Residual Seal Force: A Powerful Vial Seal Quality Test

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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. Takeaways

Seal Quality Tests

- *USP <1207.3>:*

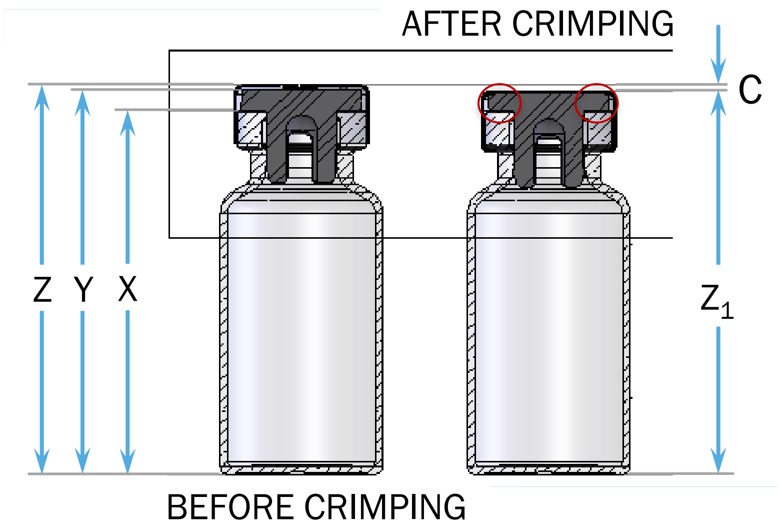
  "Package seal quality tests" are checks used to ***characterize and monitor*** *the* ***quality and consistency*** *of a seal parameter related to the package seal, providing some assurance of the package's ability to remain integral*

  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 are **NOT** leak tests

"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



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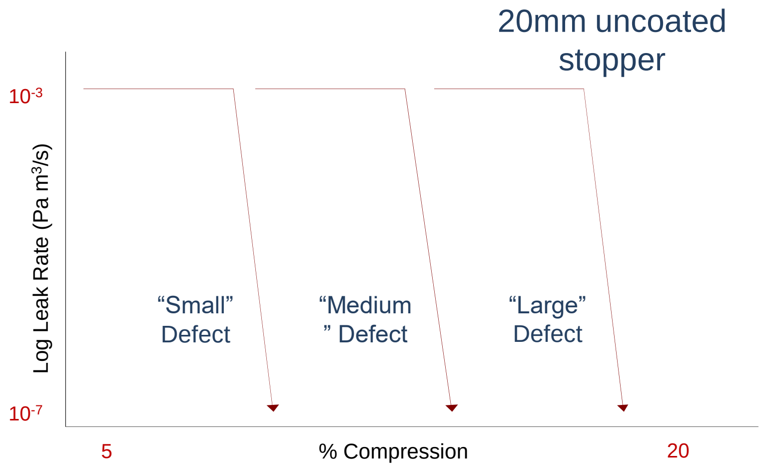
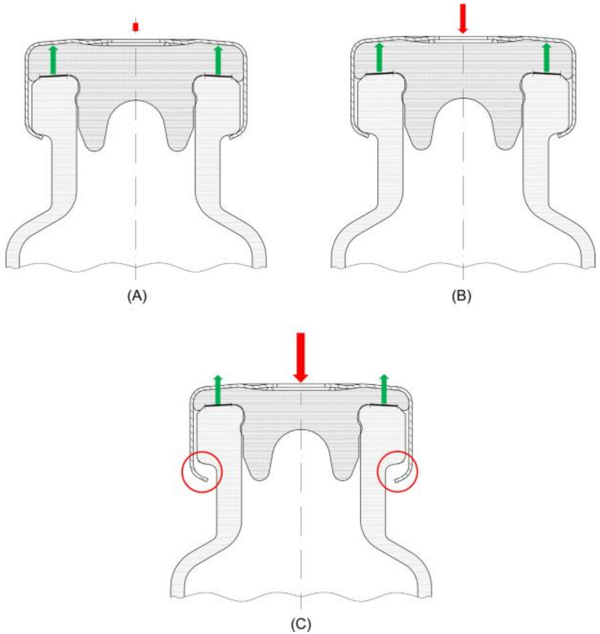


