Supplementary Training Modules on Good Manufacturing Practice

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
Non sterile product process validation

Part 7

Objectives

To discuss non-sterile process validation, focusing on:

- General recommendations
- Prospective validation
- Concurrent validation
- Retrospective validation
- Revalidation
- Change control
Validation

Principle

- Documented evidence: Process is capable of *reliably and repeatedly* rendering a product of the required quality
- Planning, organizing and performing process validation
- Process validation protocols
- Data collected and reviewed against predetermined acceptance criteria – recorded in validation report
Scope

- General aspects of process validation for the manufacture of non-sterile finished products
- Should cover at least the critical steps and parameters, i.e. those that may have an impact on the quality of the product
Validation

General

- Policy and approach to be documented
  - *e.g. in a validation master plan – including critical process steps and parameters*

- Process validation to start after qualification of support systems and equipment is completed

- In some cases - concurrently with PQ
  - *Normally completed prior to the manufacture of finished product that is intended for sale (prospective validation)*
  - *During routine production (concurrent validation)*
Prospective validation

- Critical factors or parameters possibly affecting finished product quality to be identified during product development
  - Breakdown of production process into individual steps
  - Evaluate each step

- Determine the criticality of these factors through a “worst-case” challenge where possible
Prospective validation protocol should include:

- *description of the process and of the experiment*
- *equipment and/or facilities to be used including measuring or recording equipment (and its calibration status)*
- *variables to be monitored*
- *details of the samples to be taken*
- *product performance characteristics/attributes to be monitored, together with the test methods*
- *acceptable limits and time schedules*
- *personnel responsibilities*
- *details of methods for recording and evaluating results, including statistical analysis*
Validation

Approach:

- Equipment, production environment and analytical testing methods – already fully validated
  - e.g. during installation qualification and operational qualification

- Appropriately trained personnel and batch manufacturing documentation prepared after these critical parameters have been identified, and machine settings, component specifications and environmental conditions have been determined and specified
Approach (2)

- A number of batches of the final product should then be produced

- What number of batches?
  - sufficient to allow the normal extent of variation and trends to be established and
  - to provide sufficient data for evaluation

- Data within the finally agreed parameters
  - from at least three consecutive batches, giving product of the desired quality may be considered acceptable
Approach (3)

- Same size batches
- Full-scale production batch size
  - If not possible – reduced batch size considered
  - Validity of assumptions made should be demonstrated when full-scale production starts
- Extensive testing at various stages in the manufacturing process
  - Including on the final product and its package
Setting Limits: may include

- Marketing authorization limits
  - stability specifications
- Release specification
- Validation limits
Validation

Determining critical control point: example of a tablet granulation process

- Particle size distribution of the active(s)
- Blending time for the powder
- Granulating time and speed; amount of granulating fluid and binder concentration
- Drying time — final moisture content, granule particle size distribution
- Granule active content and homogeneity, blending time of external phase
Validation

Determining critical control points

<table>
<thead>
<tr>
<th>Process step</th>
<th>Operation</th>
<th>IQ/OQ/PQ requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Measure humidity with humidity meter</td>
<td>IQ/OQ calibration</td>
</tr>
<tr>
<td>XIV</td>
<td>Weigh granules - balance</td>
<td>IQ/OQ calibration</td>
</tr>
<tr>
<td>XV Sponge 1/2</td>
<td>Alve with alve type 1</td>
<td>Training records for technician</td>
</tr>
<tr>
<td>XVI Blend 1/2 granulate</td>
<td>Mixer (speed 1, 1 minute)</td>
<td>Instrument operation, cleaning, calibration and maintenance</td>
</tr>
<tr>
<td>XVI Blend 2 with 3/4 granulate</td>
<td>Mixer (speed 1, 10 seconds)</td>
<td>Clean equipment, update records, validate equipment</td>
</tr>
<tr>
<td>XVIII</td>
<td>Weigh granules</td>
<td>Clean equipment, update records, validate equipment</td>
</tr>
</tbody>
</table>

World Health Organization
Solid dose mixing (1)

- Homogeneity in blending – the key to quality!
- Sampling strategy
- Sample site, label, container
- Storage
- Transport
- Sample thief
Validation

Solid dose mixing (2)

- In situ analysis

- Methods of analysis

- Statistical analysis
  - inter-batch
  - intra-batch
  - within-sample-site
Validation

Tablet compression variables

- Fill volume
- Pre- and compression force
- Turntable speed
- Dwell time
- Granule size and feed
- Ejection force, lubrication
Validation

Tablet compression parameters

- Mass
- Hardness
- Moisture
- Friability
- Disintegration
- Dissolution
- Thickness
Validation

Tablet coating variables

- Spray rate
- Inlet and outlet air temp
- Coating weight
Results in the report that includes, e.g.

