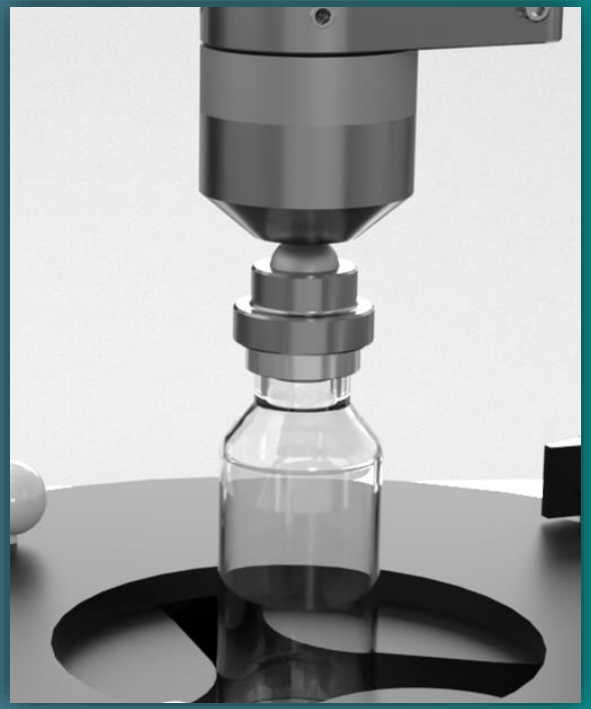
Residual Seal Force: A Powerful Vial Seal Quality Test



Carolina González Gaitán, PhD
Parenteral Packaging Scientist
Genesis Packaging Technologies

2023 PDA Container Closure Integrity Testing – Basic Course
Apr 20 – 21, 2023
Lido di Venezia, Italy

Agenda

1. Seal quality tests
2. Characterizing a “well-sealed” vial
3. RSF
    a) Concept
    b) Basis of RSF testing – Methodology
    c) RSF Variability considerations
    d) Significance and use of RSF
4. Case Studies
5. Summary

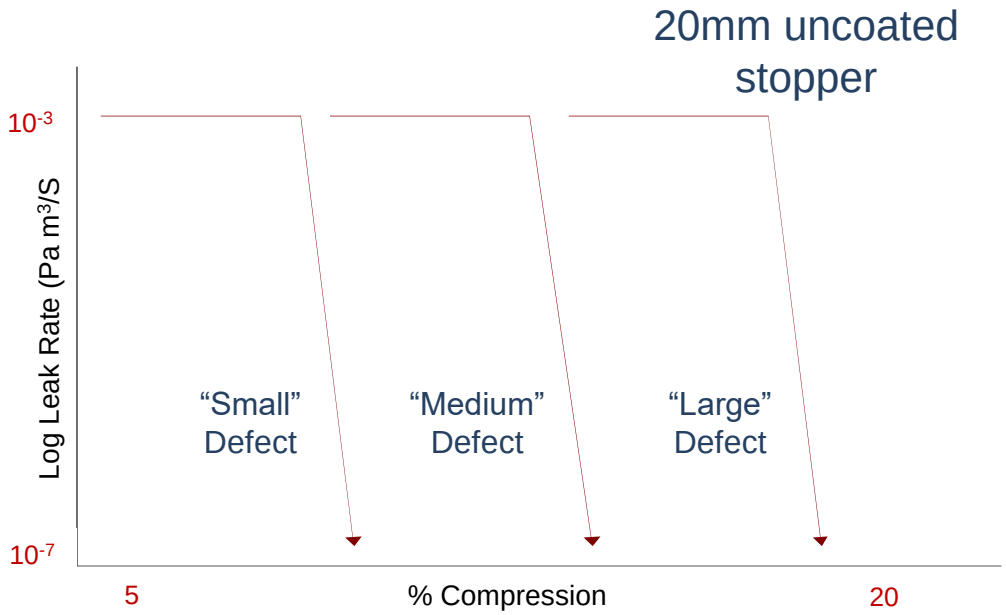
Seal Quality Tests

- Tests used to **characterize and monitor** the **quality and consistency** of a seal parameter providing some assurance of the package's ability to maintain integrity
- Parameters monitored:
  - Seal quality
  - Package materials
  - Package components
  - Sealing process
- Seal quality test 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



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 crown 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

RSF Test Method Concept

- Optimum window of stopper compression → Not too little, not too much force
- Poor compression cannot be visually detected→ RSF testing is an indirect measure of compression