Morton, Dana K. "Quantitative and Mechanistic Measurements of Parenteral Vial Container/Closure Integrity. Leakage Quantitation" *PDA J of Pharm Sci and Technol* 1989, 43 (2) 88-97

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

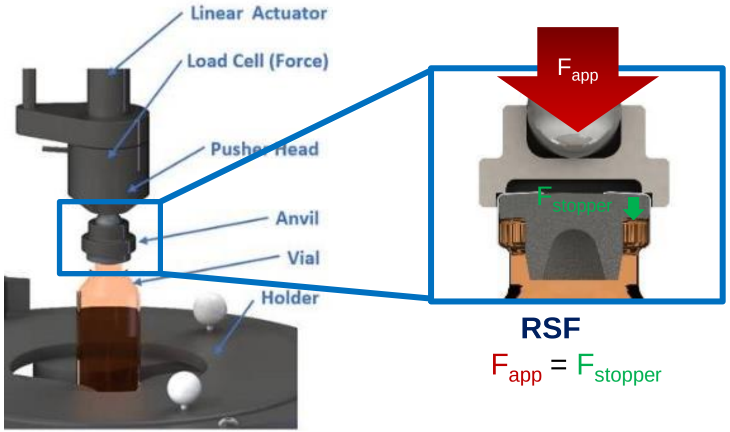
Basis of RSF Testing

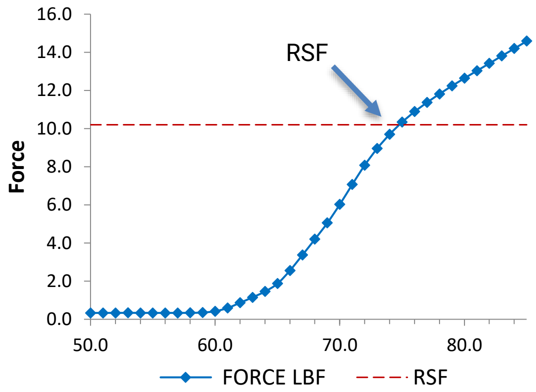


- Upon capping, the stopper flange is compressed against the vial land sealing surface
- The stopper flange acts like a "compressed spring"
- The tester apply a force on the cap and stopper
- When the tester force exceeds the closure compression force → RSF

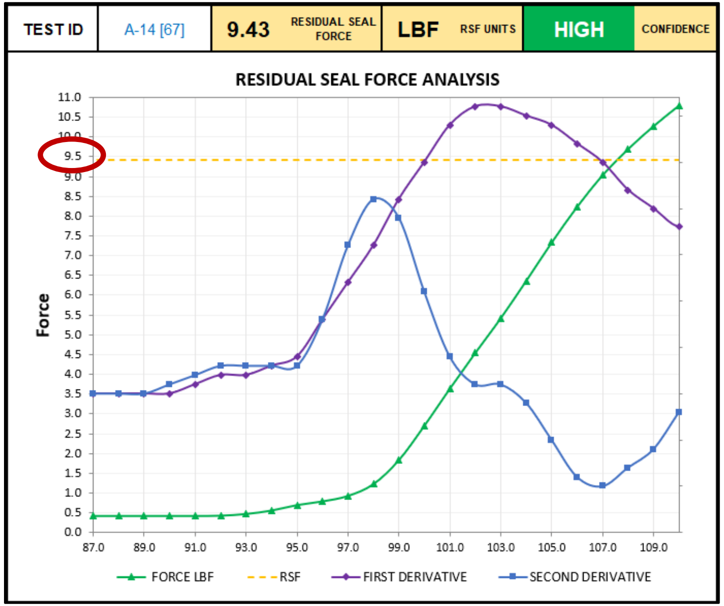
R. Mathaes et al. "The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests" *European Journal of Pharmaceutics and Biopharmaceutics* 99 (2016) 54–64

