Lifecyle Validation Strategy
(Case Study: Bottle Line Transfer)

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AGENDA:
• Guidance
• Overview
• Strategy
• Approach
• Case Study
• Assessment
• Learnings
GUIDANCE:

- Validations provide evidence the process consistently delivers quality product under defined and controlled manufacturing conditions.
- Validations follow guidance:
  - Stage 1 (S1): Process Design
  - Stage 2 (S2): Process Qualification
  - Stage 3 (S3): Process Monitoring

PACKAGING TRANSFER:

- Lifecycle Management:
  - Legacy Product @ Stage 3 (Monitoring)
  - Operations Project (Capacity, Cost, .......)
  - Process Transfer (Case Study: Bottling Line Transfer)
- Engineering Notification:
  - Change requires line validation
- Validation Strategy:
  - What is Current State
  - What is Change Risk
  - Validation plan as per strategy and rationale
STRATEGY:

- Strategy is a tool to identify variables and risks which may impact process validation.
- Potential areas of variability include materials lots, equipment performance, procedure interpretation.
- Strategy can support rationale for “worst case”.
- Strategy can provide rationale for bracketing.

APPROACH:

- Identify Cross Functional team to deliver science and experience based decisions. (Technical, Manufacturing, Quality, …)
- Define project scope (Components).
- Identify product metrics (batch sizes, demand, availability).
- Consult prior validations; realize linkages to upcoming validation (same packaging, same product, same line).
- Conduct an assessment of risk:
  - Define risk rankings
  - Define subject areas to assess
- Rationalize "worst case"
- Rationalize bracketing
- Prepare a strategy for validation with rationale from a science and experience based risk assessment.
STRATEGY TEAM:

- Process
- Manufacturing
- Statistics
- Quality
- Planning
- Operations
- Line Management

Team capable to share knowledge and discuss change risks (science and experience)

CASE STUDY:

- Bottle Line (Secondary Packaging)
- Mature Product:
  - Launch 5 years ago.
  - Validated based upon “3 batches”
- Process:
  - Current 50 bottles/minute.
  - Future 150 bottles/minute.
- History:
  - Since launch multiple markets have been added including those requesting bottles in cartons.
  - Line is now capacity constrained and driving up speed finds quality issues with broken tablets.
- Deliverable:
  - Transfer existing product to a new line, high speed process.
CONSIDERATIONS:

• Since launch multiple markets have been added:
  – Did these markets adopt the initial validation. (apples – apples)
  – Were any CI improvements implemented under market expansion projects. (apples – oranges)
  – What was/is filed with regulatory agency for this product/packaging.

• Since launch have guidance / policy revisions occurred:
  – AQL vs. RQL
  – Attributes vs. Variables
  – Method updates
  – What was previously validated may not have utilized a formal three stage approach.

Consider this risk assessment as an investigation of what to validate

RISK ASSESSMENT: (PACKAGING PRODUCT & PROCESS)

• Create a Risk Ranking:
   Define Inputs and Outputs:
     Define scope (Products, Components)
     Define process (Map of major steps and areas of change)
   Rank Packaging Components:
     Risk to Manufacturing (S1, Equipment, Facility, Down Time, Efficiency)
     Risk to Process (S2, Validation, Quality Limits)
     Risk to User (S3, Monitoring, Quality History)
   Rank Packaging Process:
     Risk to Manufacturing (S1, Equipment, Facility, Down Time, Efficiency)
     Risk to Process (S2, Validation, Quality Limits)
     Risk to User (S3, Monitoring, Quality History)
SCOPING:

- Component Focus
- Continuum (small,lrg,short)
- Find Patterns
- Create Buckets

<table>
<thead>
<tr>
<th>Strength</th>
<th>Market</th>
<th>Bottle Count/Size</th>
<th>Coller Length</th>
<th>Outsert Size</th>
<th>Serialise</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>Q</td>
<td>SMALL</td>
<td>SHORT</td>
<td>MED</td>
<td>NO</td>
</tr>
<tr>
<td>LOW</td>
<td>Q</td>
<td>SMALL</td>
<td>SHORT</td>
<td>MED</td>
<td>NO</td>
</tr>
<tr>
<td>LOW</td>
<td>Q</td>
<td>LRG</td>
<td>LONG</td>
<td>MED</td>
<td>NO</td>
</tr>
<tr>
<td>LOW</td>
<td>Q</td>
<td>MED</td>
<td>SHORT</td>
<td>MED</td>
<td>NO</td>
</tr>
<tr>
<td>MED</td>
<td>Q</td>
<td>SMALL</td>
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<td>NO</td>
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<tr>
<td>MED</td>
<td>Q</td>
<td>LRG</td>
<td>LONG</td>
<td>MED</td>
<td>NO</td>
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<tr>
<td>MED</td>
<td>Q</td>
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<td>SHORT</td>
<td>MED</td>
<td>NO</td>
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<tr>
<td>HIGH</td>
<td>R</td>
<td>SMALL</td>
<td>SHORT</td>
<td>LRG</td>
<td>YES</td>
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<tr>
<td>HIGH</td>
<td>S</td>
<td>SMALL</td>
<td>SHORT</td>
<td>LRG</td>
<td>YES</td>
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<tr>
<td>LOW</td>
<td>S</td>
<td>SMALL</td>
<td>SHORT</td>
<td>LRG</td>
<td>YES</td>
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<tr>
<td>LOW</td>
<td>S</td>
<td>LRG</td>
<td>LONG</td>
<td>SM</td>
<td>YES</td>
</tr>
<tr>
<td>MED</td>
<td>S</td>
<td>SMALL</td>
<td>SHORT</td>
<td>LRG</td>
<td>YES</td>
</tr>
<tr>
<td>MED</td>
<td>S</td>
<td>LRG</td>
<td>LONG</td>
<td>SM</td>
<td>YES</td>
</tr>
</tbody>
</table>

List all components for review of packaging patterns and potential bracketing.