1980's

West introduced the WG-005 Seal Force Tester with stereo scope and force gage

Instron introduced stress / strain testers

1990's

2001

Genesis launched the RSF tester – AWG 1.0

2008

Guidance for Industry

Container and Closure System Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products

<1207> PACKAGE INTEGRITY EVALUATION – STERILE PRODUCTS

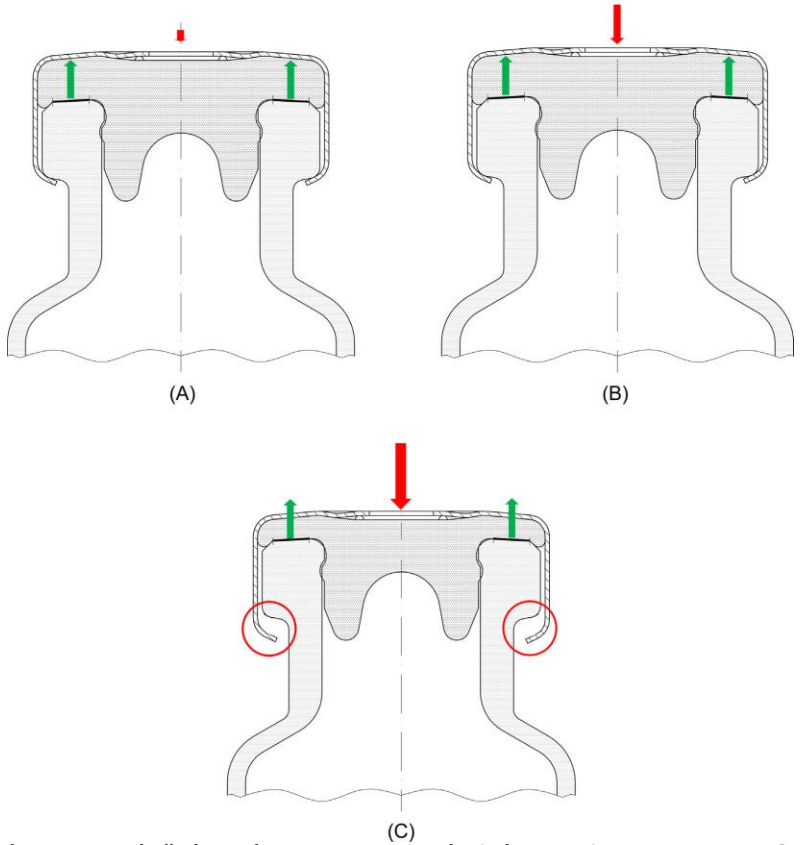
<1207.3> Package Seal Quality Test Methods

