Process Validation

By

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The most common questions in validation

- What is the process validation?
- Why do we have to perform process validation?
- Who will get involved in the validation?
- What do we have to do for the validation?
- How many trials do we have to do?
- What is the validation protocol?
- What is the sampling plan?
- What is the acceptance criteria?
Process Validation

Process Validation is:

- An approach for verifying process performance
- An approach for demonstrating that the process is consistent, reproducible and controlled
- Documented
Process Validation

It is preferred that the batches made should be the same size as the intended batch size for full scale production. This may not always be practical due to a shortage of available starting materials and in such cases the effect of the reduced batch size should be considered in the design of the protocol. When full scale production starts, the validity of any assumptions made should be demonstrated.
Process Validation

- Process validation is establishing documented evidence which demonstrate that the manufacturing process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

  New Product <=> Trial Batch, Development Batch
  Transferred Product <=> Products produced at the sending site
  Revalidation Product <=> The original product before revalidation
Process Validation

Type of Process Validation

- Retrospective
  - Based on accumulated historical production, testing and control data
  - Generally requires data from 10-30 batches
  - Use data only from batches made by the same process

- Prospective
  - Conducted prior to market the product

- Concurrent
  - Based on information generated during actual implementation of the process (each batch will be released separately)
Re-validation

Re-validation provides the evidence that changes in a process and/or the process environment, introduced either intentionally or unintentionally, do not adversely affect process characteristics and product quality.

- There are two basic categories of Re-validation:
  - Re-validation in cases of known change (including transfer of processes from one company to another or from one site to another),
  - Periodic Re-validation carried out at scheduled intervals.
Re-validation in cases of known change

Changes that are likely to require Re-validation are as follows:

- Changes of raw materials (physical properties such as density, viscosity, particle size distribution may affect the process or product)
- Change of starting material manufacturer
- Changes of packaging material (e.g. substituting plastic for glass)
- Changes in the process (e.g. mixing times, drying temperatures)
- Changes in the equipment (e.g. addition of automatic detection systems).
Re-validation in cases of known change

Changes that are likely to require Re-validation are as follows:

- Changes of equipment which involve the replacement of equipment on a 'like for like' basis would not normally require a Revalidation,
- Production area and support system changes (e.g. rearrangement of areas, new water treatment method),
- Transfer of processes to another site,
- Unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).
Change Control

Change control is an important element in any Quality Assurance system.

- Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or support system operation.
Periodic Re-validation

The following points should also be considered:

- The occurrence of any changes in the master formula, methods or starting material manufacturer
- Equipment calibrations carried out according to the established program
- Preventative maintenance carried out according to the program
- Standard operating procedures (SOPs) up to date and being followed
- Cleaning and hygiene program still appropriate,
- Unplanned changes or maintenance to equipment or instruments.
Validation of Liquid Solution and Suspension

Solution:
A homogenous liquid system in which the active ingredient is completely solubilized

Suspension:
A heterogeneous liquid system consisting of two phases. The continuous or external phase is generally a liquid or semisolid, and the dispersed or internal phase is made up of the particulate matter that is essentially insoluble in, but dispersed throughout the continuous phase.
Validation of Liquid Solution and Suspension

Validation Team: Production, QC, QA, Engineer, Planner

- To prepare the validation protocol
- Verify the calibration and maintenance status of equipment
- Verify change control
- Schedule the validation activities
- Training production operators
- Conduct validation study
- Monitor the critical steps in manufacturing process
- Assure that the approved testing standard is being used
- Evaluate all test results,
- Prepare the validation report.
Validation of Liquid Solution and Suspension

Pre-validation Requirements:

- Preventive Maintenance for Facilities and Utilities
- Calibration of Equipment
- Cleaning Validation
- Equipment Qualification
- Raw Materials/Components/Test Methods
- Process Justification
- Change Control
- Training operators

All must be proven suitable and reliable for the manufacturing process before the process can be validated.
Validation of Liquid Solution and Suspension

Process Justification:

- To identify critical process steps & process parameters
- For Suspension, settling studies to determine the acceptable duration that a bulk may sit idle after mixing
- Anti-microbial preservative efficacy testing
- Uniformity of dosage assay result for the fill containers for suspension.
- To determine the minimum product volume cut-off point during transfer to filling for suspension using agitated bulk tank
Validation of Liquid Solution and Suspension

Validation Protocol

A document stating how validation will be conducted, including test parameters, product characteristics, production equipment to be used and decision points on what constitutes acceptable test results.
Validation of Liquid Solution and Suspension

Validation Protocol should contain:

