PDA Parenteral Drug Association

Training and Research Institute

Residual Seal Force: A Powerful Vial Seal Quality Test

Carolina González Gaitán, PhD
Genesis Packaging Technologies

PDA Container Closure Integrity Testing - Basic Course
23 - 24 October 2025 Vienna, Austria

PDA Parenteral Drug Association Training and Research Institute

Agenda

1. Seal quality tests
2. Characterizing a “well-sealed” vial
3. Residual Seal Force – *Concept, basis of testing, methodology, variability considerations, significance and use of RSF test*
4. Studies – *Effect of time, effect of FO button, correlation with CCIT*
5. Summary

Seal Quality Tests

USP <1207.3> Package Seak Quality Test Methods

"Package seal quality tests" are checks used to characterize and monitor the quality and consistency of a parameter related to the package seal, providing some assurance of the package's ability to remain integral. Seal quality tests ensure that seal attributes, package materials, package components, and/or the assembly process are consistently kept within established limits, thus further supporting package integrity. Seal quality tests differ from leak tests in that they provide no information relative to actual package integrity; thus, a package that meets the requirements of a seal quality test may still be defective and leak. Therefore, seal quality tests and leak tests work together to ensure package integrity.

JP XVIII Packaging Integrity Evaluation of Sterile Products <G7-4-180>

2.1.2. Seal quality test

The seal quality test is used to indirectly ensure ability to maintain package integrity by confirming that parameters related to the container seal or fitting are valid. Conducting the seal quality test set based on evidence is useful for the continuous understanding of the characteristics required for closure and maintaining package integrity. In addition to examples shown as the seal quality test methods (Table 1), various methods are used.

ChP <9650> Guidelines for Research on Pharmaceutical Package Integrity

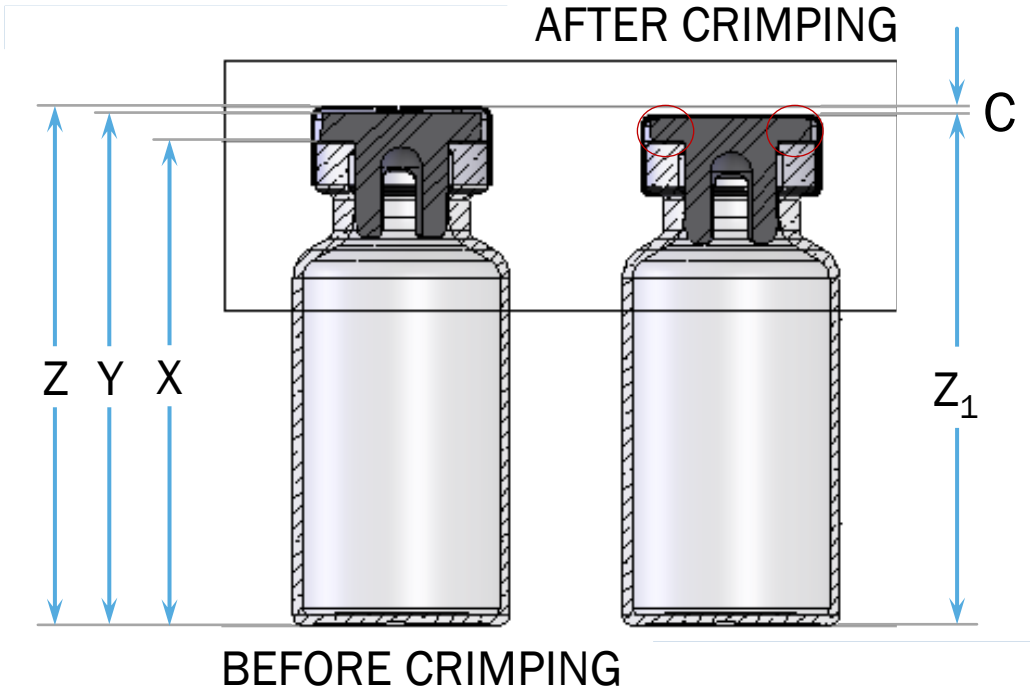
II. Package Seal Quality Test

The package seal quality is related to whether the sealing performance meets the limit in specification, such as the heat sealing strength of pouches. It is ensured, through seal quality test, that sealing property, packaging materials, packaging components and/or assembly processes are consistently maintained within a defined range, can characterize the package seal quality, monitor the consistency of process parameters, and further ensure package integrity.

Seal quality test cannot replace package integrity test. Packages meeting the seal quality requirements may still have defects resulting in leakage. For example, flexible bag packages with seal strength meeting requirements may have leakage due to the perforations on bag bodies.

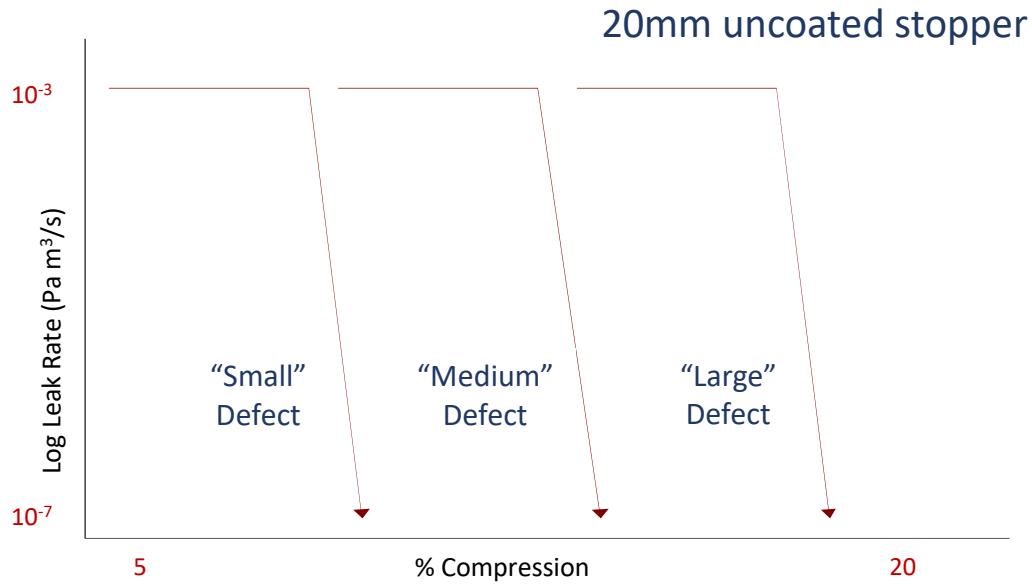
Well-Sealed Vial

- Sufficient compression to achieve Leak Rate Cut-off
- An applied force compresses the stopper flange.
  1. Cross section of the component(s)
  2. Durometer (hardness) of the rubber
  3. The percent of compression required to achieve leak rate cut-off



Well-Sealed Vial

- Sufficient compression to achieve Leak Rate Cut-off
- An applied force compresses the stopper flange.
  1. Cross section of the component(s)
  2. Durometer (hardness) of the rubber
  3. The percent of compression required to achieve leak rate cut-off



Morton, Dana K. "Quantitative and Mechanistic Measurements of Parenteral Vial Container/Closure Integrity. Leakage Quantitation" *PDA J of Pharm Sci and Technol* 1989, 43 (2) 88-97

PDA Parenteral Drug Association Training and Research Institute

Residual Seal Force - RSF

RSF is the strain a compressed elastomeric rubber stopper flange continues to exert on the vial sealing surface after the crimping of an aluminum seal