2016

2020

Genesis launched 2nd Gen RSF tester *Vera*

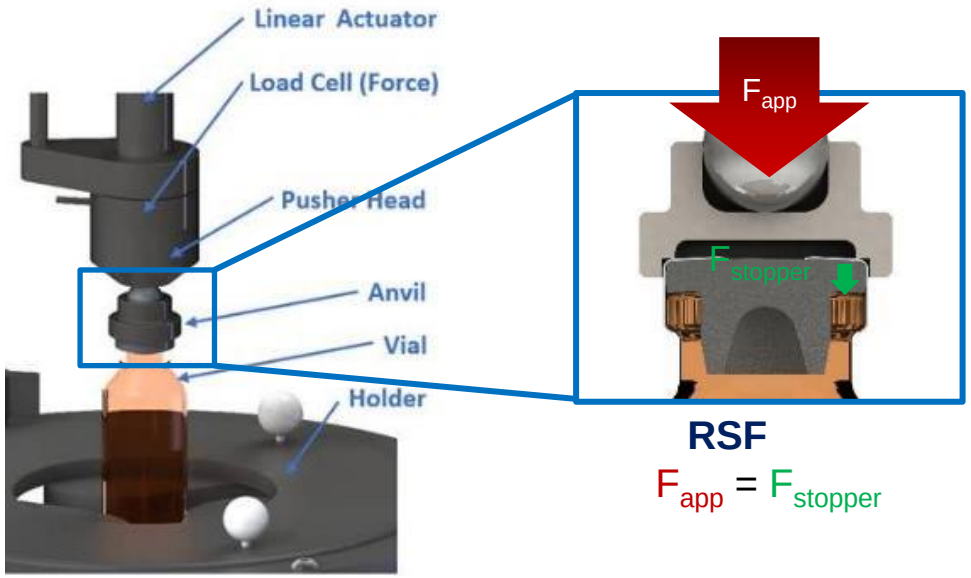
Basis of RSF Testing

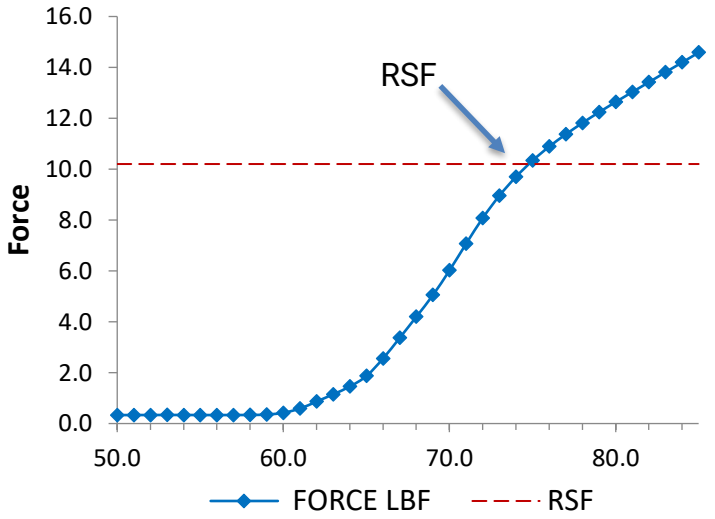


- Upon capping, the stopper flange is compressed against the vial land sealing surface
- The stopper flange acts like a “compressed spring”
- The tester apply a force on the cap and stopper
- When the tester force exceeds the closure compression force → RSF

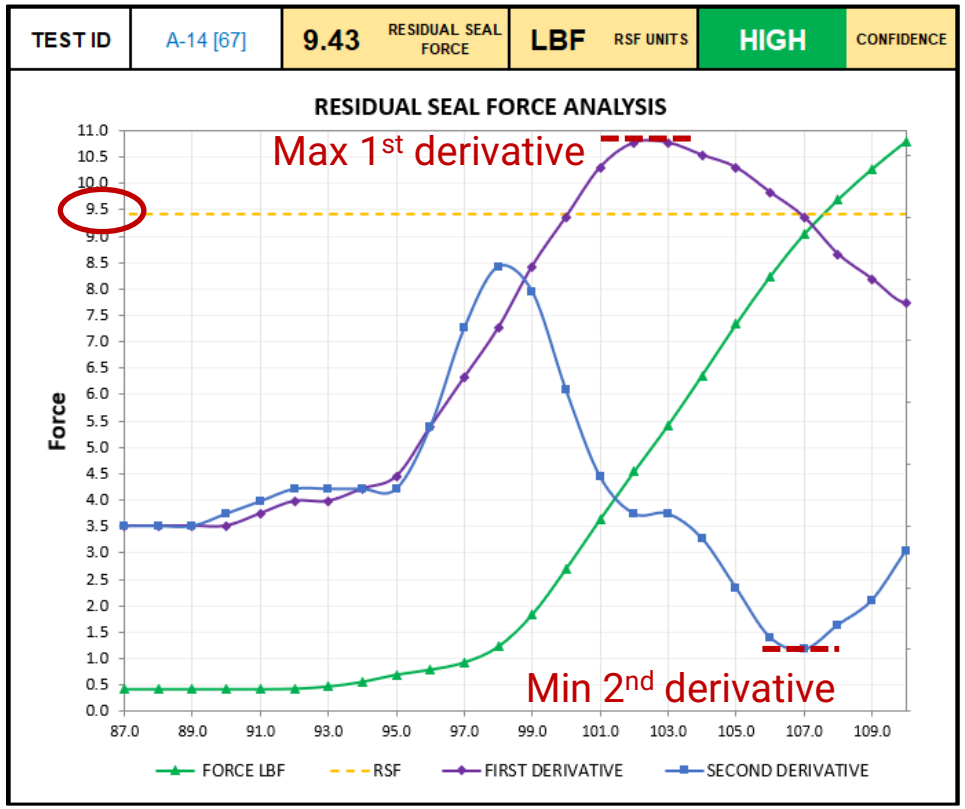
R. Mathaes et al. “The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests” *European Journal of Pharmaceutics and Biopharmaceutics* 99 (2016) 54–64

