Impact of the Vial Capping Process on Residual Seal Force and Container Closure Integrity

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Roche Project

Head of Roche PTDE-P

Roche PTDE-P
Established Product Support

Roche PTDE-P
Primary Packaging

Roche DP Fill&Finish Sites
Roche DP MSAT Teams

Roche PTDE-DV
Device Verification

Roche PTDU
Process Development
Outline

Introduction

Lab scale experiments

GMP Manufacturing

Conclusion

Capping, Regulatory Framework

RSF, CT, He-Leak

Large Scale capping equipment

Process parameter setting
Motivation

1. The capping process can impacts container closure integrity (CCI) and can cause cosmetic defects.
2. Authorities increasingly recognize the criticality of the vial capping process (USP <1207.3> revision).
3. Across the clinical and commercial manufacturing sites a variety of capping techniques and packaging configurations are implemented.
4. Capping equipment independent methods are insufficiently described.

Mathaes et al., The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests, EJPB, 2015
Capping Associated Issues

<table>
<thead>
<tr>
<th>Examples of defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scratches on vial neck, crimp cap wrinkles, scratches on the crimp cap</td>
</tr>
<tr>
<td>Partially crimped vials</td>
</tr>
<tr>
<td>Dimpling rubber stoppers</td>
</tr>
<tr>
<td>Removal of the crimp cap upon flip-off button removal</td>
</tr>
<tr>
<td>CCI failure because of low stopper compression</td>
</tr>
<tr>
<td>Time consuming validation process</td>
</tr>
<tr>
<td>Subjective visual inspection of capped vials</td>
</tr>
</tbody>
</table>

Partially crimped vials:

Dimpling:
Residual Seal Force

The RSF tester measures the force / distance curve (green line). The RSF (56 N, yellow line) is derived from the minimum of the 2nd derivative of the force / distance curve.
Aim of the Project

• Define and investigate key capping process parameters

• Establish a capper independent method (residual seal force (RSF) tester) to monitor the capping process

• Define a safe and robust RSF range for container closure systems (CCS)

➢ Improve the robustness of the capping process → less risk for major and minor defects

➢ Standardize capping → simplify the capping equipment validation
Experiment Setup: Lab Scale

<table>
<thead>
<tr>
<th>Vial neck</th>
<th>Rubber stopper</th>
<th>Crimp Cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 mm 20 mm</td>
<td>Serum D777-1</td>
<td>Datwyler</td>
</tr>
<tr>
<td></td>
<td>Serum D713</td>
<td>Datwyler</td>
</tr>
<tr>
<td></td>
<td>Serum West 50</td>
<td>Datwyler</td>
</tr>
<tr>
<td>13 mm 20 mm</td>
<td>Lyo D777-1</td>
<td>Datwyler</td>
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<td>Lyo D713</td>
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<td>Lyo West 50</td>
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</tr>
</tbody>
</table>

Integra West Capper:
### Capping Equipment Settings

Capping equipment settings

<table>
<thead>
<tr>
<th>Setting No.</th>
<th>Capping plate to plunger [mm]</th>
<th>Force [N]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.19</td>
<td>44.48</td>
</tr>
<tr>
<td>2</td>
<td>8.86</td>
<td>44.48</td>
</tr>
<tr>
<td>3</td>
<td>8.48</td>
<td>44.48</td>
</tr>
<tr>
<td>4</td>
<td>8.35</td>
<td>75.62</td>
</tr>
<tr>
<td>5</td>
<td>7.98</td>
<td>222.41</td>
</tr>
</tbody>
</table>

Key capping parameters

1. Capping force
2. Capping plate height
RSF 20mm Neck Vials

Different rubber stopper types

- Increased RSF with increased rubber stopper flange height (West vs. Daikyo).
- The rubber stopper shore A hardness had only a minor effect (D777 vs. D713).

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016
Rubber stopper design (lyo vs. serum)

- The rubber stopper design had only a minor effect.

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016
RSF - Influence of the Flip-off Button

RSF without flip-off button

RSF with flip-off button

West cap, without flip-off button

West cap, with flip-off button
RSF - Influence of the Flip-off Button

Measuring with flip-off button vs. without flip-off button

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016
Extended characterization: Stopper Compression

Stopper compression as a function of RSF

CT measurements:

Vial height measurements:

\[
\text{Stopper compression} = \frac{\text{Flange height before capping} - \text{Flange height after capping}}{\text{Flange height before capping}}
\]
Rubber stopper compression is a function of RSF. CT and vial height measurements showed good correlation.

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016
Rubber Stopper Defects

All formats were measured with CT and were visually inspected

CT measurements:  Visual inspection:

Worst case Capper setting 6, D777-1 liquid, RSF = 101 N
The soft D777-1 liquid rubber stopper showed dimpling.

Mathaes, R., Impact of Vial Capping on Residual Seal Force and Container Closure Integrity, PDA, 2016
Defining an Adequate RSF Range for a CCS

CCI or microorganism tightness not assured
Partially folded crimp cap

Vials capped with different capping equipment settings
Measure RSF and use extended characterization methods
Define a safety margin
Define a secure RSF range for each CSS configuration
Run commercial capping equipment in the secure RSF range
Example: Defining an Adequate RSF Range

13 mm Neck Vial, D777-1 liquid rubber stopper, West crimp cap

- Vials capped with RSF 16 N – 101 N
- No vials showed helium leakage, vials with RSF 101 N showed dimpling
- Define a safety margin of e.g. 10 N
- Acceptable RSF range of 26 N – 66 N
- Capping equipment RSF set value 46 N
Experimental Setup: Drug Product Manufacturing

- Different process parameter
- Different formats
- Different capping equipment

Describe the key capping parameters for the commercial capper
Ensure that commercially produced vials correlate to the lab scale data
Capping Process Parameters

Commercial capping equipment

Key capping parameter

1. Capping force
2. Capping plate height
3. Rotation speed of the turntable
Commercial Site: 6 ml Serum Vials

Influence of the **capping pre-compression force**

**RSF measurements**

![RSF measurements graph]

**CT measurements**

![CT measurements graph]

The capping pre-compression force had only a minor influencing on RSF.

Mathaes et al., Critical Process Parameters of Capping Equipment used in GMP DP manufacturing, PDA, 2016
Commercial Site: 6 ml Serum Vials

Influence of the rotation speed of the turntable

RSF measurements

CT measurements

The rotation speed of the turntable had only a minor influence on RSF.

Mathaes et al., Critical Process Parameters of Capping Equipment used in GMP DP manufacturing, PDA, 2016
Commercial Site: 6 ml Serum Vial

Influence of the **capping plate-plunger distance**

**RSF measurements**

![RSF measurements graph]

**CT measurements**

![CT measurements graph]

The capping plate-plunger distance has a major influence on RSF.

Mathaes et al., Critical Process Parameters of Capping Equipment used in GMP DP manufacturing, PDA, 2016
Conclusion

- RSF technology is a reliable and precise tool to characterize the quality of the capped product in dependence of the capping process parameters, independent of the used CCS and capping equipment.
- Capping pre-compression force is not the only RSF influencing capping process parameter.
- Stopper compression can be measured by CT or vial height measurements and is a function of RSF.
- A secure RSF range can be defined with less risk of major and minor defects.
References


RSF - Influence of the Flip-off Button

Lonza: Drug Product Services
Hanns-Christian Mahler

Roche

Genentech

Holger Röhl
Jürgen Eder
Sascha Dreher
Michael Lammel
Yves Roggo
AAlejandra Nieto

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Thank you