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

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

Significance & Use of RSF Method

Package Development
- Determine effects of CCS component variables
- Characterize a "well-sealed" vial

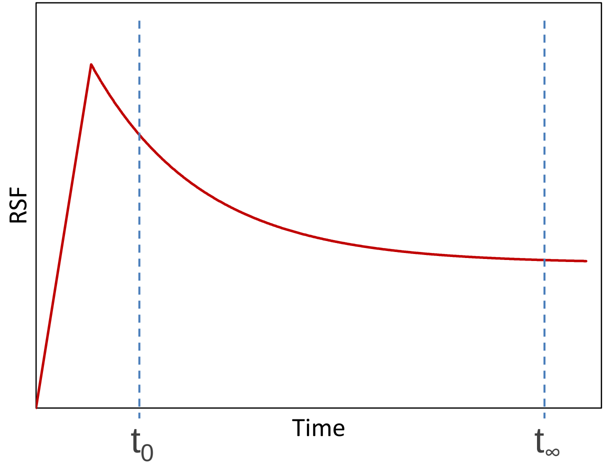
Validation
- Establish optimum capping parameters
- Evaluate variation

Production
- Verify capping equipment set-up
- Capping process monitor

RSF – Influence of Time

Influence of Elastomer Relaxation

Maxwell-Weichert Degeneration Curve

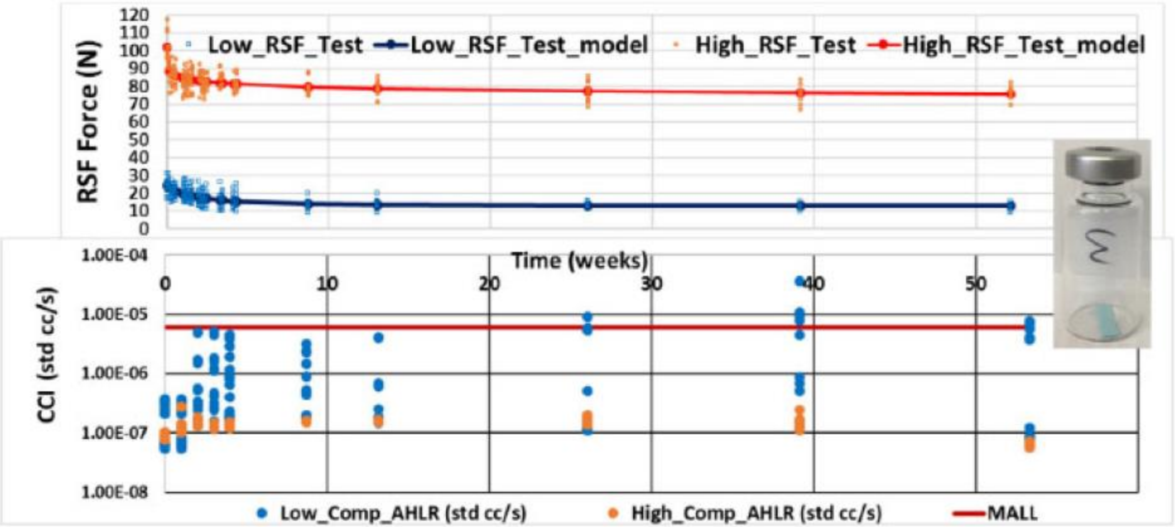


- Elastomer is the base material of the stopper
- Exhibit viscoelastic behavior
- Relaxes over time → RSF decay over time

