Container Closure Integrity Testing (CCIT): a Risk Management Application

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Bonfiglioli Engineering
Quality Control Solutions
Scenario

- Process: Container Closure

  Integrity Testing for Blow-Fill-Seal

- In line equipment to test 100% of the production:
  - downstream of a Blow-Fill-Seal machine for aseptic primary packaging providing a 60 Container Per Minute (CPM) output rate
  - upstream of a secondary packaging machine

- Standard ASTM F-2338-09:
  - “Standard Test Method for Non-destructive detection of Leaks in Packages by Vacuum Decay”
  - FDA (CDRH) Recognised Consensus Standard
# Technical Specifications

<table>
<thead>
<tr>
<th>Tested Container</th>
<th>BFS, FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container Filling</td>
<td>Filled</td>
</tr>
<tr>
<td>Container Content</td>
<td>Liquid</td>
</tr>
<tr>
<td>Machine Type</td>
<td>Rotative Leak Tester</td>
</tr>
<tr>
<td>Testing Methods</td>
<td>Vacuum Decay</td>
</tr>
<tr>
<td>Max speed</td>
<td>82 Cpm</td>
</tr>
<tr>
<td>Min Container Dimension</td>
<td>5,00 x 150,00 x 8,00 mm</td>
</tr>
<tr>
<td>Max Container Dimension</td>
<td>5,00 x 5,00 x 45,00 mm</td>
</tr>
<tr>
<td>Testing Heads Number</td>
<td>from 6.00 to 10.00</td>
</tr>
</tbody>
</table>
“Vacuum Decay Method” (ASTM F-2338-09)

Working principle:

a) Vacuuming: the period of vacuum setting within the test chamber

b) Stabilization: the time necessary to get a homogeneous vacuum distribution within the test chamber

c) Testing: the time frame in which the vacuum level is monitored.

Two measurements are taken (First and second reading)

Decision-making:

✓ Δ ≤ THR → Accepted

✗ Δ > THR → Rejected (Micro leakage)

✗ 1< M_LEV → Rejected (Gross leakage)
MSc thesis in cooperation with Parma University

- **State of Art:**
  - ✓ to find out proper statistical approach

- **Project:**
  - ✓ to elaborate a model to relate data trends and failures

- **Implementation & test:**
  - ✓ MATLAB®
  - ✓ Simulation
    - Simulated data with noise
    - Real data from the field
“SPCA” System Implementation

- Statistical Process Control Algorithm

Industrialization:

- To increase process reliability
- To improve the equipment productivity
- To minimize forced downtime
- To quickly identify errors or anomalies causes

Techniques:

- Quality Risk Management (QRM)
- Process Analytical Technology (PAT) & Statistical Process Control (SPC)
- Six Sigma
QRM Process (ICH Q9)

Definition and analysis

Control Strategy Development

Continuous Improvement

Systematic approach to risk management
## Preliminary Risks Assessment

<table>
<thead>
<tr>
<th>General issues</th>
<th>Impact Quality</th>
<th>Impact Business</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease of process reliability</td>
<td>High</td>
<td>-</td>
</tr>
<tr>
<td>Variability</td>
<td>High</td>
<td>-</td>
</tr>
<tr>
<td>Performance drift</td>
<td>-</td>
<td>High</td>
</tr>
<tr>
<td>Need for corrective actions</td>
<td>-</td>
<td>Med</td>
</tr>
<tr>
<td>Extraordinary maintenance costs</td>
<td>-</td>
<td>Med</td>
</tr>
<tr>
<td>Component wear</td>
<td>-</td>
<td>Low</td>
</tr>
</tbody>
</table>
Test Raw Data and Normal Distribution

- Continuous Data $\rightarrow$ Process described by Gaussian curve

$$f(x) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{1}{2} \left( \frac{x-\mu}{\sigma} \right)^2}$$

- Dispersion could vary in different ways:
  
  - Mean Deviation
  - Variance Deviation
  - Shape Deviation
Common Causes

- Natural process dispersion
- Affect process capacity
- Always present in the system
- Predictable

Special Causes

- Non predictable dispersion
- Affect process stability
- Intermittent
Considerations

☐ Case studies show that...

☑ Most of the processes run off-control
☑ It’s fundamental to identify the main cause of variation
☑ Targeted interventions improve the process

Vision:

🤔 PAT methodology could help?

