A Novel Process Analytical Technology Approach to Automated Pharmaceutical Container Closure Integrity Testing

**Introduction**

This article provides the overview of Process Analytical Technology (PAT) methodology application to an automated equipment developed for 100% Container Closure Integrity Testing (CCIT) of pharmaceutical items.

PAT is a scientific approach which is designed to facilitate continuous process improvement in terms of reliability, effectiveness and efficiency. PAT is based on process understanding and in particular it looks at the identification, determination and management of all critical sources of variability, so to guarantee that the expected quality is compliant with its requirements from the start ("right first time").

The CCIT, here referred to, is based on ASTM F-2338-09 “Standard Test Method for Non-destructive detection of Leaks in Packages by Vacuum Decay Method” (1); it is a proven integrity testing technology and it can be applied to all possible containers. CCIT, as all other physical processes, is affected by variability, resulting both in common and special causes. While common causes are predictable and removable through equipment improvements, special causes effects are intermittent, unpredictable and therefore can be mitigated through user direct actions only.

The article describes the methods and controls to be used while implementing and managing the CCIT process so to consistently ensure the required level of quality, stability and repeatability, proposing the Statistic Process Control Algorithm (SPCA) as a solution for improving production rates, minimizing downtimes and quickly identifying the root cause behind failures or anomalies.

In the following sections a specific case study, developed from a MSc thesis (2), is presented.

**Equipment Overview**

The equipment under analysis is of the “in line” type at continuous operation, to test 100% of the production by using the Vacuum Decay Method, and is designed to be installed

- downstream of a Blow-Fill-Seal machine for aseptic primary packaging providing a 60 containers per minute (cpm) output rate
- upstream of a secondary packaging machine

the loading and unloading of Blow-Fill-Seal containers (BFS) to be carried out by means of automatic systems as conveyors and transfer devices. The equipment was set to work at a speed of 60 cpm, so to comply with the BFS primary packaging machine output rate.

The case study here reported refers to a scenario in which the equipment was installed in the supplier factory, where the simulation of a production-like environment was realized with the aid of a closed loop conveyor, continuously feeding the equipment with a suitable set of 500 conforming BFS.

The reference time frame for the case study was of 50 hours, comprising of

- 45 hours of uptime
- 5 hours of downtime for:
  - periodic replacement of the 500 conforming BFS looping in the conveyor
  - failures simulation and management
  - data collection and preliminary review

resulting in approximately 150000 closure integrity tests.

**Test Chamber**

Ten test chambers with the same characteristics are installed on the equipment central turret; test chambers are mounted on shafts which are vertically actuated by a mechanical cam. A test chamber (refer to Figure 1 and Figure 4) is made up of:

- a fixed top part which is connected with pneumatic actuators and vacuum transducer;
- a mobile bottom part for BFS holding, which is lifted and lowered by means of the mechanical cam in phase with BFS loading and unloading. The mobile bottom part stroke provides for the test chamber closure.

Each test chamber performs a CCIT cycle composed of the following steps in correspondence to one complete rotation of the central turret:

1. loading of BFS in the test chamber;
2. hermetic closure of test chamber;
3. CCIT process execution and decision making on BFS closure integrity (further details are given in the next section);
4. opening of test chamber;
5. unloading or rejection of BFS;
6. arranging the next operation.

**Container Closure Integrity Testing**

The CCIT is performed while the BFS is held within the hermetically sealed test chamber. The principle underlying the CCIT is that, as a consequence of the application of vacuum within the test chamber and hence of a differential pressure between the inside and the outside of the BFS, the air moves from the high pressure zone (within the BFS) to the low pressure zone (outside the BFS), causing a progressive increase of the pressure (that is a vacuum decrease) outside the BFS. A vacuum decrease greater than a given threshold at end of the testing phase points out a failure in the BFS closure integrity (leakage).
The CCIT process comprises the following phases (refer to Figure 2):

- **Vacuuming**: the period of vacuum setting within the test chamber;
- **Stabilization**: the time necessary to get a homogeneous vacuum distribution within the test chamber;
- **Testing**: the time frame in which the vacuum level is monitored by means of a dedicated transducer; two measurements are taken respectively at the beginning (1st reading) and at the end (2nd reading) of this phase.

Following the testing phase the CCIT decision-making is performed by means of comparing the vacuum variation \( \Delta (\Delta = 1^{st} - 2^{nd} \text{ reading}) \) to a previously determined threshold \( \text{THR} \):

- If \( \Delta \leq \text{THR} \) the BFS is accepted;
- If \( \Delta > \text{THR} \) the BFS is rejected (a micro leakage is detected).

In case that a preset minimum level (M_LEV) of Vacuum is not reached at 1st reading time, the BFS is rejected as well (a gross leakage is detected).