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

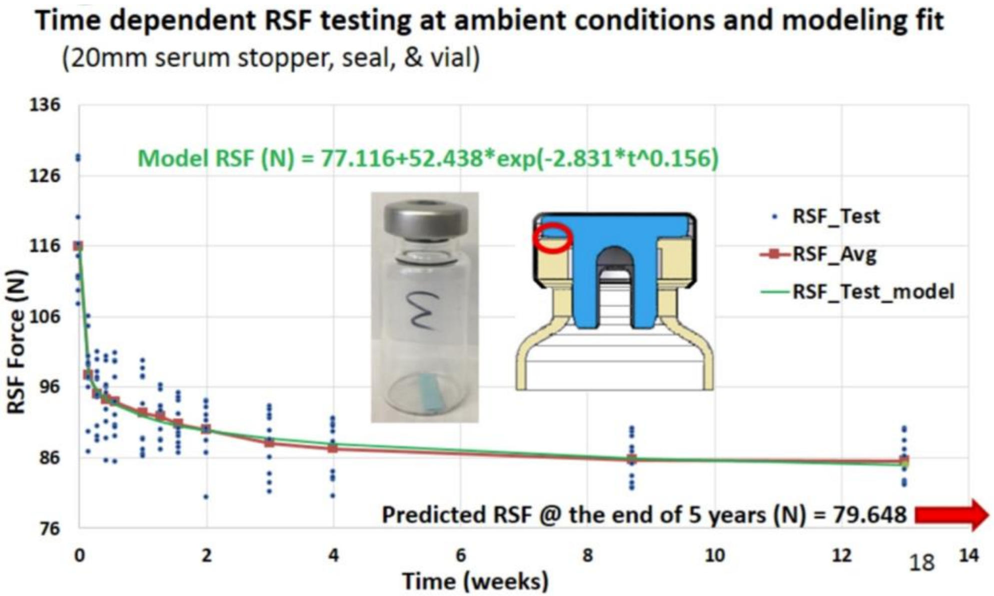
RSF – Time

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

RSF – Time



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

RSF – Time

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

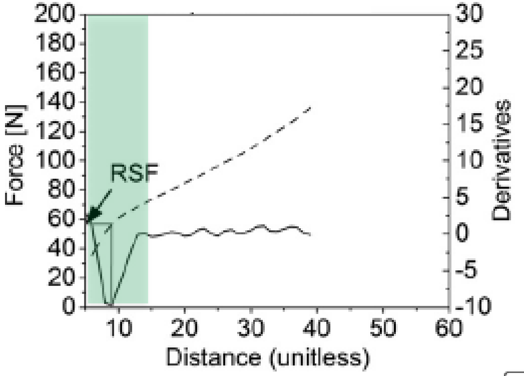
RSF – Time

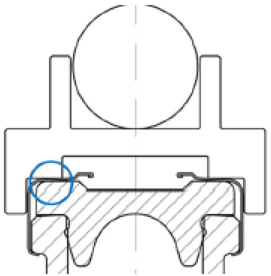
- Stress-relaxation of the rubber stopper is time-dependent affecting the sealing force
- Rubber will relax with time
  - RSF decay
  - Greater variability at $t < 10$ min
  - Greater decrease with higher crimping forces

