Process Validation for Drug Product
AGENDA

• Policies and practices
• Examples of good practices
• Discussion and clarification
Policies

• Scope
  • Production Processes used for producing a Drug Product or In-Process Material for a drug product
  • Existing, new and modified processes
  • Includes the filling of the product into the primary package where the filling process may impact the critical quality attributes of the drug product
  • Filling of tablets and capsules is defined in Packaging Validation
POLICIES

• Responsibility
  • The Site Validation Team is accountable for ensuring that process validation is executed according to the guidelines
  • Prepare Validation Requirements and Documentation
Policies

- **Prospective validation**
  - Use for substantially modified or new processes
  - Complete validation before any batches release

- **Concurrent validation**
  - For orphan drugs, infrequently manufactured products, legacy processes without changes and minor changes to validated processes
  - One batch released at a time

- **Retrospective**
  - Legacy processes without changes
  - Historical look back, no batch release involved
POLICIES

• To Use Concurrent or Retrospective
  • Well understood and documented process
  • Critical process parameters and quality attributes identified and used
  • Sufficient data available generated using Validated or Pharmacopoeia Test Methods
  • In-process controls and acceptance criteria established
  • No significant product/process failures attributable to causes other than operator error or equipment failure
  • Impurity profiles established for the API
POLICIES

- Retrospective Data Sources
  - Lot records
  - Process control charts
  - Maintenance log books
  - Change control records
  - Process performance (e.g., capability studies)
  - Finished product data including trend and stability results
  - Examine 10-30 consecutive and most recent lots for consistency, include failures
POLICIES

• Critical Process Parameters & Quality Attributes
  • Define and justify
  • A parameter is critical if it can affect a Critical Quality Attribute
  • A process step containing a critical parameter is critical
  • Normal Operating Ranges in protocol must have supporting data (e.g., Tech Transfer Package, historical site data)
  • Must be within Proven Acceptable Range and Regulatory Range
  • Use risk assessment to determine critical parameters for validation
  • If supporting data is not applicable to commercial scale, establish and reference in validation report
Figure 1 - Process Parameters

- Lower Normal Operating
- Lower Regulatory
- Lower PAR
- Lower Edge-of-Failure
- Normal Operating Range
- Regulatory Range
- Proven Acceptable Range
- Upper Normal Operating
- Upper Regulatory
- Upper PAR
- Upper Edge-of-Failure

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POLICIES

• Critical Process Parameters
  • Include Environmental Controls if applicable
  • Include Microbiological Quality if applicable
CASE STUDY: POWDER ORAL SUSPENSION (POS) TRANSFER FROM DEVELOPMENT TO VALIDATION

• Critical process parameters are often defined during development and qualified during validation

• Milling was defined as a critical processing step
  • Formulation is predominantly sucrose and particle size reduction is required for the final POS presentation
  • Issue: no acceptance criteria ("report value") for screens testing of mill samples

• Resolution:
  • Comparison of screens data both before and after milling serves to qualify milling parameters
  • Comparison of biobatch data to validation lot data showed similarity and therefore, consistency of process
POLICIES

• Validation lot size
  • Same as commercial
  • Small scale can be used
  • Scale changes can be concurrently validated

• Number of validation lots
  • At least 3, consecutive
  • Must be run within approved ranges
  • All must meet protocol acceptance criteria
  • Manufactured to manufacturing instructions defined in protocol
POLICIES

• Master Manufacturing Instructions
  • Must be developed prior to the protocol being written
  • Must be approved prior to validation execution
  • Master Production Order is based on this

• Validation protocol
  • critical steps, critical process parameters, sampling requirements and acceptance criteria
  • approved by the validation team before validation activity begins
Policies

• Changes to approved protocols
  • Issue new revision or supplemental documentation
  • Document justification of change
  • Approvals as original protocol, attach to original
  • Document in report

• Changes in parameters
  • Critical assessed as to impact on validation
  • Non critical documented and justified
  • All must be within regulatory
CASE STUDY: DEVIATION HANDLING

- Progressive levels of documenting quality anomalies (any or all of the following may be required):
  - Validation Deviation Worksheet
    - Protocol specific
    - Evaluates the need for corrective action
  - Corrective Action Worksheet
    - Requires applicable department mgmt sign-off
    - Includes due date
  - Validation Test Result Out Of Acceptance Criteria Form
    - Created as a result of a recent 483
    - Must be completed without exception
    - Requires Quality review and sign-off
  - Laboratory Investigation Report
    - Applies to all routine and validation results that are outside of acceptance criteria
  - Quality Assurance Report – Investigation
    - Documents all manufacturing deviations
    - Documents conclusions regarding lot release
POLICIES

• Validation test conditions
  • Standard production conditions
  • Challenge/extremes documented in development and/or Quality

• Hold times (includes storage times)
  • Documented evaluation
  • Consider using batches for stability
POLICIES

• Homogeneity (J, .9)
  • Where identified as a critical quality attribute
  • Physical and chemical homogeneity as applicable
  • Sample at discreet critical steps (e.g., mixing, freeze drying)
  • Representative samples
  • Account for start-up, interruptions, final units
PROCESS CAPABILITY