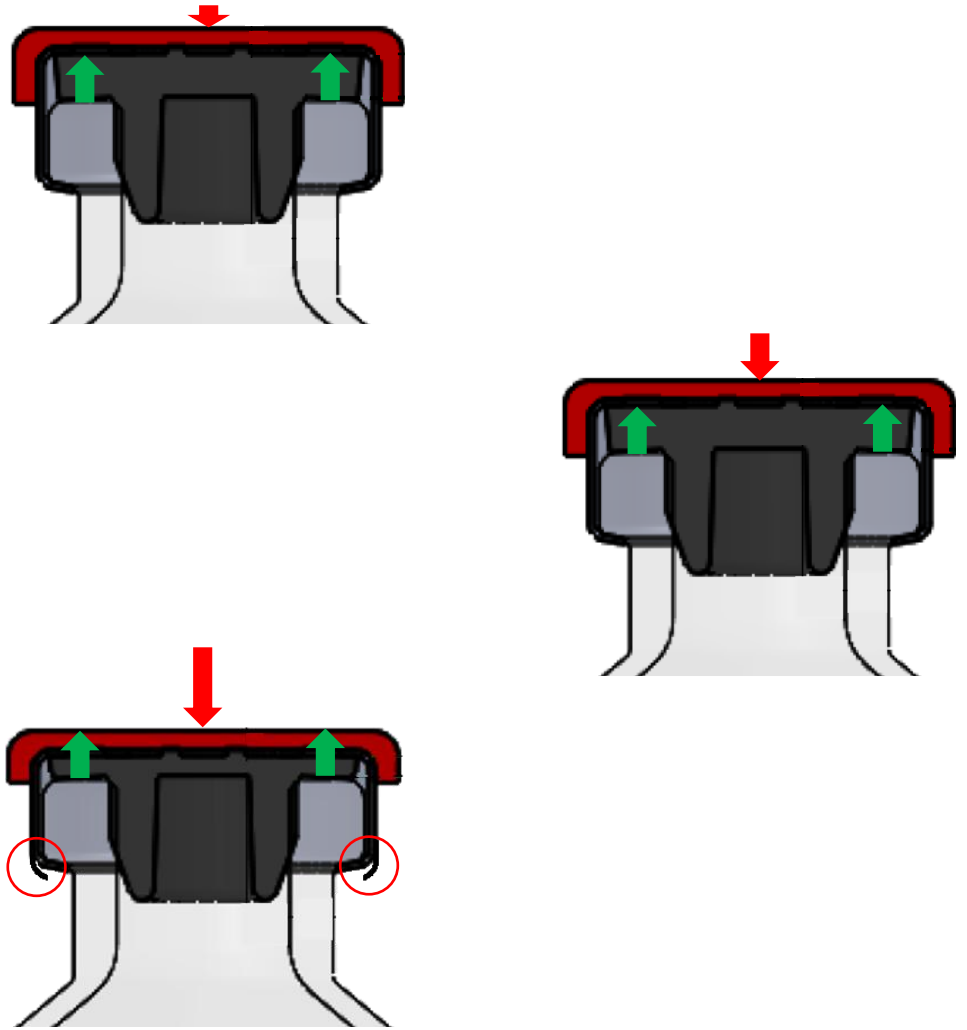
RSF is an easy-to-use quantitative method to standardize seal quality regardless of the capping equipment used for crimping

RSF helps to set up capping parameters to ensure consistency and ease capper validations

Correlation of RSF with CCITs will provide guidance on setting acceptable ranges

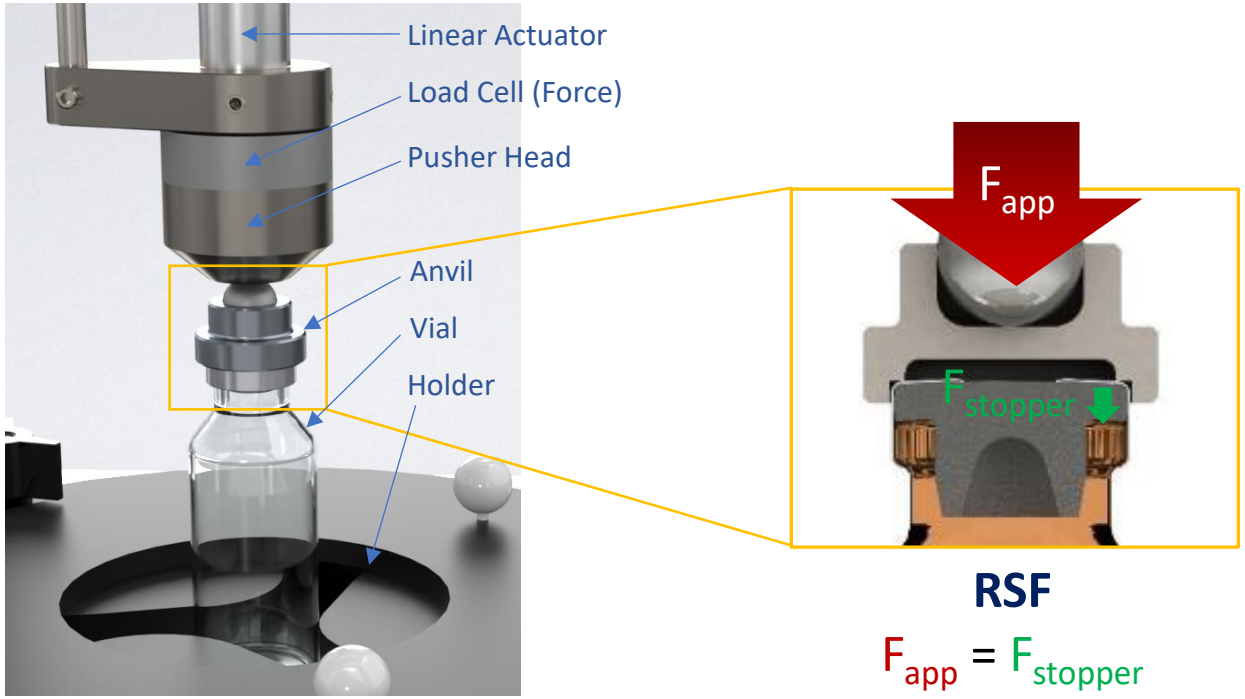
Basis of RSF Testing

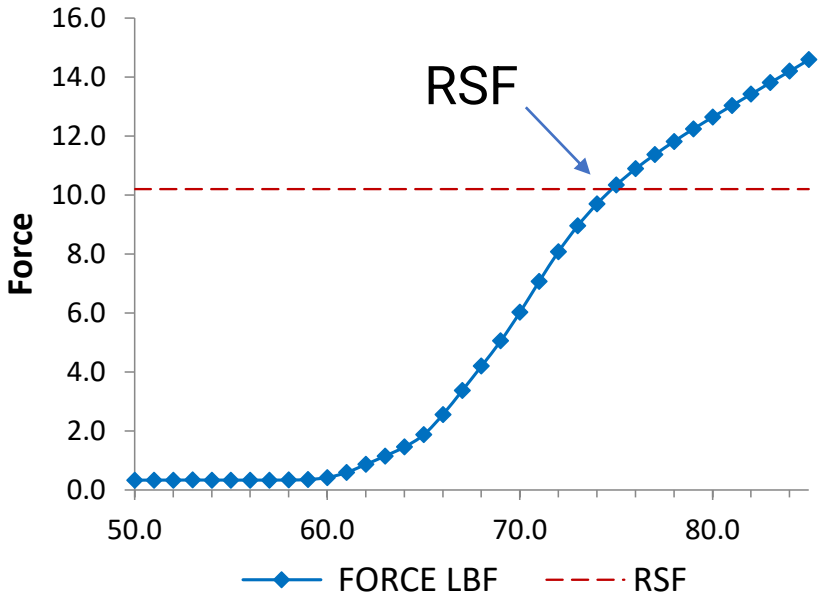
- Upon capping, the stopper flange is compressed against the vial land sealing surface
- The stopper flange acts like a “compressed spring”
- The tester apply a force on the cap and stopper
- When the tester force exceeds the closure compression force → RSF



