrate that personnel are appropriately qualified, where relevant
- These include for example:
  - *laboratory analysts;*
  - *personnel following critical procedures;*
  - *personnel doing data entry in computerized systems; and*
  - *risk assessors.*

13.1 – 13.2