- Title Page, Review/Approval Page
- Purpose and Overview
- Equipment List
- Ingredients and Component List
- Process Flow Diagram and Description
- Equipment Critical Process Parameter
- Process Validation Sampling Plan/Testing Requirements
- Acceptance Criteria
- Stability Requirements
- Process for evaluation of any deviations occurring during validation
# PV Protocol Requirements

<table>
<thead>
<tr>
<th>PV Rationale</th>
<th>PV Protocol Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical steps are validated</td>
<td>Define critical steps to validate</td>
</tr>
<tr>
<td>Critical process parameters and limits must be identified</td>
<td>Define critical process parameters and their limits</td>
</tr>
<tr>
<td>The process when operated within the process limits performs as intended</td>
<td>Demonstrate that critical product data meet the specifications (an experiment)</td>
</tr>
<tr>
<td>The process does perform consistently as intended</td>
<td>Demonstrate that critical product data consistently meet the specifications</td>
</tr>
</tbody>
</table>
Critical Parameters
## Critical Parameters – Liquids

### Critical Steps

<table>
<thead>
<tr>
<th>Critical Steps</th>
<th>Critical Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing</td>
<td>Mixing time</td>
</tr>
<tr>
<td></td>
<td>Mixing speed</td>
</tr>
<tr>
<td></td>
<td>Mixing volume (batch size)</td>
</tr>
<tr>
<td></td>
<td>Stirrer angle (IQ)</td>
</tr>
<tr>
<td></td>
<td>Turbulent mixing (no vortex, non-vigorous, no air bubbles)</td>
</tr>
</tbody>
</table>
Validation of Liquid Solution and Suspension

Equipment Critical Process Parameter:
- Mixing Speed
- Homogenizing Speed
- Mixing Time
- Heating / Cooling Time
- Pumping Speed (Flow Rate)

Critical Manufacturing Step
- Dissolving Step
- Melting Step
- Homogenizing Step
Validation of Liquid Solution and Suspension

Critical Processing Parameter

- Mixing Speed
- Mixing Time
- Cooling Time

- Homogenizing Speed
- Homogenizing Time
Validation of Liquid Solution and Suspension

Critical Processing Steps

Dissolved Active Ingredient → Filtration → pH Adjustment → Final Mixing
Validation of Liquid Solution and Suspension

Acceptance Criteria

- Dissolved Active Ingredient → Clear Solution
- Filtration → No Residue on filter
- pH Adjustment → pH within specification
- Final Mixing → pH, Vicosmometer, Appearance, Assay Content
Validation of Liquid Solution and Suspension

Number of Validation Trials
For New Product, Product Transfer or Having Major Changes

- Generally at least three consecutive successful batches are required
  - One Right = Accident
  - Two Right = Coincidence
  - Three Right = Validated
Validation of Liquid Solution and Suspension

Product Testing

- Validation testing of bulk and F/G must be based on testing standard release criteria and in-process testing criteria.
- Typically involves non-routine sampling/testing throughout the entire process, with special emphasis on critical process parameters.
- Routine QC release testing should be performed on a routine sample. These samples should be taken separately from the validation samples.
Validation of Liquid Solution and Suspension

Validation Batch:

- New product and product transfer, Prospective validation is required
- Manufacturing Process, Formula, Equipment and Batch Size have to be fixed during the validation trials.
- Batch Size should be the same size as commercial production batch
- The batch size must be fixed for production. However, it can be changed up to 10% with the on-going study by using the same equipment.
- Different lots but same manufacturer of active ingredients should be used during validation trials.
Validation Batch: (Continued)
Matrixing by batch size is permitted if using the same equipment.

• 2 batches of the largest batch size + 1 batch of the smallest batch size

• For Suspension, the difference in batch size must not greater than 50% of the smallest batch size. (2 batches of 750 L + 1 batch of 500 L)

• For Solution, the difference in batch size must not greater than 100% of the smallest batch size. (2 batches of 1000 L + 1 batch of 500 L)
Validation Batch:(Continued)

- For Suspension, 1 entire bulk should be filled into 1 batch of the smallest container size to demonstrate the largest filling run time.
- For Solution, the product having more concentration (using the same batch size, same equipment, process parameters), we can validate only the highest concentration.
- For Solution, the lowest filled volume must be validated at least 2 lots and the highest filled volume must be validated at least 1 lot.
Sampling Plan & Acceptance Criteria
Validation of Liquid Solution and Suspension

Validation Batch: Bulk Sampling and Testing

- Samples may be taken by
  - Collecting during Transfer
  - Using a sampling device
- For Solution, take at least 2 samples at top and bottom
- For Suspension, take at least 2 samples at top, Middle and Bottom of the bulk
- Individual Testing of sample must be done and the result must meet the testing standard specification
Validation of Liquid Solution and Suspension