**DMAIC Strategy**

Six Sigma uses a problem solving methodology known as DMAIC (Define opportunities, Measure performance, Analyze opportunity, Improve performance, Control performance) (3); SPCA works within the application of a specific DMAIC strategy (defined into Table A and Figure 3) to provide means to successfully carry on the “Analyze” and “Improve” phases.

**Preliminary Experiments**

The background for the SPCA integration within the process stability stage was the performance of a Preliminary Experiments phase, during which the equipment was exposed to a focused and exhaustive set of standard failures affecting the CCIT process and the reference Critical Process Parameters (CPP) indicators. The resulting data were subsequently analyzed with the aim of:

- identifying the impact of mechanical, pneumatic, electrical and configuration anomalies;
- isolating the effects of each failure on the CPP indicators curves, modeling such effects as “noise sources” superposed to the CPP data (refer to Figure 5).

The Preliminary Experiments phase allowed to observe that the presence of special causes determines a process drift that gradually brings CPP indicators Out-of-Control (OOC), causing test outcomes alteration and equipment, as well as CCIT process, performance degradation.

Furthermore, as a result of this analysis, a one-to-one correspondence between subsets of standard failures and the mathematical models describing their effects as noise sources affecting the CPP data was set, allowing SPCA to leverage it for the timely detection of anomalies: if CPP curves match one of the models, SPCA infers that one of the corresponding failures is present. The Stability Management section of this article provides more detail on how SPCA establishes this relation.

**Stability Management**

SPCA provides the CCIT process stability monitoring by means of tracking a continuous stream of incoming CPP values on Control Charts (individually for each test chamber) and analyzing the resulting data, triggering a suitable alarm in case a deviation in the form of a trend or a set of OOC points is detected.

If the deviation pattern is recognized by SPCA as corresponding to a given subsets of standard failures, the triggered alarm provides the user with specific information on the equipment components to be troubleshot; on the contrary a generic alarm is displayed.

**Trends Detection**

On the one hand SPCA provides the detection of potential trends by means of the least squares method. The user may choose the confidence interval (CI) between one of the following values: 90%, 95%, 99%, 99.5%, 99.7%. The current case study shown that a CI value of 99.7% is the optimal solution for a timely detection of most of the expected anomaly conditions.
OOC Points Detection

On the other hand SPCA provides OOC points detection, taking advantage of the Western Electric Rules (WER) (4); only the first 4 WER are applied, so to minimize the likelihood of activating false alarm conditions.

The WER were chosen due to their relevance in the statistical process control field, where they are widely adopted to determine the detection of OOC points and anomalous data trends.

Following is a list of the WER, reporting for each rule the violation condition and the corresponding score (a partial score is assigned to the violation of each of the WER).

WER1: a single point more than three standard deviations from center line (score is 3).

WER2: two out of any three consecutive points more than two standard deviations from center line on one side of center (score is 1).

WER3: four out of any five consecutive points more than one standard deviation from center line on one side of center (score is 1).

WER4: eight consecutive points on one side of center (score is 1).

Once the analysis is completed, the sum of the partial scores for all the violations occurred in the reference time frame (that is the period in which the measurements reported in Table C matrix are taken) is compared with an acceptance threshold (WE_THR). The WE_THR parameter is set by the user and when the scores sum exceeds it the reference CCIT process is deemed OOC.

![Diagram](image.png)

Table A: DMAIC phases

<table>
<thead>
<tr>
<th>Define Phase</th>
<th>Measure Phase</th>
<th>Analyze Phase</th>
<th>Improve Phase</th>
<th>Control Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of: 1. CCIT Critical Quality Attributes (CQA) as: • stability • reliability • repeatability 2. CCIT Critical Process Parameters (CPP) as the measurable variables having impact onto CQA: • 1st reading • Δ</td>
<td>1. Characterization of the natural variation of CQA and CPP, the purpose being monitoring the overall CCIT process behavior over a length of time appropriate for allowing the detection of relevant changes. 2. Setting the Control Limits (CL) for CCIT stability acceptance. 3. Setting the Specification Limits (SL) for CCIT capability acceptance.</td>
<td>Control charts based process stability analysis aimed at detecting special causes for CPP values non aligned with the reference CL.</td>
<td>In case: 1. CCIT is In-Control: continuous monitoring is performed 2. CCIT is Out-of-Control: corrective actions are implemented for removing the identified special causes (see the considerations arisen in the Preliminary Experiments section) and preventing them.</td>
<td>Control the improved CCIT process over time to ensure keeping it on track and correcting any outstanding variation before negatively affecting the process itself.</td>
</tr>
<tr>
<td>Process capability analysis aimed at estimating common causes for CCIT outcome non compliant with the reference SL.</td>
<td>If capability does not fulfill the SL the process is to be adjusted and common causes reduced according to the desired cost-benefit trade-off.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table B: Failures affecting CPP indicators and the corresponding mathematical models