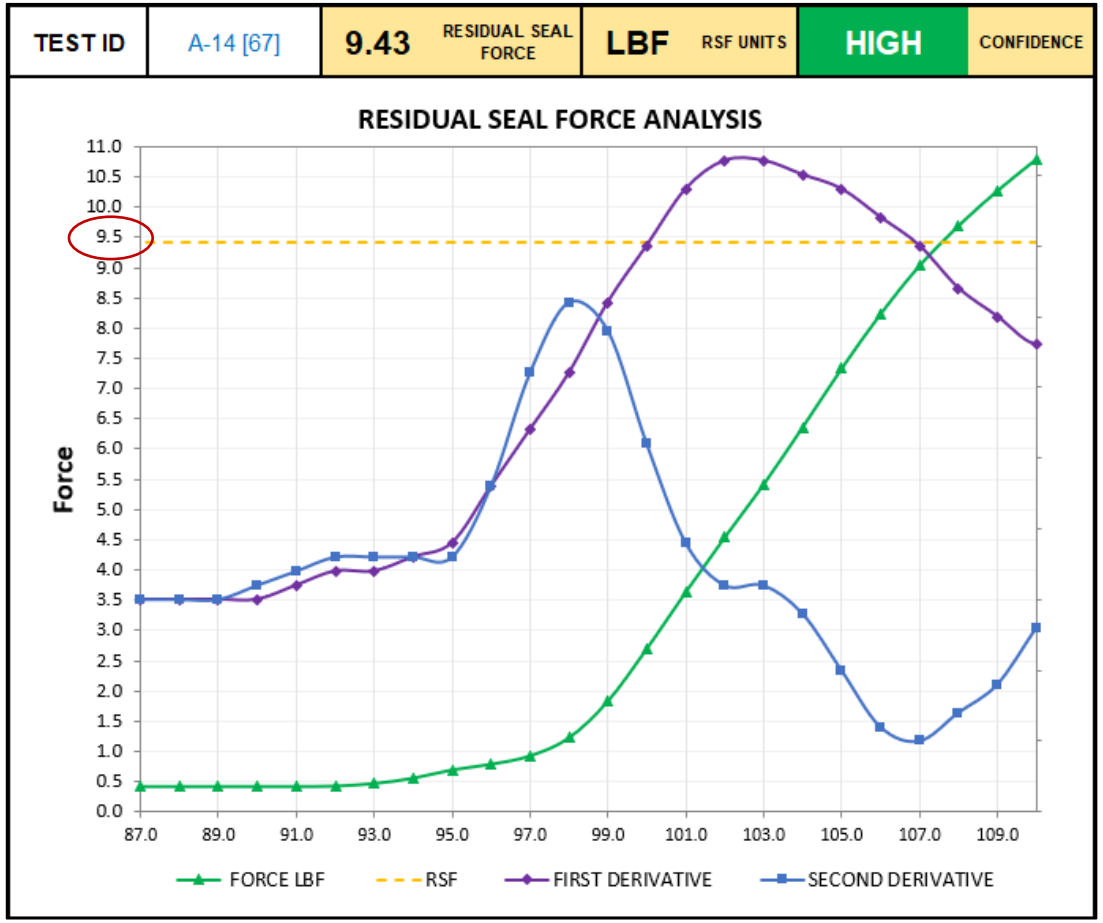
R. Mathaes et al. “The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests” *European Journal of Pharmaceutics and Biopharmaceutics* 99 (2016) 54–64

RSF Tester and Methodology





Determining RSF



- Stress-strain curve (green) is a combination of the viscous and elastic response to the stress from tester load
- RSF is determined using the stress-strain curve: the "knee" (yellow)
- An algorithm* is applied, using the 1st (purple) and 2nd (blue) derivatives to accurately identify that knee

* Ludwig J, Nolan P, Davis C, Automated method for determining Instron residual seal force of glass vial/rubber stopper closure systems, *PDA J of Pharm Sci and Technol* 1993, 47 (5) 211-253

PDA Parenteral Drug Association Training and Research Institute

Significance & Use of RSF Method

Package Development

- Determine effects of CCS component variables
- Characterize a “well-sealed” vial

Validation

- Establish optimum capping parameters
- Evaluate variation

Production

- Verify capping equipment set-up
- Capping process monitor

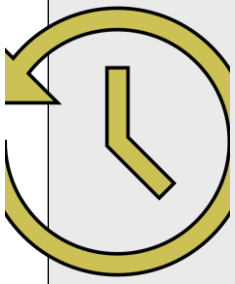
Variability Considerations

Instrument

- Gage R&R
  - Custom compressed spring fixture ~2%
- Orientation & centering
- Anvil design
- Button removal