**Qualification of Maximum Bulk Hold Time**

- The maximum period of time which the bulk can be held prior to fill
- It will be counted after finished final mixing step until transfer to fill
- One full scale batch should be held for most practical maximum time period prior to filling
- If there is not enough support information / qualification done. The period of 24 hours will be used
- Hold time qualification must simulate actual storage condition
Validation of Liquid Solution and Suspension

- Finish Product Testing
  - Net Contents
    - Perform testing on filled containers.
  - Microbial
    - 10 samples from each of the beginning and end of the filling run. Samples must represent all filling nozzles.
    - Preservative Efficacy testing should be tested.
  - Content Uniformity
  - Other Testing
    - Assay, pH, Viscosity, Preservative Content etc.
Validation of Liquid Solution and Suspension

- Sampling
  - Solution
    - Take samples from the beginning, middle and end of the filling run for assay
  - Suspension
    - Suspension bulk should be continuous mixing during filling operation
    - Samples must be representative of each filling nozzle
    - Samples tested for validation must equal or exceed what is required for routine release
Validation of Liquid Solution and Suspension

- Sampling
  - Suspension
    - For single filling size
      - Take 10 samples each at the beginning, middle and end of the filling run. All samples must be tested
    - Multiple filling size
      - Take 10 samples each at the beginning, middle and end of the filling size.
  - Multiple Tanks and Multiple filling size
    - Take 10 samples each at the beginning and end of the filling tank and take 10 samples each at the beginning and end of the filling size.
Validation of Liquid Solution and Suspension

- Testing
  - Net Content
    - Take samples from the beginning, middle and end of the filling run. Perform testing per testing standard.
  - Microbiology
    - Take 3 samples which represent beginning, middle and end of the filling run. Perform testing per testing standard.
    - Appropriated antimicrobial preservative efficacy testing is required.
Establishing Bulk Homogeneity Acceptance Criteria: Solutions

<table>
<thead>
<tr>
<th>Product Parameters</th>
<th>Acceptance Criteria</th>
<th>Sampling Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk Homogeneity</td>
<td>UPL &amp; LPL within 90 – 110% LA*</td>
<td>2 replicate samples from top, middle and bottom (test 3 samples)</td>
</tr>
<tr>
<td></td>
<td>RSD ≤ 2.0%</td>
<td></td>
</tr>
</tbody>
</table>

For bulk in mixing, storage or holding tank; * Prod Spec; UPL = Upper Prediction Limit; LPL = Lower Prediction Limit
Establishing Bulk Homogeneity
Acceptance Criteria: Suspensions

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<tbody>
<tr>
<td>Bulk Homogeneity</td>
<td>UPL &amp; LPL within 90 – 110% LA*</td>
<td>2 samples** each from two levels of 3 locations each (test 6 samples)</td>
</tr>
<tr>
<td></td>
<td>RSD ≤ 3.6%</td>
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</tbody>
</table>

For bulk in mixing, storage or holding tank; * Prod Spec; UPL = Upper Prediction Limit; LPL = Lower Prediction Limit; ** samples are taken after turbulence disappears
### RSD Limits for Bulk Samples

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M</th>
<th>N</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>RSD</td>
<td>2.0</td>
<td>2.8</td>
<td>3.3</td>
<td>3.6</td>
<td>3.8</td>
<td>4.0</td>
<td>4.1</td>
<td>4.2</td>
<td>4.3</td>
<td>4.4</td>
<td>4.4</td>
<td>4.5</td>
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| 4   |     |     |     |     |     |     |     |     |     |     |     |     |
| 5   |     |     |     |     |     |     |     |     |     |     |     |     |
| 6   |     |     |     |     |     |     |     |     |     |     |     |     |

**Product Spec = 90-110% LA, 110-100=10**

=10/(TINV(0.05,B2-1)*(1+1/B2)^0.5)

<table>
<thead>
<tr>
<th>A</th>
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<td>8</td>
<td>9</td>
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<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>RSD</td>
<td>1.4</td>
<td>2.0</td>
<td>2.3</td>
<td>2.5</td>
<td>2.7</td>
<td>2.8</td>
<td>2.9</td>
<td>3.0</td>
<td>3.0</td>
<td>3.1</td>
<td>3.1</td>
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</tr>
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|     |     |     |     |     |     |     |     |     |     |     |     |     |
| 10  |     |     |     |     |     |     |     |     |     |     |     |     |
| 11  |     |     |     |     |     |     |     |     |     |     |     |     |
| 12  |     |     |     |     |     |     |     |     |     |     |     |     |