RSF Tester and Methodology





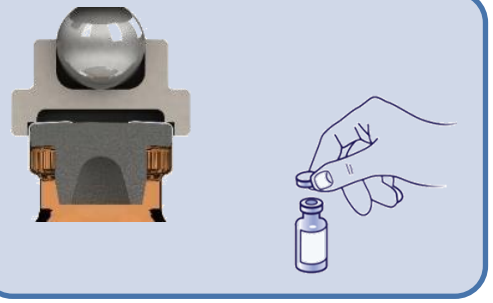
Determining RSF



- 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

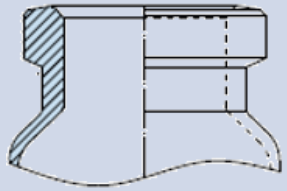
* Ludwig J, Nolan P, Davis C, Automated method for determining Instron residual seal force of glass vial/rubber stopper closure systems, *PDA J of Pharm Sci and Technol* 1993, 47 (5) 211-253

Variability Considerations



Methodology

- Anvil design
- Button Removal

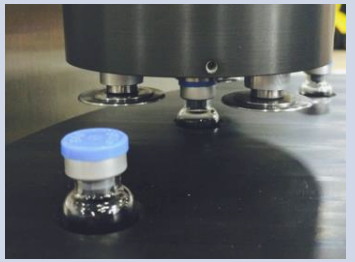


Components Variation

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

Time

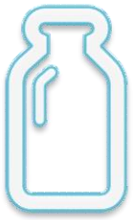
- Elastomer relaxation



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

Importance and Use of RSF Test Method

- "RSF values may be used in effectively setting up vial cappers and for monitoring the crimping process. With an understanding of compression and leak rate cut-off, RSF can be further used as a predictor of leakage risk."

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

- "The RSF tester can be used to characterize the resulting residual seal force of a capped vial independent of the capping equipment used, which can facilitate the comparison of seal quality of DP units manufactured in different facilities. In addition, a suitable RSF range that would still show full CCI, is recommended specific for each CCS combination and can be established using different capping equipment."

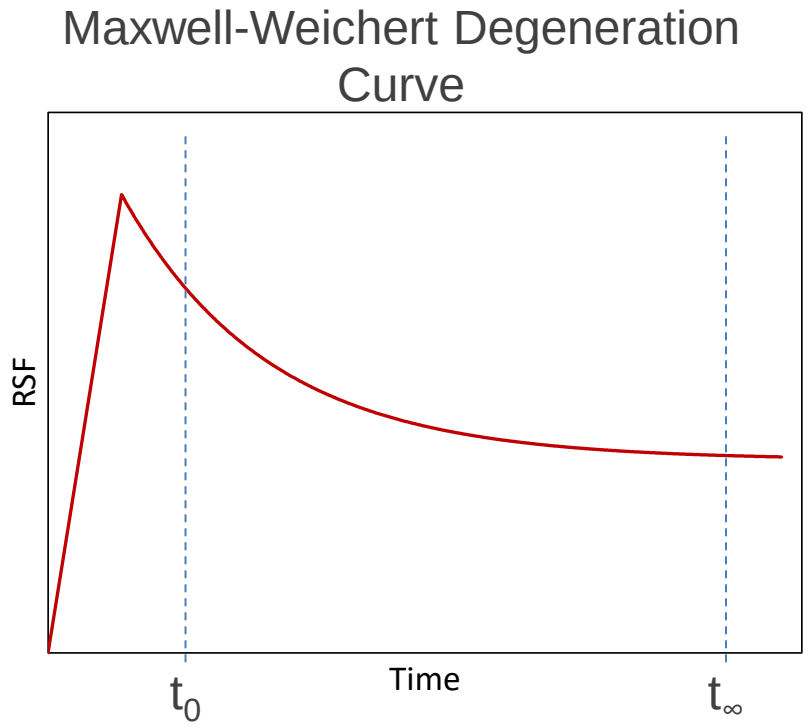
  Mathaes, R.; Mahler, H.; Roggo, Y.; et al. Influence of Different Container Closure Systems and Capping Process Parameters on Product Quality and Container Closure Integrity in GMP Drug Product Manufacturing, PDA J Pharm Sci & Technol 70, (2016) 109-119

- "The ultimate goal of capping is to achieve long-lasting CCI of the container closure system. Thus, the relationship between RSF and CCI should be understood to allow the use of the RSF tester during routine commercial manufacturing"

  Ovadia, R; Streubel, A; et al. "Quantifying the Vial Capping Process: Residual Seal Force and Container Closure Integrity" PDA Journal of Parenteral Science and Technology 73 (2019)