RSF - Flip-Off Cap Impact

Flip-Off Cap Impact

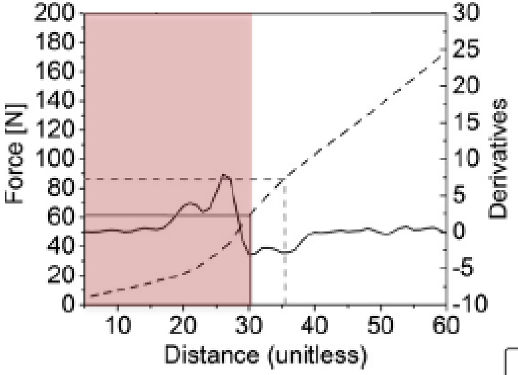
Without flip-off button

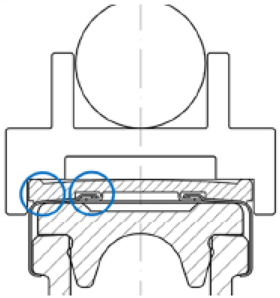




One clear minimum on 2nd derivative

With flip-off button



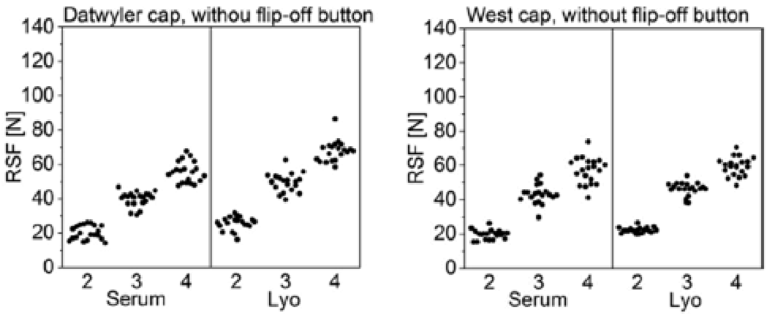


More complex and noisier signal

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

Flip-Off Cap Impact

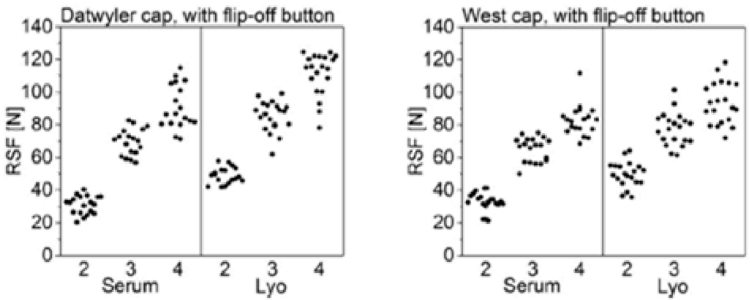