• During initial process validation, process capabilities were calculated for dosage uniformity of a new tablet product:
  • 20 mg (n=250 cores) – 2.40
  • 40 mg (n=380 cores) – 2.35
  • 80 mg (n=330 cores) – 2.41
• “Good” process capability is defined as between 1.34 and 3.00
PROCESS CAPABILITY (CONT’D.)
40 MG CPK ANALYSIS

Uniformity

<table>
<thead>
<tr>
<th>Samples: 380</th>
<th>Mean: 39.9908</th>
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</thead>
<tbody>
<tr>
<td>Std Dev: .84992</td>
<td>Target: 40</td>
</tr>
<tr>
<td>Cpk: 2.35</td>
<td>Min, Max: (37.5, 42.4)</td>
</tr>
<tr>
<td>Spec Lim: (34, 46)</td>
<td>Est % out: (.0000, .0000)</td>
</tr>
</tbody>
</table>

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POLICIES

- Bracketing & Matrixing
  - Used for multiple strengths, lot sizes, process parameters, and equipment items
  - Minimum 3 lots worst case
  - Documented rationale for approach and justification of worst case
  - Be careful, may need to review with Regulatory Agency
  - Consistency must be demonstrated for all batches
  - Entire study must be written as a single final report
## CASE STUDY: MQ PROCESS VALIDATION

<table>
<thead>
<tr>
<th>Group</th>
<th>Filling Solution Strengths</th>
<th>Target Filling volume</th>
<th>Protein concentration (mg/ml)</th>
<th>Solid concentration (mg/ml)</th>
<th>% Total Solids</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.1</td>
<td>2.2</td>
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<td>1.7</td>
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<tr>
<td>1</td>
<td>0.4</td>
<td>0.1</td>
<td>4.4</td>
<td>18.9</td>
<td>1.9</td>
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<tr>
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<td>0.15</td>
<td>4.4</td>
<td>14.3</td>
<td>1.4</td>
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<tr>
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<td>0.15</td>
<td>5.9</td>
<td>15.5</td>
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<td>0.15</td>
<td>7.3</td>
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<td>1.7</td>
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</table>
# CASE STUDY: MQ PROCESS VALIDATION

<table>
<thead>
<tr>
<th>Group</th>
<th>Strength (mg)</th>
<th>Bulk Size (kg)</th>
<th>FD Capacity (magazines)</th>
<th>No. of Batches</th>
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<tr>
<td>1</td>
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<td>42-84-84</td>
<td>3</td>
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<td>7</td>
<td>42</td>
<td>1</td>
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<td>42-210-420</td>
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<td>1.4</td>
<td>8-22-40</td>
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<tr>
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<td>2.0</td>
<td>22</td>
<td>210</td>
<td>1</td>
</tr>
</tbody>
</table>
POLICIES

• Raw Materials and components
  • purchased, stored and approved according to approved procedure
  • Changes in API for multiple strength products must include one lot at high dose and low dose
• Changes in API supplier (previously Policy Memo)
  • Chemical and physical evaluation of three lots of API with comparison to multiple lots of old API
  • Drug product validation for multiple strengths must include one lot at high dose and low dose
  • For multiple dosage forms, include one lot of each dosage form
POLICIES

• Prerequisites
  • Approved Master Formula, Master Production Order and SOPs
  • Identification of All Critical Process Parameters
  • Equipment Qualification (exceptions to this requirement must be approved by the validation team)
  • Supporting process validated (e.g., sterile filtration)
  • Calibration of critical instruments
  • Approved Specifications. Any change to the specification shall be assessed for its impact on the validation study
  • Validated Test Methods
  • Personnel training
POLICIES

• Validation failures
  • Investigate and assess impact
  • Exclude only if assignable cause is not process related
  • Summarize in validation report
CASE STUDY: POWDER ORAL SUSPENSION
FAILURE OF ACCEPTANCE CRITERIA

• Setting significant, yet realistic acceptance criteria is essential!
• Consequences? Having to explain failures that are not indicative of process weaknesses
• For Example:
  • Dissolution criteria set at Q=80% for a reconstituted POS product
  • Development concluded that dissolution is unrelated to API particle size
  • Third validation lot failed dissolution criteria and coincidentally was manufactured with an API having larger particle size than the first two lots
  • Consequences:
    1. Must reinforce (with development data) that API particle size is not related to dissolution of this POS product
    2. Must explain (using potency and uniformity results) that dissolution test results for POS product are not indicative of amount of active that will be administered to the patient
    3. Must propose to remove the acceptance criteria (a big undertaking) to avoid future misleading dissolution failures
POLICIES

• Validation report
  • Final report at end of study
  • Interim reports as required (time, product release for concurrent)
  • Summarize and assess deviations
  • Review lot yields and critical process parameters
  • Comparison to previously produced lots if applicable
  • Conclusion on validation status of process
POLICIES