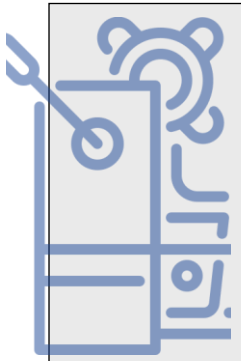
Components Variation

- Dimensional tolerances
- Stack-up, interference fit
- Mismatch of components



Time

- Elastomer relaxation

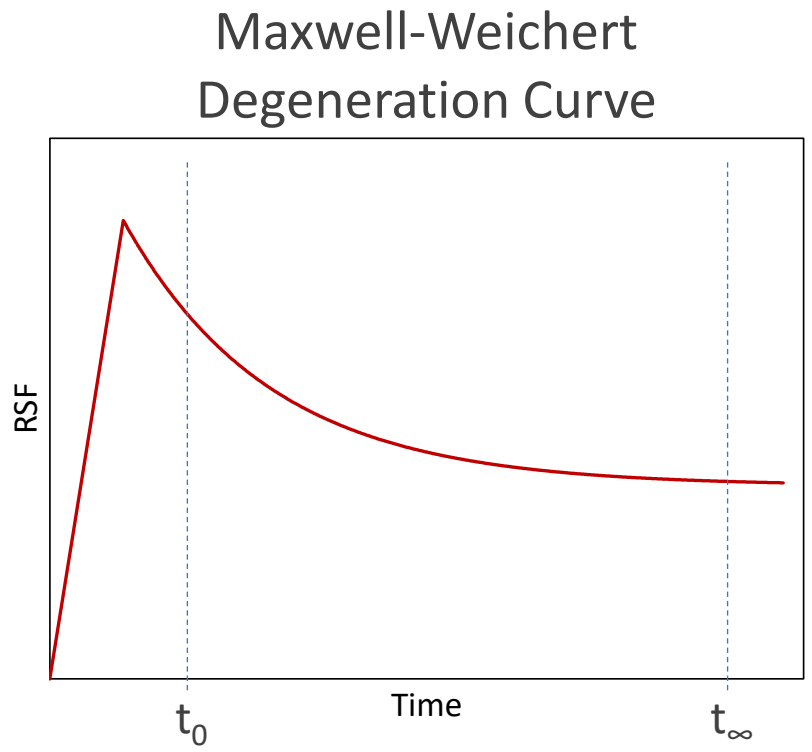


Capping Process

- Optimization of settings
- One head vs. Multiple heads

Time Dependency

Influence of Elastomer Relaxation

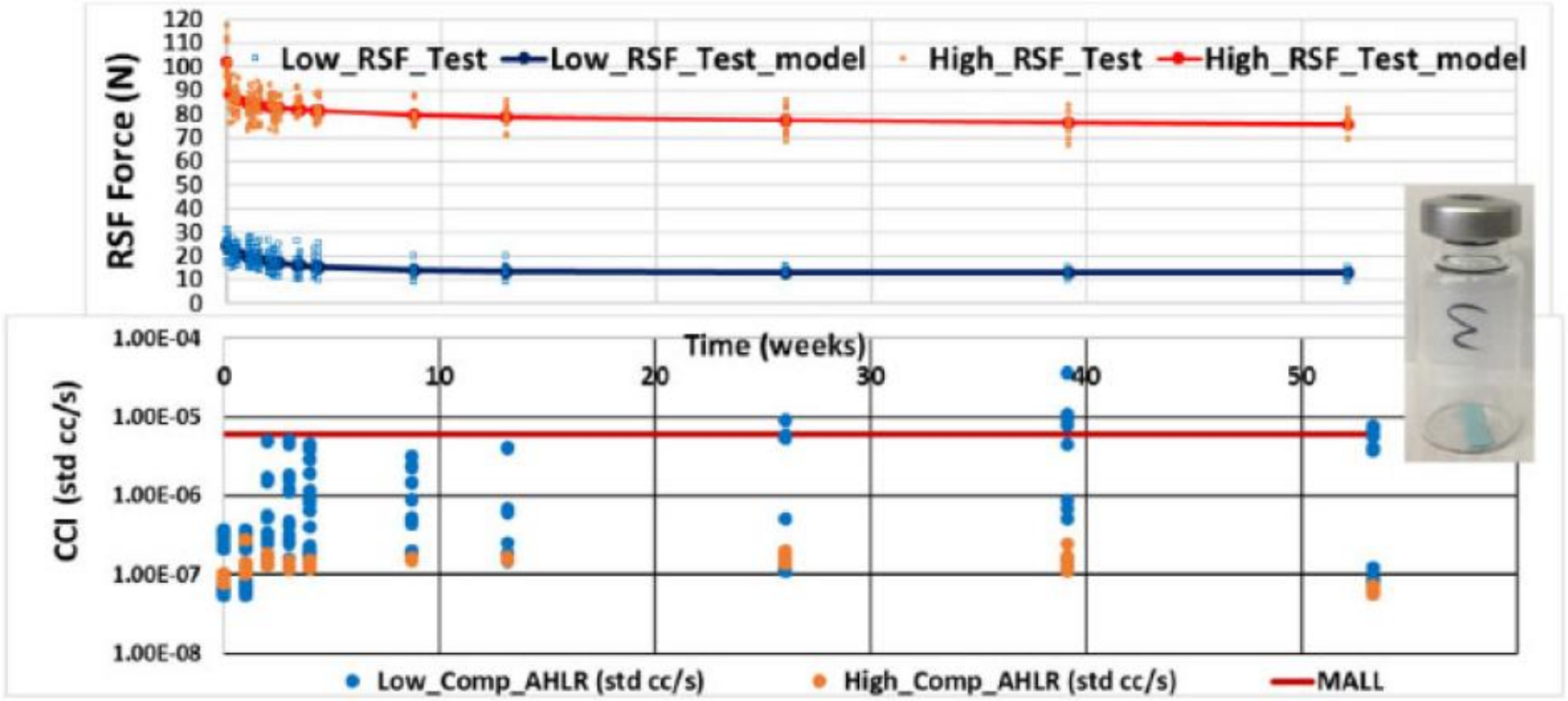


- Elastomer is the base material of the stopper
- Exhibit viscoelastic behavior
- Relaxes over time → RSF decay over time

Morton D., Lordi N. "Residual Seal Force Measurements of Parenteral Vials: I. Methodology" PDA J Pharm Sci and Technol 1998, 42 23-29

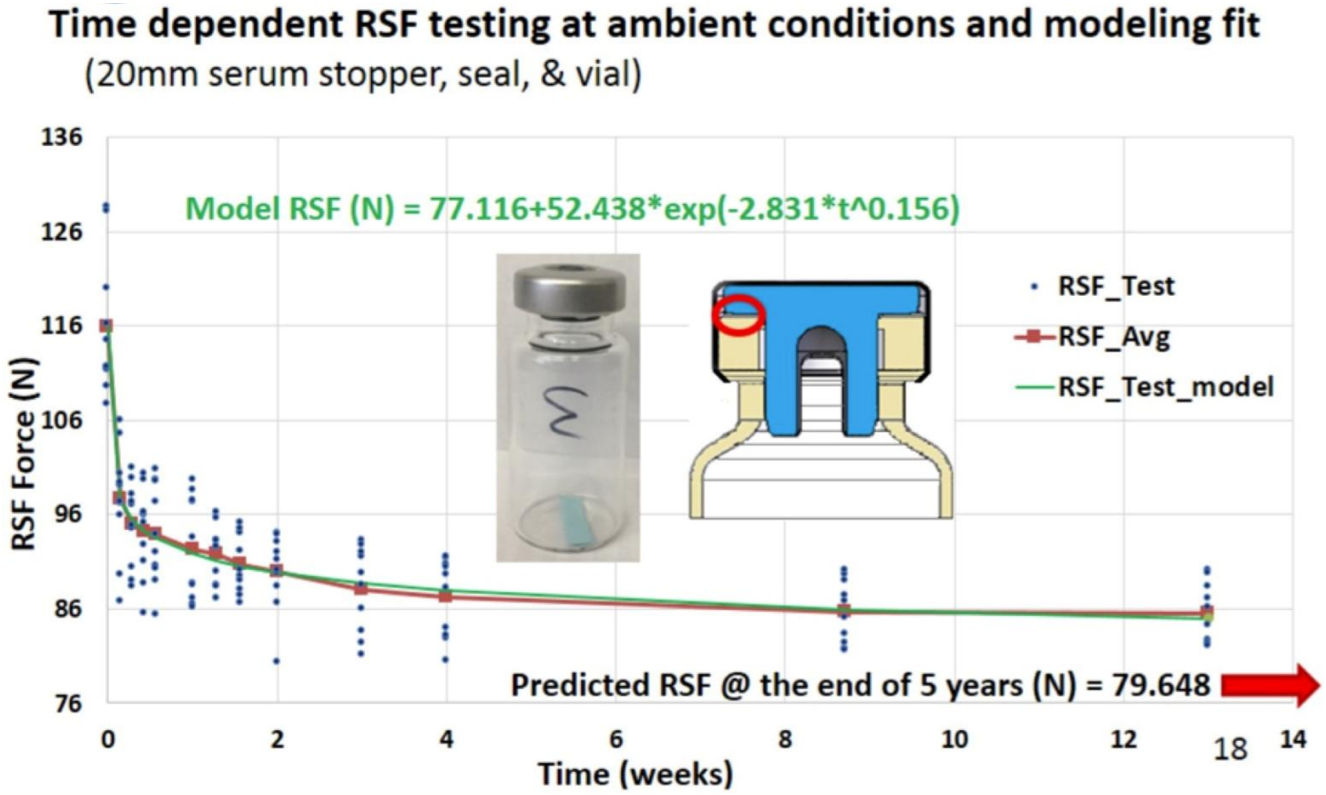
Time Dependency

Figure 1: RSF and helium leak testing data for vial CCS using a 20 mm butyl elastomer stopper and a 10 mL glass vial fully filled with helium at ambient pressure, tested at ambient temperature through a vacuum chamber [8, 9].