Case Study 1 – Effect of Time

Influence of Elastomer Relaxation

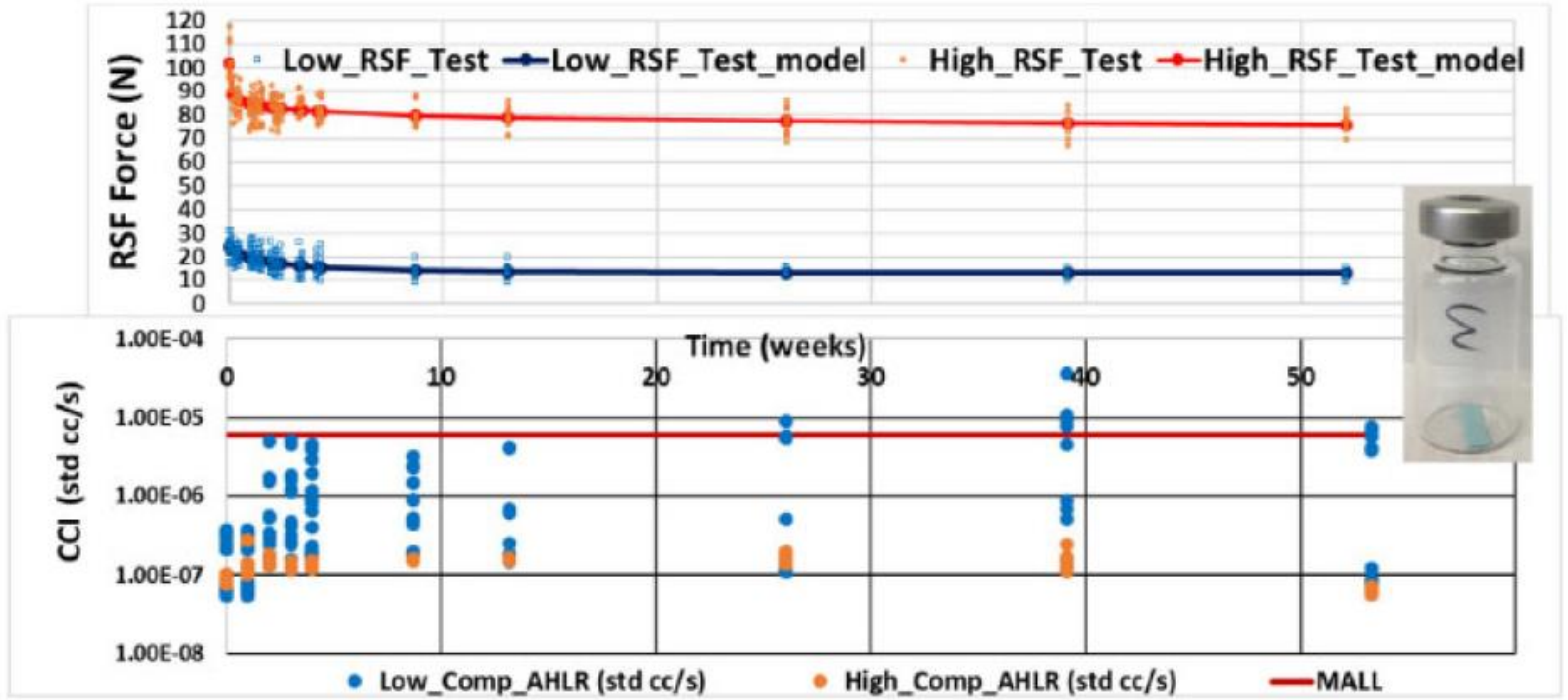


- Elastomer is the base material of the stopper
- Exhibit viscoelastic behavior
- Relaxes over time → RSF decay over time