**Product Spec = 93-107% LA, 107-100=7**

=7/(TINV(0.05,B8-1)*(1+1/B8)^0.5)
RSD Limit Criteria

\[
UPL = \bar{x} + t_{0.025, n-1} s \sqrt{1 + \frac{1}{n}}
\]

\[
110 = 100 + t_{0.025, 2} s \sqrt{1 + \frac{1}{3}}
\]

\[
10 = 4.3027 \times s \times 1.1547
\]

\[
s = 2.01
\]
## Filled Product: Content Uniformity – Solutions

<table>
<thead>
<tr>
<th>Product Parameters</th>
<th>Acceptance Criteria (n = 10)</th>
<th>Sampling Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content Uniformity</td>
<td>UPL &amp; LPL within 90 – 110% LA*</td>
<td>3 – 4 bottles from beginning, middle and end of filling cycle; total = 10 bottles</td>
</tr>
<tr>
<td></td>
<td>RSD ≤ 4.2%</td>
<td></td>
</tr>
</tbody>
</table>

* Product Specs
# Filled Product: Content Uniformity – Suspensions (low potency)

<table>
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<th>Product Parameters</th>
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<th>Sampling Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content Uniformity</td>
<td>UPL &amp; LPL within 90 – 110% LA*</td>
<td>10 bottles each from beginning, middle and end of filling cycle; total = 3x10 bottles (3 tests)</td>
</tr>
<tr>
<td></td>
<td>RSD ≤ 4.2%</td>
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</tbody>
</table>

* Product Specs
## Filled Product: Content Uniformity – Suspensions (medium potency)

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<tr>
<td>Content Uniformity</td>
<td>UPL &amp; LPL within 90 – 110% LA*</td>
<td>3 – 4 bottles from beginning, middle and end of filling cycle; total = 10 bottles</td>
</tr>
<tr>
<td></td>
<td>RSD ≤ 4.2%</td>
<td></td>
</tr>
</tbody>
</table>

* Product Specs
Validation of Liquid Solution and Suspension

- **Validation Report**
  - Validation Team must prepare the report
  - Report must be reviewed and approved by QA.
  - Written Notification or either successful completion or failure of the process validation must be issued to top management.
  - In case of failure, an investigation must be completed and documented prior to repeat the validation study.
Validation of Liquid Solution and Suspension

- Changes and Revalidation
  - Change of any of the following may need revalidation
    - Formula Composition
    - Raw Material Source
    - Manufacturing Process
    - Manufacturing Location
    - Equipments
    - Batch Size
    - Testing Specifications
Validation of Liquid Solution and Suspension

- Changes
  - Minor: It seems to have no impact on formulation
    - It is not necessary to validate
  - Intermediate: It could have significant impact on formulation
    - Depend on case-by-case (A minimum of 1 trial)
  - Major: It is likely to have significant impact on formulation
    - Revalidation is required (A minimum of 3 trials)
Validation of Liquid Solution and Suspension

- Minor Change
  - Delete or Decrease quantity of colorant, flavor
  - Qualitative inactive excipient change deemed minor by change control review
  - Process change deemed minor by change control review
  - For solution, Change in batch size of $\leq 100\%$ using the same equipment
  - Manufacturing location change with in same building, same equipment, personnel, procedure and utilities are used
  - Equipment change but same design, configuration
Validation of Liquid Solution and Suspension

- Intermediate Change
  - Active ingredient source or synthesis change deemed intermediate by change control review
  - Qualitative inactive excipient change deemed intermediate by change control review
  - Change in batch size $100\% < \text{batch size} \leq 200\%$ for solutions.
  - Change in batch size of $\leq 50\%$ for suspension
  - Manufacturing location change to a different building on the same site and same utilities, same equipment, personnel, and procedure are used
Validation of Liquid Solution and Suspension

- Intermediate Change
  - Process changes, such as mixing times or operating speeds for solutions.
  - Change in release specification to a tighter limit caused original validation results to be out of specification
  - Extension of the qualified in process hold time for intermediate or finished product prior to packaging
  - Equipment change deemed intermediate by change control review
Validation of Liquid Solution and Suspension

- Major Changes
  - Quantitative or qualitative formulation change deemed major by change control review
  - Inactive excipient or active ingredient source change deemed major by change control review
  - Transfer product from on site to another
  - Significant change in process
  - Change in batch size > 200% for solutions.
  - Change in batch size > 50% for suspensions.
Validation of Liquid Solution and Suspension

- **Major Changes**
  - Equipment change to a different design, configuration or operating principle.
  - New Dosage
  - Rework Procedure
  - Process changes deemed major by change control review such as mixing times or operating speeds for suspensions.
  - Change in release specification to a tighter limit caused original validation results and routine production results to be out of specification
Validation of Liquid Solution and Suspension

● Conclusion

- Process must be continually monitored and change control used to identify need for process revalidation.
- Validation Protocol identifies critical process parameters to be evaluated and predetermined acceptance criteria.
- Production and QA have to review and approve the validation result.
- Product must be held until the validation gets approval.