CONFIDENTIAL

SYSTEM DESCRIPTION (PROCESS MAPPING):

- The system description is necessary to understand major process steps.

Add Bulk → Fill Bottles → Cap & Label → Secondary PKG

- No Change
- New Line, High Speed Process
- No Change
- New Corrugate

Review for change patterns to understand key areas requiring validation.
Identify Potential Sources of Variability

New high speed filler; use of new stiffer corrugate w/transfer

Create a template and apply risk rankings

Team Discussions: (Ranking requires agreement and rationale)
- Assess current performance (Inquiries, downtime)
- Assess prior validations (quality methodology, sample sizes)
- Assess current vs transfer for potential or unknown sources of variability which require resolution.
PROCESS ASSESSMENT:

<table>
<thead>
<tr>
<th>MFG MODULE</th>
<th>PROCESS EQUIPMENT</th>
<th>RISK AS IMPACTED BY THE PROCESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unscrambler</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Filler</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Induction Sealer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metal Detector</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Retorque</td>
<td></td>
</tr>
<tr>
<td>LABELING</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Labeler</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labeler Vision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glue Unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Print and Apply System</td>
<td></td>
</tr>
</tbody>
</table>

Team Discussions: (Ranking requires agreement and rationale)
- Assess current performance (Inquiries, downtime)
- Assess prior validations (quality methodology, sample sizes)
- Assess current vs transfer for potential or unknown sources of variability which require resolution.

RATIONALE SUMMARY:

- From the component and process risk tables summarize and rationalize the identified risks

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Step</th>
<th>Risk</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component</td>
<td>Bottle</td>
<td>Small Bottle: Fill, Count, Cotton Sealing</td>
<td>Funnel size fit with small bottle and high fill rate, small bottle/count</td>
</tr>
<tr>
<td>Bottling Process</td>
<td>Induction Sealer</td>
<td>Largest bottles challenge highest fill count and largest shipper sizes</td>
<td>large bottle/count</td>
</tr>
<tr>
<td>Corrugate Process</td>
<td>Glue Unit</td>
<td>Speed and Maintenance</td>
<td>Long run to challenge corrugate, long run time</td>
</tr>
</tbody>
</table>

Worst Case: The high speed and small bottle, as well the stiff corrugate and glue unit are worst case in this validation project.
VALIDATION PLAN:

<table>
<thead>
<tr>
<th>RUN</th>
<th>STRENGTH</th>
<th>BOTTLE</th>
<th>CARTON</th>
<th>PROCESS</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HIGH</td>
<td>SM</td>
<td>YES</td>
<td>HIGH SPEED, HIGH SEAL</td>
<td>LONGEST RUN ON CORRUGATE, HIGHEST POTENTIAL FILL RISK</td>
</tr>
<tr>
<td>2</td>
<td>LOW</td>
<td>SM</td>
<td>NO</td>
<td>HIGH SPEED, LOW SEAL</td>
<td>HIGHEST POTENTIAL SEALING RISK (BOTTLE INTEGRITY)</td>
</tr>
<tr>
<td>3</td>
<td>MED</td>
<td>LRG</td>
<td>YES</td>
<td>HIGH SPEED, MED SEAL</td>
<td>CHALLENGE HIGHEST FILL COUNT</td>
</tr>
<tr>
<td>4</td>
<td>MED</td>
<td>LRG</td>
<td>NO</td>
<td>SLOW SPEED, MED SEAL</td>
<td></td>
</tr>
</tbody>
</table>

The validation plan is a team decision to rationalize and challenge all risks leaving a confidently validated packaging process.

VALIDATION READY:

- **Batch Sizes:**
  - Product itself (tablets) will challenge representative batches of commercial batch size. Ensure material is commercial quality, available, and lot traceable.
  - Packaging representative batch size considers process stability. If line is not capable to run end-end a full commercial tablet batch size it should be disclosed and accounted for in the SOP and validation.
  - From batch size calculate bottle counts, shipper counts, ext necessary to develop sample sizes.
  - As determined, AQL vs. RQL, calculate acceptance criteria for each sample size.
    - Variable Text legibility (units of bottles)
    - Bottle Integrity (units of bottles)
    - Tablet Count and tablet Quality (units of tablets)
- **Methods:** Update applicable methods or SOPs as necessary to align with latest quality expectations.
- **Monitoring Plan (S3):** The validation itself will revisit stage 1, address stage 2, and ensure control of ongoing quality as stage 3. A monitoring plan needs to be in-place for implementation through this validation.
- **Manufacturing:** Ensure equipment is properly maintained, cleaned and all associates are trained to the validation protocol and any applicable SOP or method updates.
LEARNINGS:

- Team experience and technical expertise, when used together, brings best rationales and decisions.
- Consider a transfer is not always “apples – apples”.
- History and knowledge can truly change the strategy including acceptance criteria, sample sizes, inspection methods.
- AQL vs. RQL: Consider there needs be understanding and alignment on criticality and acceptance criteria.
- Worst Case is best rationalized with risk assessment.
- This has been a case study – in practice greater detail, even DOE software can be used to rationalize and even bracket for the validation plan.
- Document your strategy for future reference and justification of this validation.