Zeng, Q. "Critical Time- & Temperature- Dependent Container Closure Integrity (CCI) Through the Sealed Drug Product Life Cycle" PDA Parenteral Packaging Conference, Rome, Italy; 2018

Time Dependency



Zeng, Q.; Zhao,C; "Time-Dependent Testing Evaluation and Modeling for Rubber Stopper Seal Performance." *PDA J Pharm Sci and Tech* 2018, 72 134-148

Time Dependency

Statistical Data Generated of 20 Vials from the RSF Time Course

Time	Mean RSF (N) (n = 20)	Difference in Mean	RSD%
1 minute	62.7	-	9.9
10 minutes	54.0	**8.7**	11.0
90 minutes	53.1	0.9	7.0
1 day	52.1	1.0	9.6
7 days	51.0	0.9	11.1
21 days	50.5	0.5	10.2

Adapted from: Ovadia, R; Streubel, A; et al. "Quantifying the Vial Capping Process: Residual Seal Force and Container Closure Integrity" *PDA J of Phar Sci and Technol*, 2019 73 (1) 2-15

PDA Parenteral Drug Association Training and Research Institute

Takeaways - Time Dependency

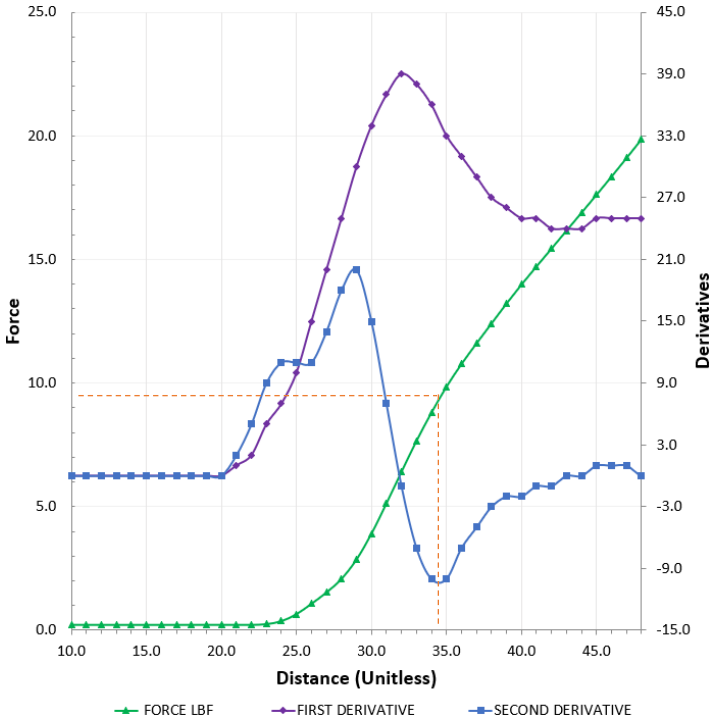
- Stress-relaxation of the rubber stopper is time-dependent affecting the sealing force
- Rubber will relax with time
  - RSF decay
  - Greater variability at t < 10 min
  - Greater decrease with higher crimping forces

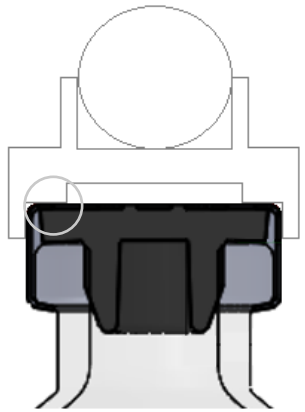
PDA Parenteral Drug Association Training and Research Institute

Flip-Off Cap Impact

Flip-Off Cap Impact

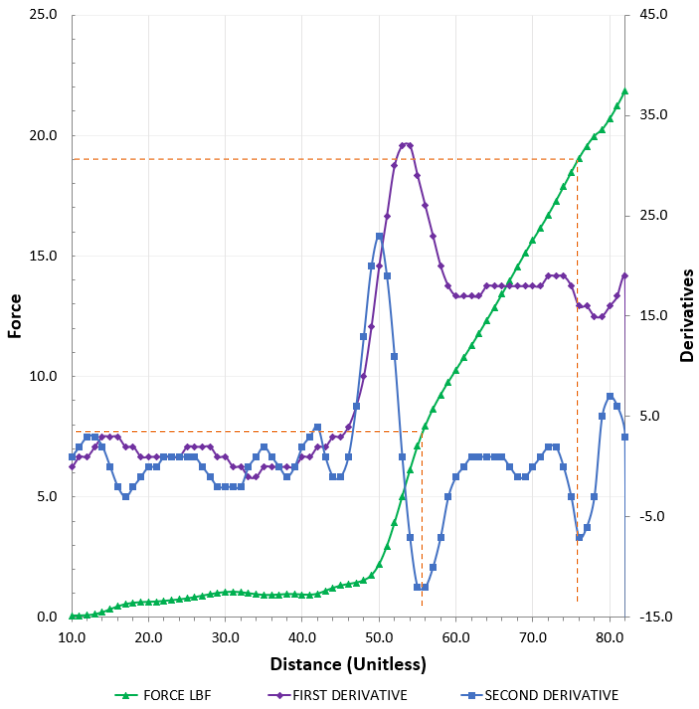
Without flip-off button

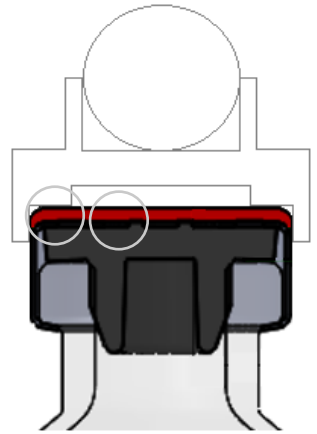




One clear minimum on 2nd derivative

With flip-off button

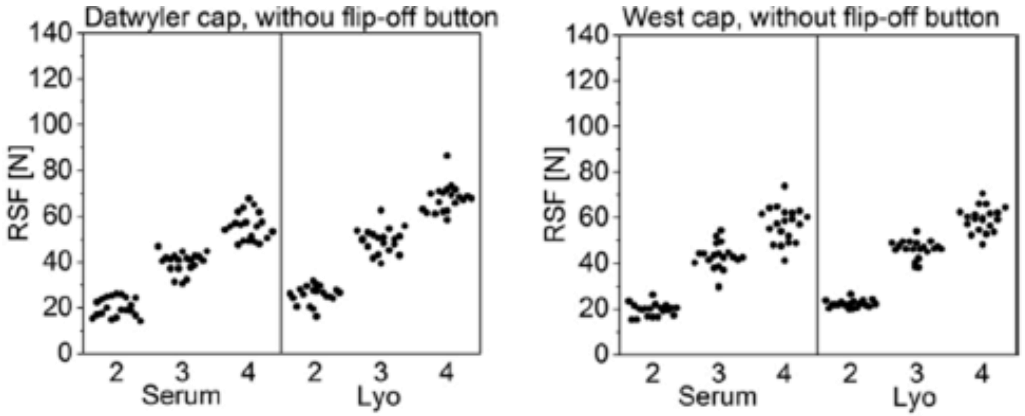




More complex and noisier signal

Flip-Off Cap Impact

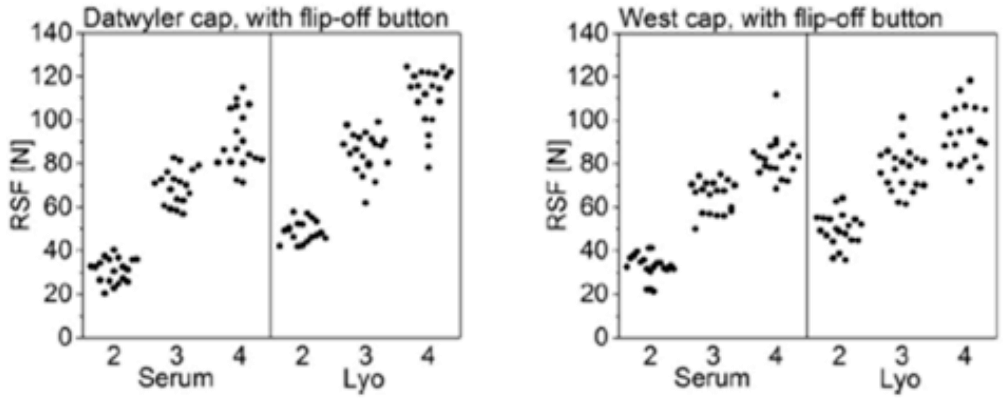
Without flip-off button



Low variability

Distinctive RSF groups

With flip-off button



High variability

Difficult to distinguish among RSF groups

R. Mathaes et al. “Impact of Vial Capping on Residual Seal force and Container Closure Integrity” *PDA J Pharm Sci and Tech* 2016, 70 12-29