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

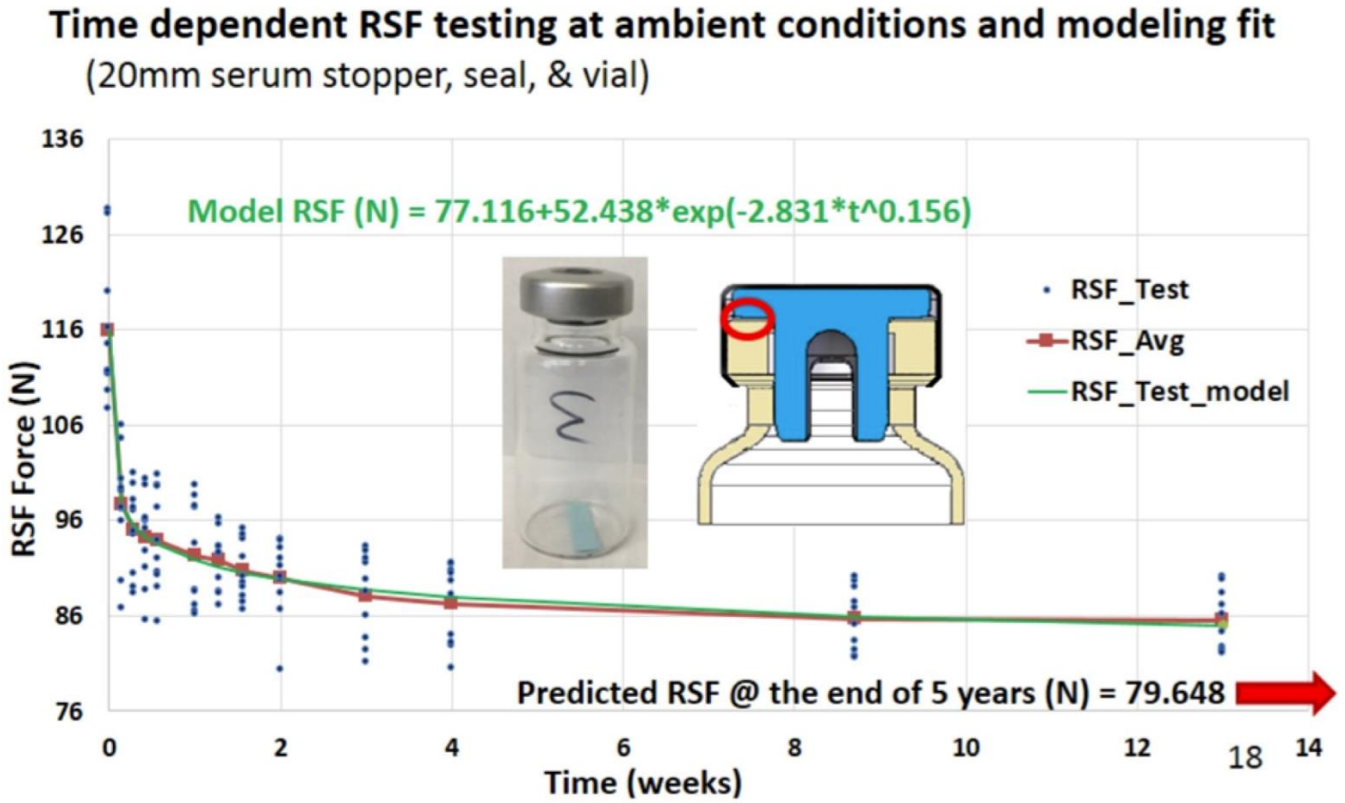
RSF – Time Dependence

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.; Zhao,C; "Critical Consideration in Time-Dependent Evaluation and Modeling for Rubber Stopper Seal Performance" PDA Parenteral Packaging Conference, Barcelona, Spain; 2017

RSF – Time Dependence



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 Dependence

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

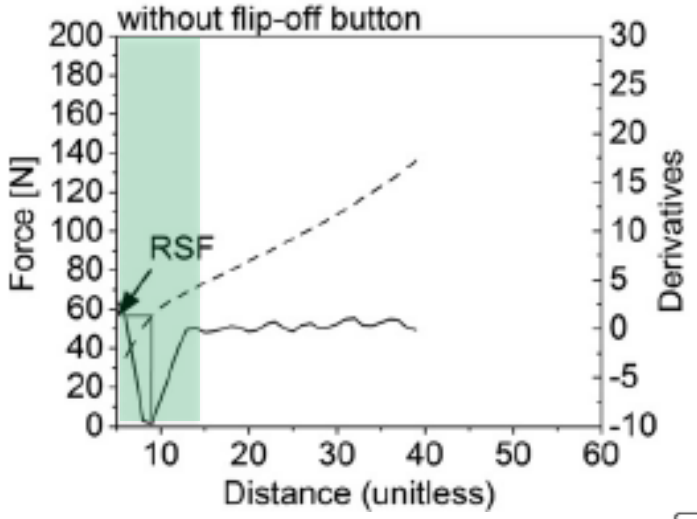
Adapted from: Ovadia, R; Streubel, A; et al. “Quantifying the Vial Capping Process: Residual Seal Force and Container Closure Integrity” *PDA J of Phar Sci and Technol*, 2019 73 (1) 2-15