• Data verification
  • relevant lot documentation reviewed prior to use in protocol or report.
  • Independently verified to confirm accurate transcription
  • Added requirement over legacy Pharmacia

• Record retention
  • At manufacturing location
POLICIES

• Release of lots
  • Status controlled per approved procedure
  • Prospective validation final report approval required
  • Concurrent interim report approval required
  • Pending approval, can be shipped to another site under quarantine

• Stability
  • Required for one lot for new to site, reformulated products, rework, other affects on stability
  • Document requirement in protocol
POLICIES

• Change control
  • Include assessment of validation requirements, if any

• Major changes
  • Affect release, metering or other characteristics of the dose delivered to the patient
  • Changes to APIs and critical recipients
  • Major facility changes
  • Major equipment size, design or operating principle
  • Rework or reprocessing procedures
  • Change in technology
  • Changes that could affect microbiological quality
POLICIES

• Minor changes
  • Equipment with same design and operating principle
  • Changes to code imprint
  • Change of imprint debossing on immediate release dosage forms
POLICIES

• **Rework**
  • Must be validated, may be concurrent
  • Assess regulatory impact

• **Non-routine reprocessing**
  • Treat as a planned deviation
  • Need for validation determined by validation team
POLICIES

• Periodic review
  • Annual – combine with Annual Product Review?
  • Assess validation status and identify any revalidation requirements
PRACTICES

• Sterile & Aseptically Filled Products

*Includes large and small volume parenterals, ophthalmics, and dry powders.*

*Evaluate critical steps (e.g., formulation, mixing, filtration, lyophilization, filling)*
• Sterile & Aseptically Filled Products (continued)
  • Suitability of material from different sources
  • In-process bioburden testing
  • Environmental conditions
  • Removal of oxygen
  • Dose and content uniformity
  • Fill weights and volume control
  • Moisture content
  • Foreign matter
  • Finished product specifications
PRACTICES

• Dry Powder Inhalers
  • Evaluate Mixing and Filling Processes
    • Formulation Effects
    • Dose Uniformity
    • Fill weight or volume; Number of deliveries
    • Airflow resistance
    • Homogeneity sampling, minimum 10 locations
    • Aerodynamic particle size, using impactor
    • Compliance to Components, including extractables
    • Finished product testing, including microbiological
    • Comparison to previous lots (e.g. biobatch, development)
PRACTICES

• Metered Dose Inhalers
  • Formulation Effects
  • Moisture Content
  • Delivered dose uniformity
  • Aerodynamic particle size, using impactor
  • Homogeneity sampling, minimum 10 locations
  • Fill Weight or volume; Number of deliveries
  • Compliance to Components, including extractables
  • Foreign Matter, including particulates
  • Finished product testing, including microbiological
  • Comparison to previous lots (e.g. biobatch, development)
PRACTICES

• Oral Solutions and Suspensions

  Includes elixirs, emulsions, gels, syrups, tinctures.

  • Compliance to specifications- APIs and excipients
  • In-process assay of bulk before filling,
  • Homogeneity sampling,
    • Suspensions- minimum 10 locations
    • Solutions- minimum top and bottom
  • Rheological properties- viscosity, thixotropy (where applicable)
  • Potency
  • Fill volume, including consistency and reproducibility of filling
  • Microbiological purity
  • Comparison to previous lots (e.g. biobatch, development)
PRACTICES

• Semi-solid Drug Products
  Includes emulsions, gels, lotions, creams, ointments and transdermal patches.

• Solubility of API in carrier
• Homogeneity samplings throughout (e.g. 10)
• Microbiological purity, consistency of microbial level
• Fill Volume (generally, in-process test)
• Rheological properties- viscosity, thixotropy
• Appearance
• Potency
PRACTICES

• Oral Solid Dosage Forms

*Includes mixing, granulation, milling, drying, blending, compression, encapsulation, coating and printing.*

• Homogeneity sampling of blends- min 10 locations

• In-process controls, including individual weights, hardness, moisture, thickness, friability, and disintegration.

• Five point dissolution profile including points close to 100 % dissolution

• Freedom from defects throughout the process (e.g. capping)

• Potency and dose uniformity

• Compliance with finished product specifications
PRACTICES

• Oral Solid Dosage Forms (Continued)

Samples – taken throughout each lot for content uniformity to demonstrate the lack of segregation during compression or encapsulation.

• Blend Uniformity
  • May be sampled directly from blender.
  • Taken from areas of blender that have greatest potential to be non-uniform.
  • If not practical to take from blender, samples may be taken from discharge stream or from drums.
  • Sample sizes to be approximately equivalent to dosage unit weight
ASSESSMENT / GAP ANALYSIS

• Creating a check sheet, for example:
  • Blend Sampling
    • At least 10 locations?
    • Is there traceability, i.e., an illustrative sampling plan?
    • Unit dose sample size?
  • Finished dosage form
    • Methodology used? (i.e., USP)
    • Number of samples and locations (i.e., 10 units from 10 stratified locations for USP uniformity)
  • Testing sufficient to qualify critical parameters?