<table>
<thead>
<tr>
<th>Standard Failures</th>
<th>Noise Source Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Reading</td>
<td>δ</td>
</tr>
<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></td>
</tr>
<tr>
<td>Transducer failure</td>
<td></td>
</tr>
<tr>
<td>Liquid presence in test chamber</td>
<td>Linear + Offset</td>
</tr>
</tbody>
</table>

Table C: Matrix for CPP data storage and control charts update

<table>
<thead>
<tr>
<th></th>
<th>(N+1)</th>
<th>...</th>
<th>(x*N+1)</th>
<th>K*N - (N-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>(N+2)</td>
<td>:</td>
<td>:</td>
<td>:</td>
</tr>
<tr>
<td>:</td>
<td>:</td>
<td>:</td>
<td>:</td>
<td>:</td>
</tr>
<tr>
<td>N</td>
<td>2*N</td>
<td>...</td>
<td>(K-1)*N</td>
<td>K*N</td>
</tr>
</tbody>
</table>

The N and K parameters are to be configured by the user, and an adequate choice of their values is required for SPCA optimal behavior.

The choice of N is based on evaluating the best trade-off between the following criteria:
- **responsiveness** (“quick variation” detection time: SPCA should detect possible CCIT drifts as fast as possible; responsiveness increases as N decreases)
- **robustness** (SPCA should avoid false detections: robustness increases as N increases)

The empirical analysis of the SPCA behavior in the reference case study shown that N=10 is the best solution for CCIT; as a consequence the control charts choice is narrowed to a combination of X and R charts (for N<12 the standard deviation method S loses efficiency (3)).

The choice of K is based on finding the best compromise between the following criteria:
- **regression accuracy** (increases with K)
- **time performance** (short chart calculation time: decreases with K)
- **responsiveness** (decreases with K)

A static choice of K that satisfies the criteria is not possible, so K needs to be adapted dynamically or chosen on a case by case basis.

Deviations Analysis

Figure 5 shows as the CPP data being processed by SPCA may be altered by a failure occurrence and how the failure effects are modeled as the addition of a noise source causing a process deviation; SPCA processes the resulting data by means of Control Charts, performing Trends and OOC points detection. The patterns shown in the detected deviations are in turn analyzed to ascertain their correspondence with the standard failures mathematical models, so to provide the user with detailed information on the troubleshooting actions to be undertaken, or start equipment automatic corrective actions.
The following sub-sections give an overview of:
- the simulation, for a given test chamber, of a failure from each of the standard failures subsets (refer to Figure 4);
- the SPCA performance corresponding to different K values.

The 1st reading CPP was the object of the analysis, nevertheless all conclusions reported for 1st reading are fully applicable to Δ as well.

**Failure modeled as “Linear + Offset”**

A failure showing this feature was induced contaminating the test chamber with liquid. This may occur in a production scenario when a defective BFS was tested during the previous test cycle, being that holes or damaged seals may cause liquid leakages from BFS. During the CCIT vacuum is established within the test chamber, leading to liquid evaporation and subsequent CPP variation.

Figure 6 shows as this anomaly caused a 1st reading quick variation (10 mbar decrease) followed by a progressive increase towards the former value (owing to Automatic Drying System (ADS) algorithm action, as detailed hereinafter). In this case the X-Chart was effective in detecting the OOC points, allowing SPCA to recognize the deviation pattern as belonging to the “Linear + Offset” class and trigger the corresponding alarm.

At this point the user may stop the equipment and provide to manually clean the test chamber. Otherwise the anomaly may be automatically managed by the equipment, by means of ADS for excluding and drying contaminated test chambers until the complete restore of the optimal condition (this automated option avoids the possibility of testing conforming BFS into contaminated chambers, causing their possible false rejection). The correct management of a failure modeled as Linear + Offset is successfully completed with the capability of detecting wrongly configured equipment parameters (e.g. if the M_LEV threshold is mistakenly set too low the ADS is not activated).

**Failure modeled as “Linear (Long Duration)”**

This noise source model was simulated with an electrovalve failure causing a 5 mbar decrease of the 1st reading. Figure 7 shows as SPCA detected the trend (highlighted in blue) by means of the X-Chart.

The collected data (refer to Table D) shown that SPCA needs at least a value of K=40 for each chart to detect effectively noise sources of this type.

![Figure 7: Linear (Long Duration) failure Charts](image)

The simulation was designed so to consider the worst case scenario, hence the failure was conventionally started at the half of the measurement sets (e.g., when working with K=50 and N=10, 500 measurements were needed, hence the noise in this case started at the 250th measurement).