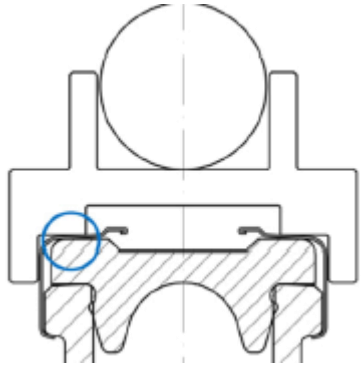
Case Study 1 – Conclusions

- 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

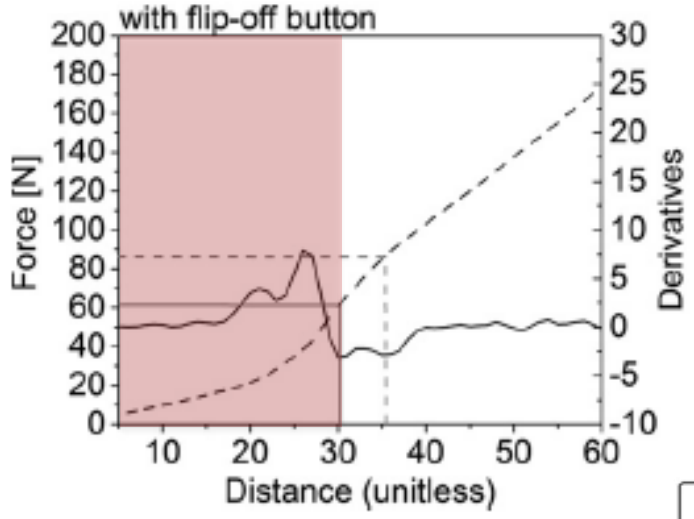
Case Study 2 – Effect of Flip-Off Cap

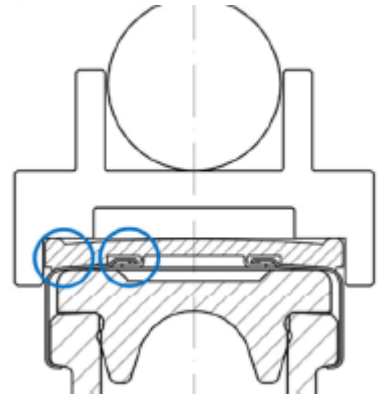
Flip-Off Cap Impact





One clear minimum on 2nd derivative

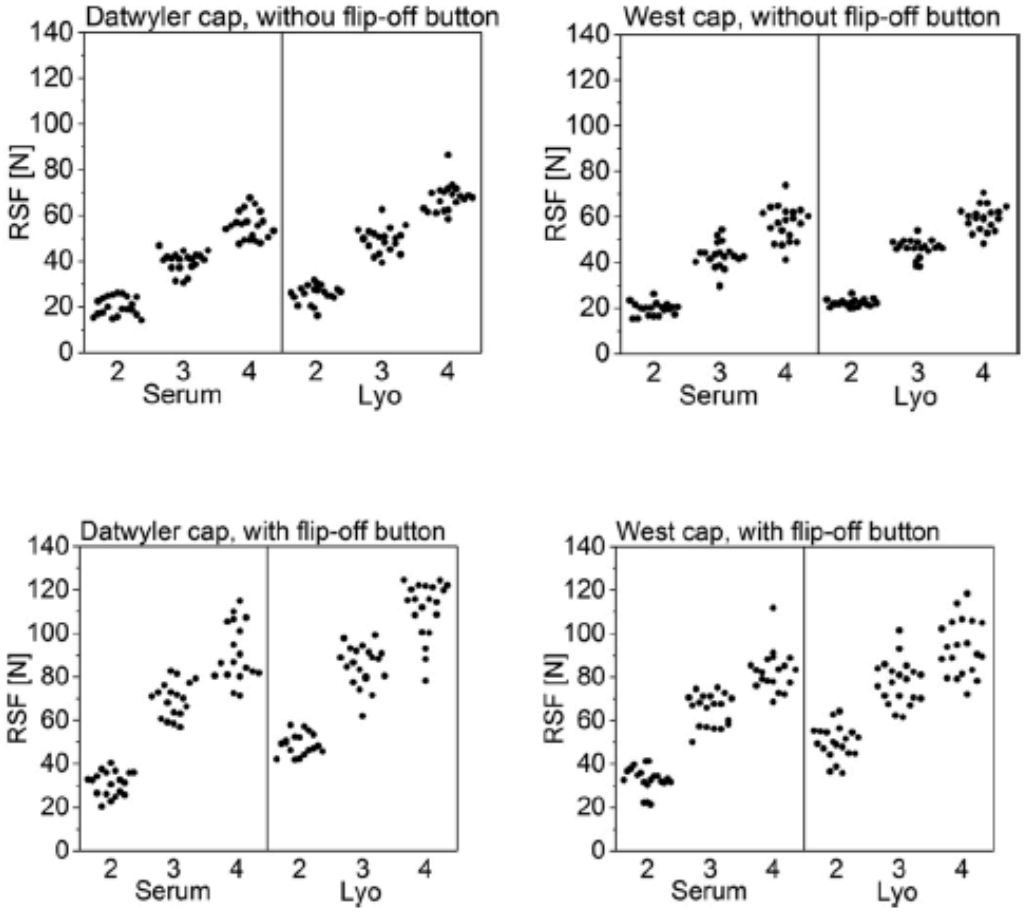