PDA Parenteral Drug Association Training and Research Institute

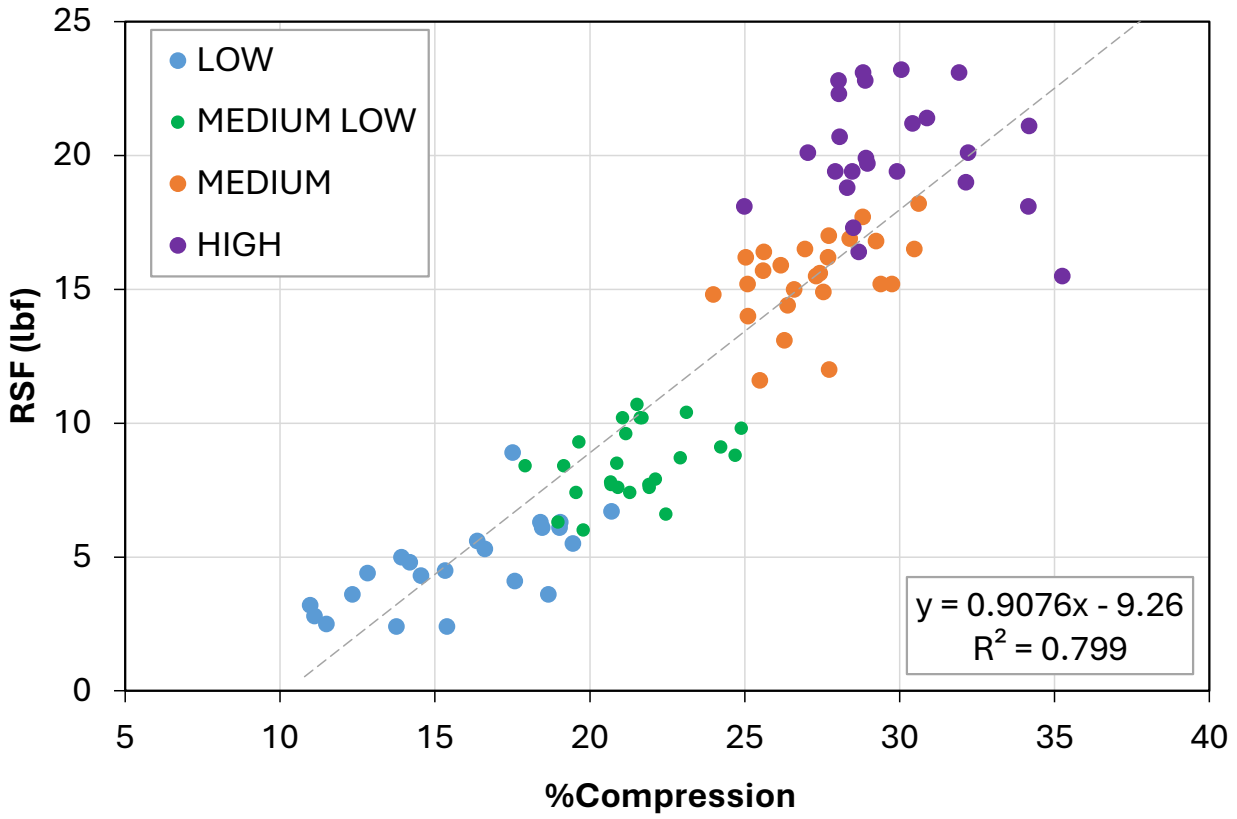
Takeaways – Flip-Off Cap Impact

- The flip-off button adds complexity to the system, preventing a clean transition of the force applied by the RSF tester
  - The stress-strain curve is more complex – sometimes with 2 minima
  - Higher variability
- More reliable results without the flip-off button → Destructive