Without flip-off button



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

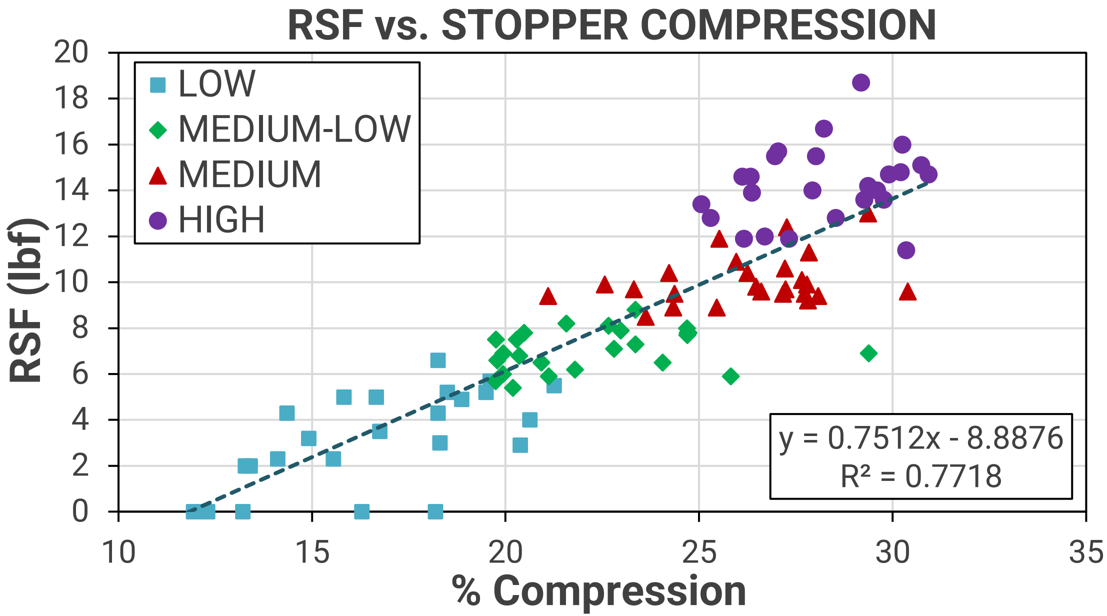
RSF – FO Cap

- 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

Correlation with CCIT

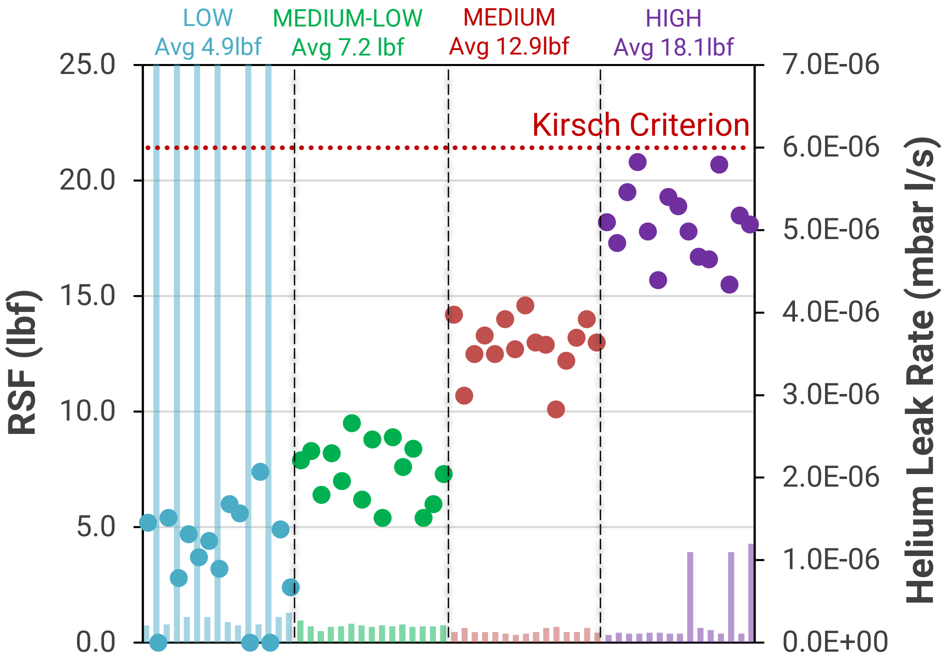
Correlation - RSF to Compression

- CCS:
  - 10R Vial
  - 20 mm serum stopper
- Sealing parameters:
  - Four (4) crimping pressures / RSF targets
- Compression, RSF and He leak