- *process description including details of critical steps*
- *detailed summary of the results obtained from in-process and final testing, including data from failed tests*
- *raw data or reference to these*
- *any work done in addition to that specified in the protocol*
- *any deviations from the protocol with an explanation*
- *a review and comparison of the results with those expected*
- *formal acceptance or rejection of the work by the team or persons designated as being responsible for the validation, after completion of any corrective action or repeated work*
Conclusion and recommendation:

- Made on the basis of the results obtained
- Incorporated into the batch manufacturing and batch packaging documents and/or standard operating procedures (SOPs) for routine use
- Limits and frequencies of testing and monitoring should be specified. Actions in case of OOL

If validation batches are to be sold or supplied:

- manufactured under GMP conditions
- Compliance with the marketing authorization

Concurrent validation

- May be appropriate to validate a process during routine production
  - Can you give any examples?
- Decision made by appropriately authorized personnel
- Premises and equipment previously qualified
- Done as per validation protocol; and results documented in the validation report
Retrospective validation

- Comprehensive review of historical data
- Requires a protocol and a report with a conclusion and a recommendation
- Not the preferred method of validation, and used in exceptional cases only:
  - e.g. for well-established processes
- Inappropriate in case of changes (e.g. equipment)
Retrospective validation (2)

- Sufficient data to be reviewed to provide a statistically significant conclusion

*Satisfactory results of retrospective validation only serve as an indication that the process does not need to be subjected to validation in the immediate future*
Validation

Revalidation

- Standard processes (with conventional equipment)
  - *data review similar to retrospective validation*

- Points to be considered:
  - *the occurrence of any changes in the master formula, methods, starting material manufacturer, equipment and/or instruments*
  - *calibrations and preventive maintenance carried out*
  - *standard operating procedures (SOPs)*
  - *cleaning and hygiene programme*
In case of changes, consider the change and its impact on the process validation.

Examples of changes (requiring revalidation):
- manufacturing process (e.g. mixing times, drying temperatures)
- equipment (e.g. addition of automatic detection systems)
- production area and support system changes
- transfer of processes to another site
- unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data)
Validation

Non sterile products

- Suspensions
- Syrups
- Capsules
- Tablets
- Creams
- Ointments
Validation

Non sterile products

- List some of the key parameters to be considered in the process validation of the dosage forms mentioned
Validation

SUMMARY

Prospective validation
Validation

SUMMARY

- Prospective validation
- Concurrent validation
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Validation

SUMMARY

Prospective validation
Concurrent validation
Retrospective validation
Revalidation

World Health Organization
Validation

SUMMARY

Prospective validation

Concurrent validation

Retrospective validation

Revalidation

Change control
You are given a tablet manufacturing flow chart to study

List the critical steps that are required to be validated

List the critical equipment required to be qualified

Identify the variables and construct a table as directed

- Dry active to <4% moisture before dispensing
- Weigh (control Relative Humidity)
- Blend & Wet Granulate
  - speed 200-300rpm
  - Water 5 - 6 litres
  - Time dependent on ammeter reading
- Sieve mesh 10
- Fluid bed drier
  - Inlet air temperature 55-75°C
  - Time 2 - 4 hours
- Sieve mesh 10
  - Not time dependent
- Blend with lubricant
  - 5-10 minutes in cube blender
- Compress
  - Speed: 300 - 400 rpm
  - Compaction force 12-20 tonnes
- Prepare coating solution
  - use within 24 hours of preparation
  - Stir while coating
- Coat
  - Spray rate 1 - 2L/hour
  - Speed 40 - 50 rpm
  - Drying temperature 55 - 70°C