PDA Parenteral Drug Association Training and Research Institute

Correlation with CCIT

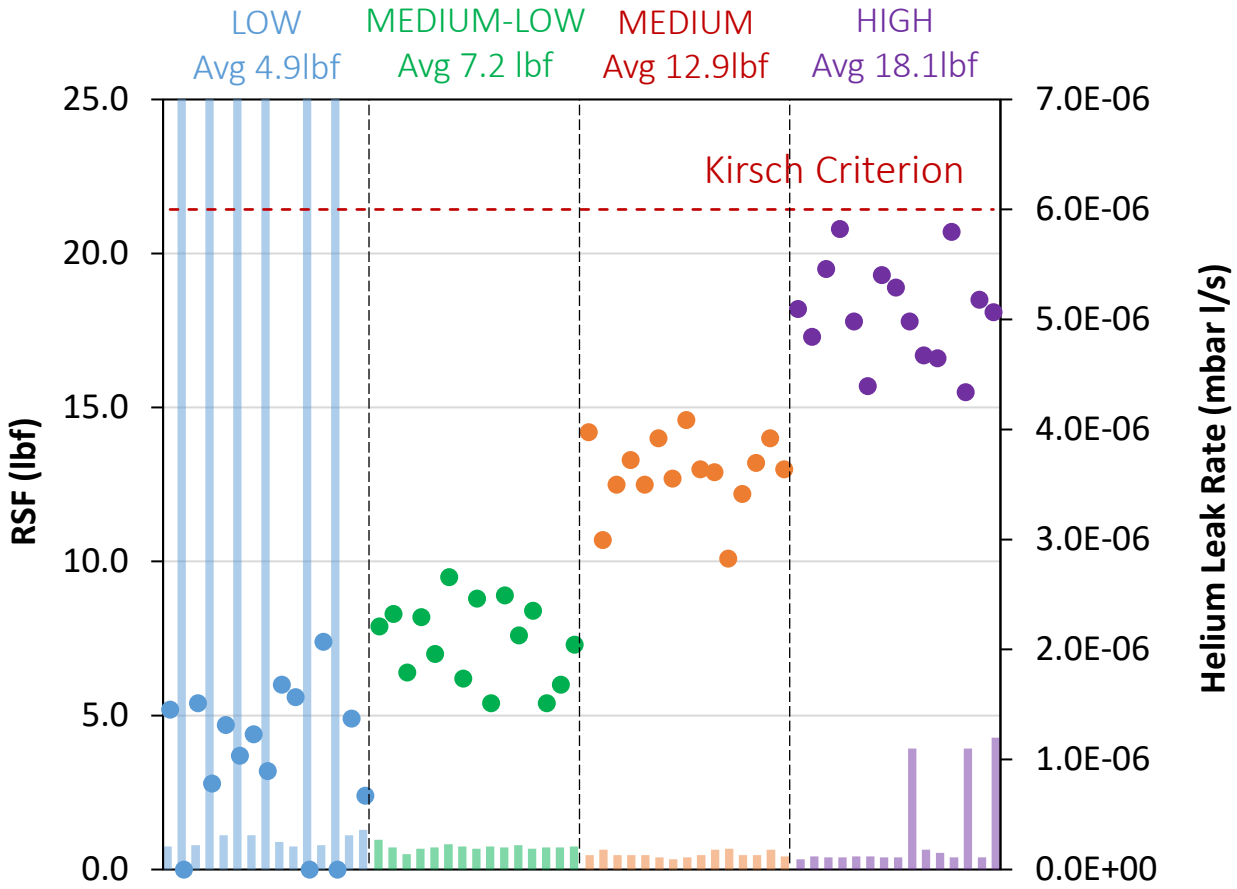
RSF vs. Compression



20R - 20 mm serum stopper

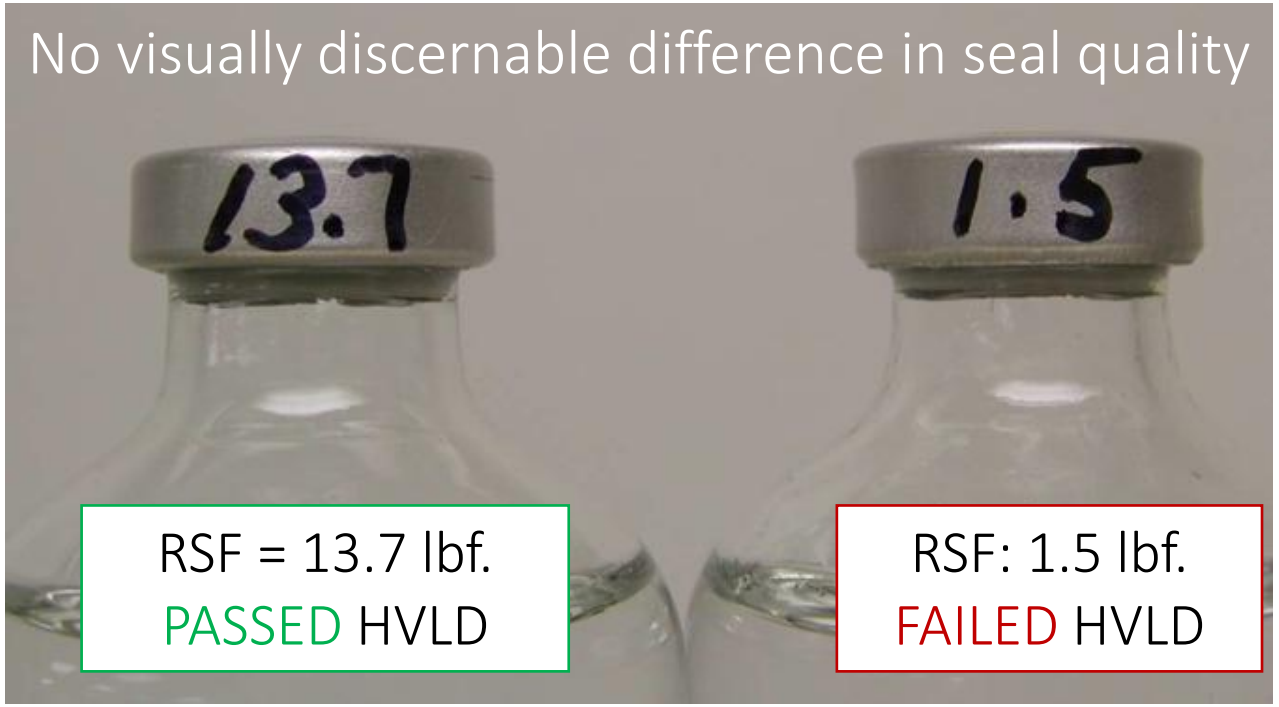
RSF vs. He Leak Rate

- Kirsch criterion*: Helium leak rates lower than 6 x 10^{-6} std cc/s have been associated with acceptable microbial challenge results
- Low group have several samples that failed based on the Kirsch Criterion



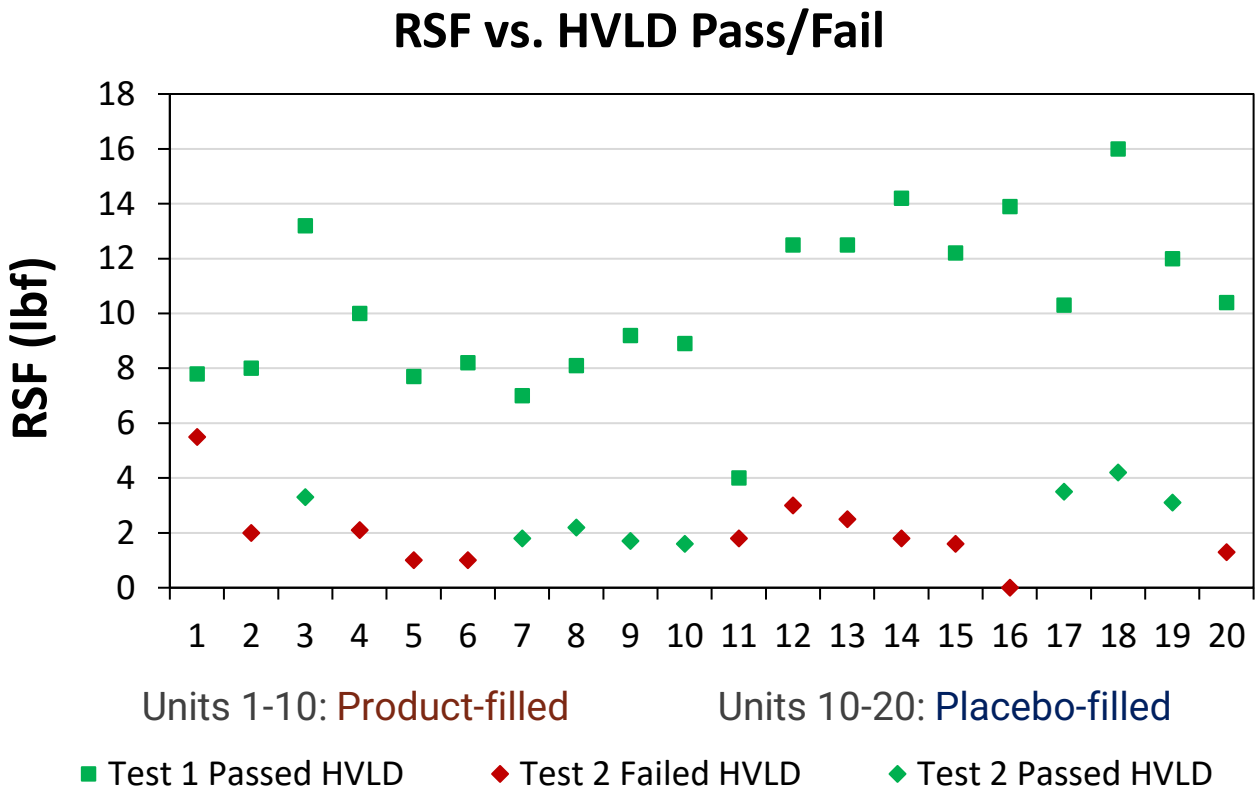
*Kirsch, L et al. "Pharmaceutical container/closure integrity II: The relationship between microbial ingress and helium leak rates in rubber-stoppered glass vials" *PDA J of Pharm Sci and Technol 51* (5) 195-202 (1997)

RSF vs. HVLD



S. Orosz and D Guazzo, "*Leak Detection and Product Risk Assessment*" presented at PDA Annual Meeting, Mar 2010, Orlando, FL