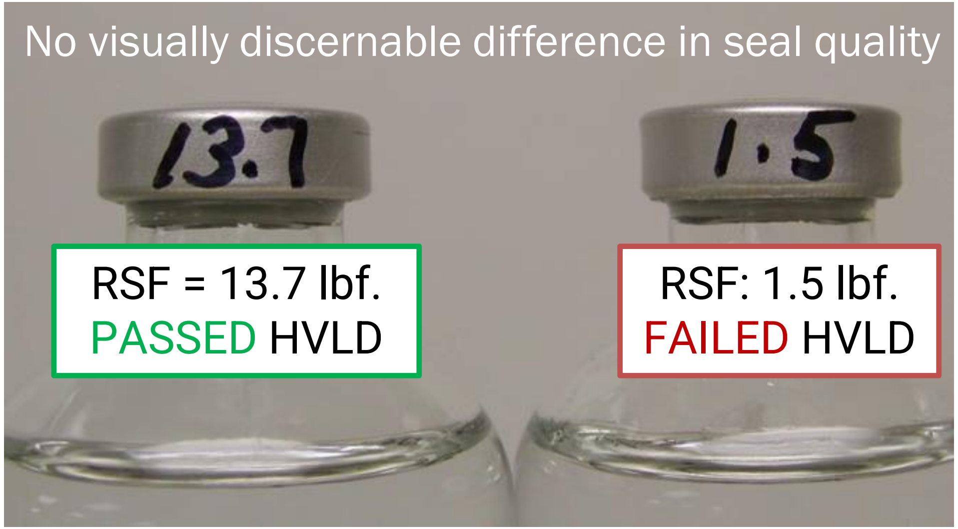
Correlation - RSF to He Leak Rate

- Kirsch criterion*: Helium leak rates lower than $6x10^{-6}$ 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)

Correlation - RSF to HVLD



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

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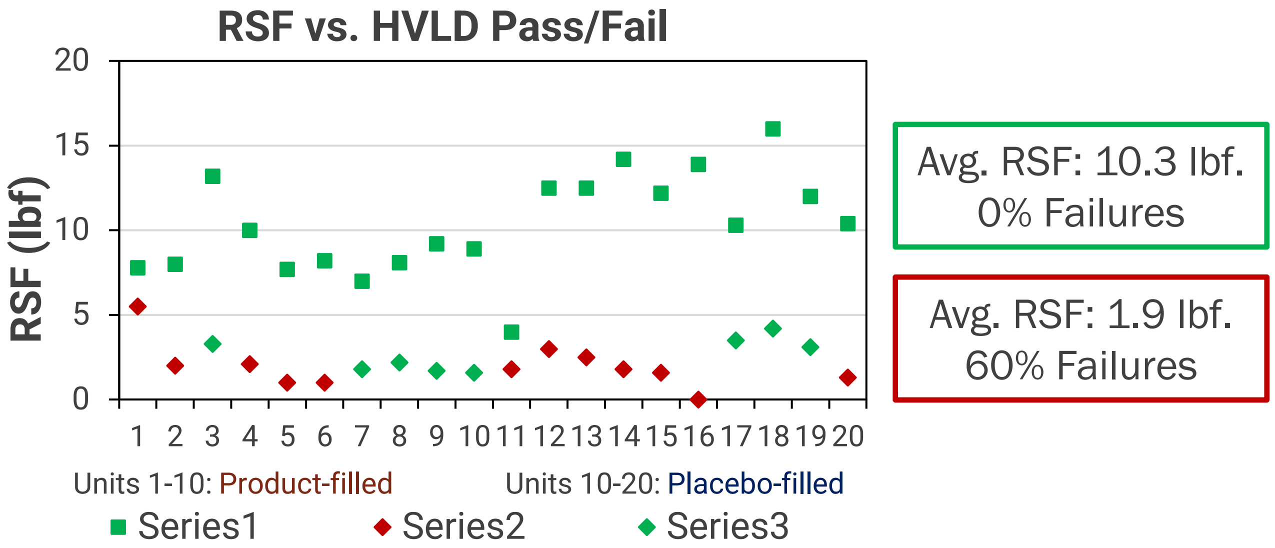
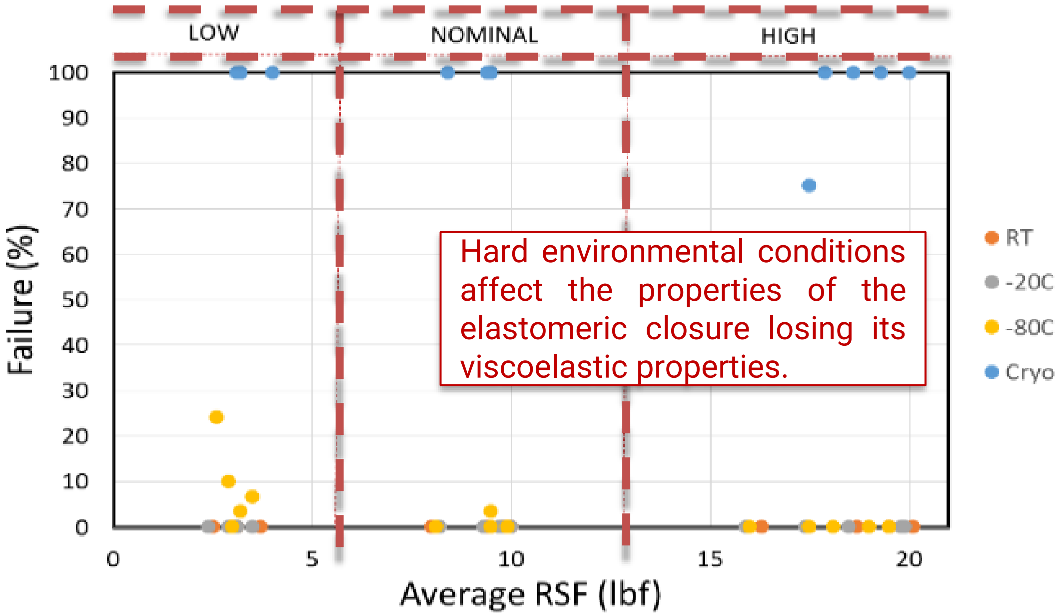