?(:) Food and Drug Administration (FDA) references:

○ “Guidance for industry: PAT — A framework for innovative pharmaceutical development, manufacturing and quality assurance; September 2004”

○ “Pharmaceutical cGMPs for the 21st century — A risk based approach; Final Report, September 2004”
Process Analytical Technology (PAT)

- **Principles:**
  - “Enhance understanding and control the manufacturing process”
  - “Quality cannot be tested into products; it should be built-in or should be by design”

- **Transposition:**
  - PAT is intended for drug manufacturing
  - The concept can be extended to other processes

- **Tools:**
  - SPC: Control charts
  - Six Sigma: DMAIC model
Integrating QRM, PAT and Six Sigma

Risk management process

PAT application in a DMAIC structure

Define

Measure

Analyse

Improve

Control

Process Understanding

CQA  CPP

Process Assessment

DoE  Simulation  Modeling

Process Analysis

SPC: Stability  SPC: Capacity

Process Improvement

Reduce Dispersion  Manage Anomalies

Process Control

Continuous Monitoring  Produce High Quality

Risk assessment

Risk identification

Risk analysis

Risk evaluation

Risk control

Risk reduction

Risk acceptance

Output / Result of the Quality Risk Management Process

Risk review

Review events

Initiate Quality Risk Management Process

Risk management tools

unacceptable

Define

Measure

Analyse

Improve

Control

Risk communication

Risk assessment

Risk identification

Risk analysis

Risk evaluation

Risk control

Risk reduction

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Output / Result of the Quality Risk Management Process

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Review events

Process Understanding

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DoE  Simulation  Modeling

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SPC: Stability  SPC: Capacity

Process Improvement

Reduce Dispersion  Manage Anomalies

Process Control

Continuous Monitoring  Produce High Quality
SPCA uses DMAIC for Analysis, Improvement and Control

Target: monitor and manage the process

- Stability: detection of special causes
- Capacity: estimating the effects of the common causes
Definitions: Quality Risks – CQA and CPP

Assessment:

✓ Internal know-how
✓ Testing process decision-making

CQA: Property to ensure the Quality of the Process

→ Stability
→ Reliability
→ Repeatability

CPP: Variables that affect CQA

✓ 1st Reading
✓ Delta
Definitions: Business Risks – \( C_p \) & \( C_{pk} \)

Process Capability: “measurable property of a process to the specification, expressed as a process capability index”

\( C_p \): the ability of a process to \textit{potentially} produce output within specification limits

\( C_{pk} \): the ability of a process to \textit{actually} produce output within specification limits

Standard:

- ASTM E2281 “Standard Practice for Process and Measurement Capability Indices”
Measure: DoE

- Running a comprehensive and targeted set of faults

- Results analysis
  - Identify the impact of mechanical, pneumatic, electrical and configuration anomalies during the period of activity
  - Highlight the effect that each anomaly has on the CPP

- The presence of special causes determines a process drift
  - Indicators deviation CPP (Out Of Control “OOC”)
  - Altering test results
  - Deterioration of the machine performances
# Measure: Simulation and Modeling

## Standard Failures

<table>
<thead>
<tr>
<th>1st Reading</th>
<th>Noise Source Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test chamber seal loss or significant physical damage</td>
<td>Electrovalves/transducer support seal(s) wrong positioning or absence</td>
</tr>
<tr>
<td>Electrovalve failure</td>
<td>Cut/scratch onto test chamber seal</td>
</tr>
<tr>
<td>Dust and other materials (glass, debris, plastic) presence onto closing seals</td>
<td>Dust presence onto test chamber mobile bottom part</td>
</tr>
<tr>
<td>Vacuum supply downfall</td>
<td>Linear + Offset</td>
</tr>
<tr>
<td>Transducer failure</td>
<td></td>
</tr>
<tr>
<td>Liquid presence in test chamber</td>
<td></td>
</tr>
</tbody>
</table>
Analysis: Stability

- SPCA:
  - Control charts
    - A. Detection OOC points
    - B. Trend Detection

- Sequence:
  1. Investigation
  2. Verification
  3. Corrective actions
  4. Variability elimination
Control Charts Implementation

- How to organize data ➔ Matrix
  - N rows = Measurements **number**
  - K columns = Measurements **sets**

- Sampling ➔ tradeoff
  - N:
    - reactivity (detect rapid changes): ↑ se N ↓
    - robustness (avoid false detections): ↑ se N ↑
  - K:
    - accuracy of the regression: ↑ se K ↑
    - sampling time: ↓ se K ↓
    - prompt response: ↓ se K ↓

<table>
<thead>
<tr>
<th>K₁ ID</th>
<th>K₂ ID</th>
<th>Kₓ ID</th>
<th>Kₙ ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(N+1)</td>
<td>(x*N+1)</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>(N+2)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>N</td>
<td>2*N</td>
<td>...</td>
<td>K*N</td>
</tr>
</tbody>
</table>

N = 10

Need for dynamic adaptation
N = 10 → X–R Charts

Dispersion type

Mean Deviation

Variance Deviation

X-Chart

R-Chart
Western Electric Rules (WER)

- Only the first four rules to minimize the risk of false alarms

- Score associated with each violation:
  
  i. WE1: 1 or more points outside the control limits ±3σ (Score S = 3)
  
  ii. WE2: 2 out of 3 consecutive points outside the warning limits ±2σ (S = 1)
  
  iii. WE3: 4 out of 5 consecutive points outside the band ±σ (S = 1)
  
  iv. WE4: 8 consecutive points on the same side of the centerline (S = 1)