<table>
<thead>
<tr>
<th>K</th>
<th>Noise Start</th>
<th>Number of Charts</th>
<th>Detected Trend</th>
<th>Result</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>

Table D: Linear (Long Duration) failure collected data
Failure modeled as “Linear (Short Duration)”

This noise source model was simulated contaminating the test chamber seal with tiny plastic particles, so to compromise its airtightness during the CCIT cycle and cause a 5 mbar decrease of the 1st reading CPP.

Figure 8 shows as SPCA detected the trend (highlighted in blue) by means of the X-Chart.

<table>
<thead>
<tr>
<th>K</th>
<th>Noise Start</th>
<th>Number of Charts</th>
<th>Detected Trend</th>
<th>Result</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>

Table E: Linear (Short Duration) failure collected data

This type of failure causes a greater slope on the X-Chart curve with respect to the ones of the Long Duration Linear class, making K=20 enough for a correct failure identification (refer to Table E).

Failure modeled as “Step”

This noise source model was simulated damaging a test chamber seal so to cause a sudden decrease (step-like) of the 1st reading CPP. The minimum relevant value for the step amplitude is 0,5 mbar and is determined according to the equipment THR parameter (step amplitudes lower than THR are not able to influence the CCIT process outcome therefore are not taken in account).

The collected data (refer to Figure 9) shown that K=20 is an appropriate value for effectively detecting this type of failures.

Results

SPCA provided the possibility to perform quick data-driven decision making and identify the root cause behind CCIT process stability alterations with a high degree of certainty.

Figure 9: Step failure Charts

In particular, following the detection of OOC variations, SPCA pointed out clear indications towards the needed corrective actions to be implemented for removing special causes, and therefore avoiding a time-consuming and unnecessary troubleshooting phase. SPCA worked in the direction of complementing the equipment standard tools for runtime diagnostic of pneumatic actuators, and mechanic and electronic components (algorithm for Autodiagnostics), helping the CCIT process to perform reliably and predictably.

Capability Management

Once special causes have been detected and removed and the CCIT process stability assured, SPCA estimates the common causes impact and provides feedback about the improvements to be made to the equipment and the configuration of its computerized system, so to attain compliance with the established SL. Therefore a continuous process capability analysis is performed in order to achieve this goal: CPP values are taken as input and $C_p$ e $C_{pk}$ indicators values (5) are returned as output.

The desired quality, and therefore the common cause variability, are generally deemed acceptable for such pharmaceutical equipments when the condition $C_p \geq 1.33$ is satisfied; in case the $C_{pk}$ value is close to $C_p$ we can infer that the process CCIT is capable of producing within the SL and moreover that it is centered on the target value. In case SPCA finds that these conditions do not hold true, the CCIT process is affected by common causes which must be investigated (in particular the $C_p < 1$ condition is symptomatic of unacceptable performance behavior).

$C_p$ will remain constant unless there is a clear change made in the process or the equipment. In case that the CCIT process is not centered on the SLs mean a substantial deviation of the CQA expected behavior, therefore actions should be planned to get improvement on both capability indicators value.

The parameters to be optimized and the actions to be executed for improving process capability are to be determined according to a preliminary choice on the desired trade-off between process performance and quality on one side, and the corresponding costs on the other.
Results
The information derived from the SPCA analysis on a broad range of conditions, merged with the historical know-how of the CCIT process, allowed to lay down a list of actions to perform for process capability and equipment efficiency improvement:

• test cycle:
  o recipe configuration and set-up parameters adjustment
  o equipment hardware fine-tuning

• equipment sub-systems:
  o routine use of embedded diagnostic tools

• pneumatic system:
  o optimization of the test vacuum generation system (pipes routing and sizing, pressure regulators calibration)

• test chamber:
  o choice of materials and seals, mechanical tolerances refinement
  o calibration of compensator springs on test chamber mobile bottom part shaft

Conclusion
A method for process improvement and variability management has been presented, aimed at:

• identifying possible process weakness allowing proactive remedial;
• making respectively failures identification, resolution and prevention possible;
• driving the design of suitable and robust solutions based on thorough knowledge of processes and possible sources of variability;
• achieving excellence as long as preventing variability is the key for producing high quality.

SPCA proved is effectiveness in:

• attaining a stable, repeatable, reliable and robust CCIT process in the context of a productive environment;
• providing means for enhancing production quality, improving the equipment performance and extending its operative life span.

Possible future developments for SPCA include its full industrialization and the ability for dynamically adapting the K value for maximizing the likelihood of anomalies detection.

References


Acknowledgements
The authors would like to thank Michele Soldati and Marco Silvestri for the contribution (2) that led to the developments presented in this article.