S. Orosz and D Guazzo, "*Leak Detection and Product Risk Assessment*" presented at PDA Annual Meeting, Mar 2010, Orlando, FL

Correlation - RSF to 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

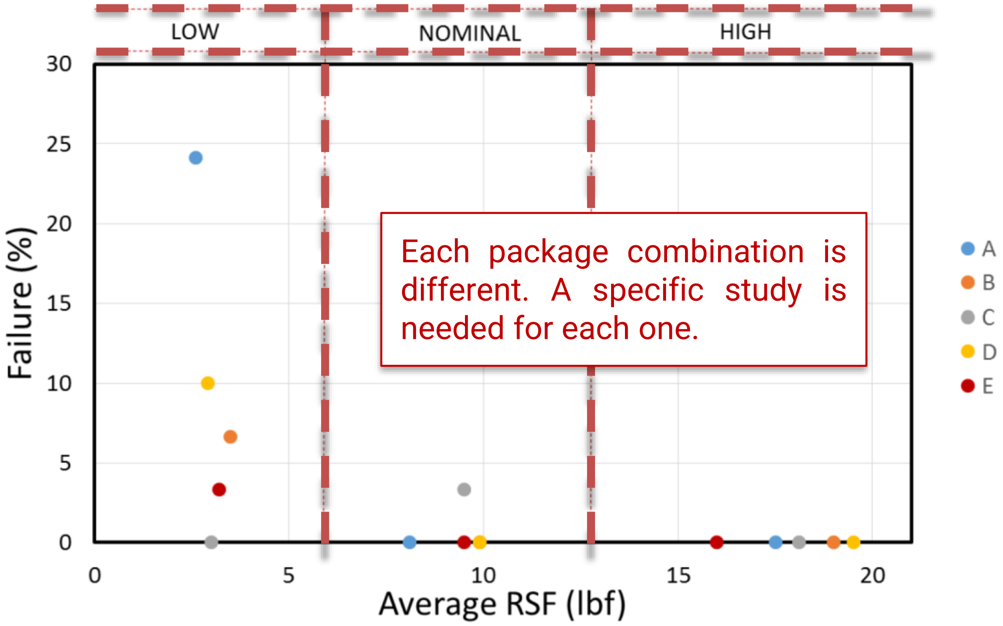


Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of PDA Parenteral Packaging Conference, Frankfurt, Germany; (2015)

Correlation - RSF to 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



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RSF – 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

Takeaways

- RSF is a reliable and precise measurement to assess the quality of sealed vial and predict CCI failure
- The stopper compression is a function of RSF
- Correlation of RSF and CCITs provides guidance on setting acceptable ranges, allowing comparison among different capping equipment & sites

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