- The sum (Σ) of all partial scores is compared with a threshold of acceptability (WE_THR):
  
  o If (Σ > WE_THR) Process is Out of Control
Stability Improvement: B. Trend Determination

- Method of least squares

- Confidence interval (CI) settable:
  - 90%, 95%, 99%, 99.5%, 99.7%

- Configuration Method:
  - CI ↓: possible false alarms
  - CI ↑: difficulty in detecting weak trend

- Trend: blue line on the Control Chart
1. Failure modeled as “Linear + Offset”

- Test chamber contaminated:
  - leakage from a defective BFS
  - liquid evaporation decreases vacuum
  - 1\textsuperscript{st} reading (10 mbar decrease)
  - X-Chart detects OOC points (3, 4, 5, 6)

- Note:
  - Automatic Drying System – ADS
  - If the M\_LEV threshold is mistakenly set too low, the ADS is not activated
2. Failure modeled as “Linear (Long Duration)”

- Electrovalve failure:
  - Switch time increases due to dust
  - 1st reading slowly decreases (5 mbar / 2880 test cycles)

- Note:
  - How many points are needed to detect this trend?
  - If K=40 X-Chart detects trend

<table>
<thead>
<tr>
<th>K</th>
<th>Start</th>
<th>Chart Nr</th>
<th>Trend</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>100</td>
<td>16</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>30</td>
<td>150</td>
<td>11</td>
<td>8</td>
<td>X</td>
</tr>
<tr>
<td>40</td>
<td>200</td>
<td>8</td>
<td>2, 3, 4, 5, 6, 7, 8</td>
<td>OK</td>
</tr>
<tr>
<td>50</td>
<td>250</td>
<td>6</td>
<td>2, 3, 4, 5, 6</td>
<td>OK</td>
</tr>
</tbody>
</table>
3. Failure modeled as “Linear (Short Duration)”

- Small seal defect:
  - Tiny plastic particles compromise airtightness
  - Quick decrease of 1st reading value
    (5 mbar / 480 test cycles → greater slope)

- Note:
  - If K=20 X-Chart detects trend

<table>
<thead>
<tr>
<th>K</th>
<th>Start</th>
<th>Chart Nr</th>
<th>Trend</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>50</td>
<td>9</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>20</td>
<td>150</td>
<td>4</td>
<td>1,2,3,4</td>
<td>OK</td>
</tr>
<tr>
<td>30</td>
<td>200</td>
<td>3</td>
<td>1,2,3</td>
<td>OK</td>
</tr>
<tr>
<td>40</td>
<td>250</td>
<td>2</td>
<td>1,2</td>
<td>OK</td>
</tr>
</tbody>
</table>
4. Failure modeled as “Step”

Severe damage of the seal:

- cut seal

1\textsuperscript{st} reading value decreases dramatically

<table>
<thead>
<tr>
<th>Step Height (mbar)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>X</td>
</tr>
<tr>
<td>0.4</td>
<td>X</td>
</tr>
<tr>
<td>0.5</td>
<td>OK</td>
</tr>
<tr>
<td>1</td>
<td>OK</td>
</tr>
</tbody>
</table>
**Analysis: Capacity**

- **SPCA:**
  - estimates the common causes impact
  - provides feedback about the improvements to be made
  - continuous process capability analysis is performed:
    - CPP values are taken as input
    - $C_p$ and $C_{pk}$ indicator values are returned as output

- **Guidelines: $C_p$ & $C_{pk}$**
  - $1.33 \leq C_p < 1.5 \rightarrow \text{OK}$
  - verify the process is centered on the target value by means of $C_{pk}$
  - $C_{pk} \approx C_p \rightarrow \text{OK}$
Capacity Improvement (1)

Action to perform for process capability and equipment efficiency:

✓ Trade-off: performance / expected quality / cost to sustain

☐ From SPCA analysis over a wide range of operating conditions...

1. Test cycle:
   i. Recipe configuration
   ii. Set-up parameters adjustement
   iii. Equipment hardware fine-tuning

2. Equipment sub-systems:
   i. Routine use of embedded diagnostic tools
Capacity Improvement (2)

3. Pneumatic system:
   i. Optimization of test vacuum generation system
   ii. Pipes routing and sizing
   iii. Pressure regulators calibrations

4. Test chamber:
   i. Choice of materials
   ii. Seals sizing
   iii. Mechanical tolerances refinement
   iv. Calibration of compensator springs on test chamber mobile bottom part shaft
Conclusions

- Requirements
  - ✓ Process control and optimization; system improvement

- Approach
  - ✓ Cooperation between academia and internal R&D

- Verification
  - ✓ Relevant operating conditions

- Results
  - ✓ Continuous improvement
Thank you for your kind attention !!!

Questions & Comments

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