RSF vs HVLD



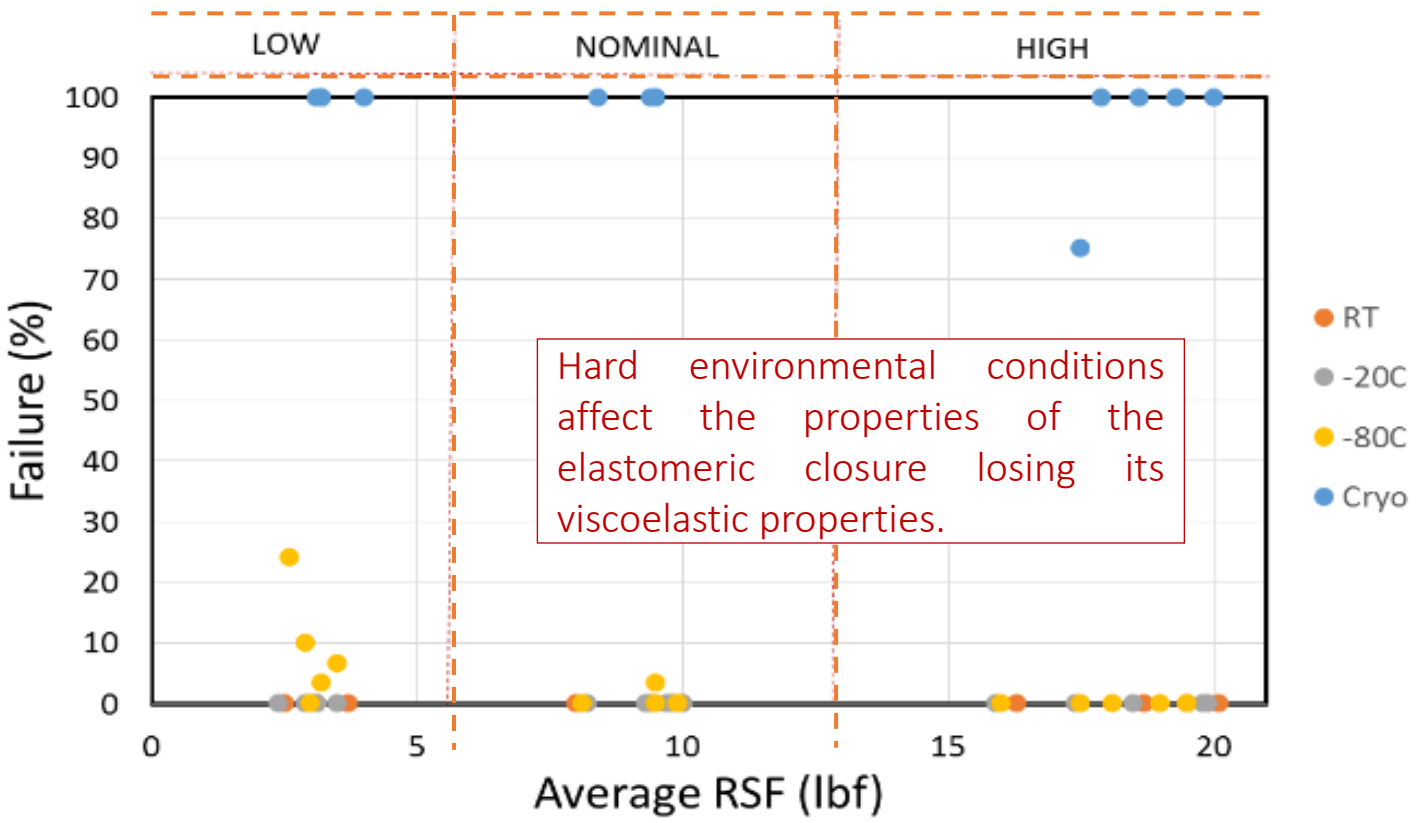
Avg. RSF: 10.3 lbf.
0% Failures

Avg. RSF: 1.9 lbf.
60% Failures

S. Orosz and D Guazzo, "*Leak Detection and Product Risk Assessment*" presented at PDA Annual Meeting, Mar 2010, Orlando, FL

RSF vs. HSA

- CCS:
  - 2 ml Vial EU BB, 13 mm Serum Stopper
  - Five (5) vial stopper combinations (A – E)
- Sealing parameters:
  - Three (3) crimping pressures – RSF targets
- Storage:
  - Four (4) storage temperatures

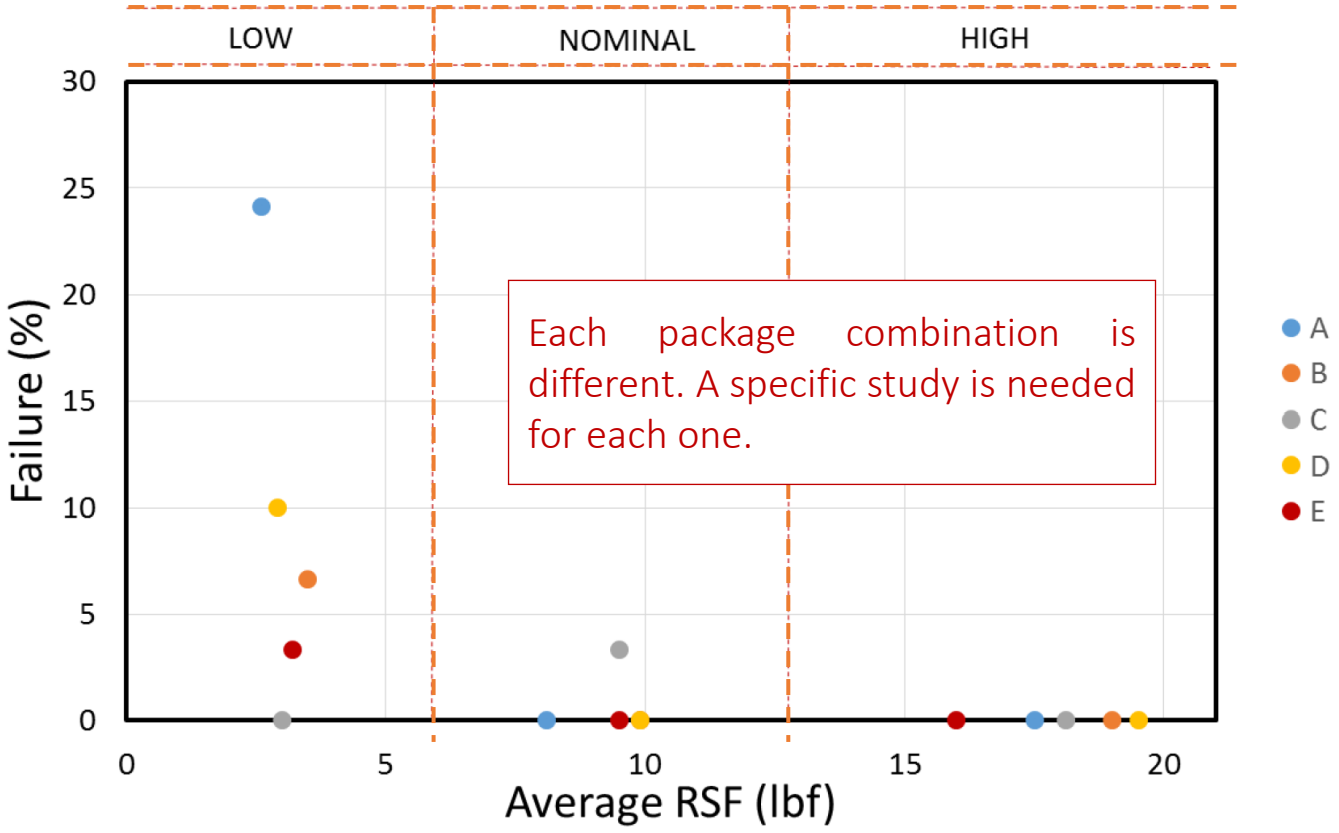


Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of PDA Parenteral Packaging Conference, Frankfurt, Germany; (2015)

RSF vs. HSA

At -80°C:

- *Package A:* 24% failures at low compression setting
- *Package B:* 7% failures at low compression setting
- *Package C:* 0% failures at low compression setting, 4% failures at Nominal compression setting
- *Package D:* 10% failures at low compression setting
- *Package E:* 4% failures at low compression setting



Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of PDA Parenteral Packaging Conference, Frankfurt, Germany; (2015)

PDA Parenteral Drug Association Training and Research Institute

Takeaways - Correlation CCIT

- Correlation of RSF to CCITs will provide guidance on setting acceptable ranges
- Once optimal RSF range is established, it can be used to standardize seal quality regardless the capping equipment used for crimping

Summary

- RSF is a reliable and precise measurement to assess the quality of sealed vial and predict CCI failure
  - It is package dependent
  - Correlation of RSF and CCITs provides guidance on setting acceptable ranges
- Significance of RSF
  - Package development – Effects of component variables, assembled processing, distribution & storage
  - Validation – Establish optimum capping parameters, process variation
  - Production – Verify capping equipment setup, IPC
- RSF can be facilitate comparison of seal quality among different capping equipment & sites

PDA Parenteral Drug Association Training and Research Institute

Genesis Packaging Technologies

Website:
www.gen-techno.com

Email:
info@gen-techno.com
CGonzalez@gen-techno.com

Phone:
+1 800 552 9980
+1 613 294 9203

Thank you!