More complex and noisier signal

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



Low variability → Distinctive RSF groups

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

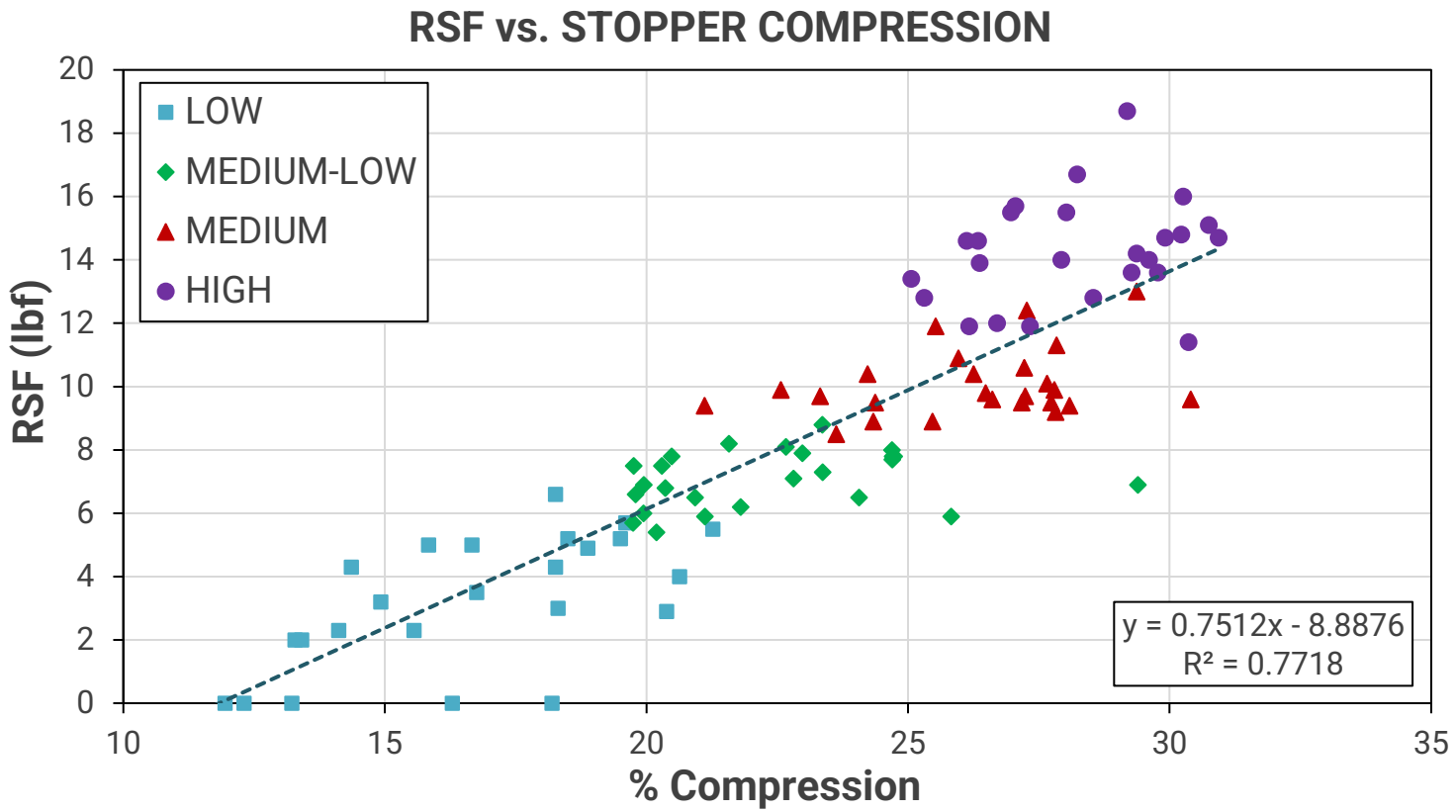
Case Study 2 – Conclusions

- 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

Case Study 3 – RSF vs. CCIT

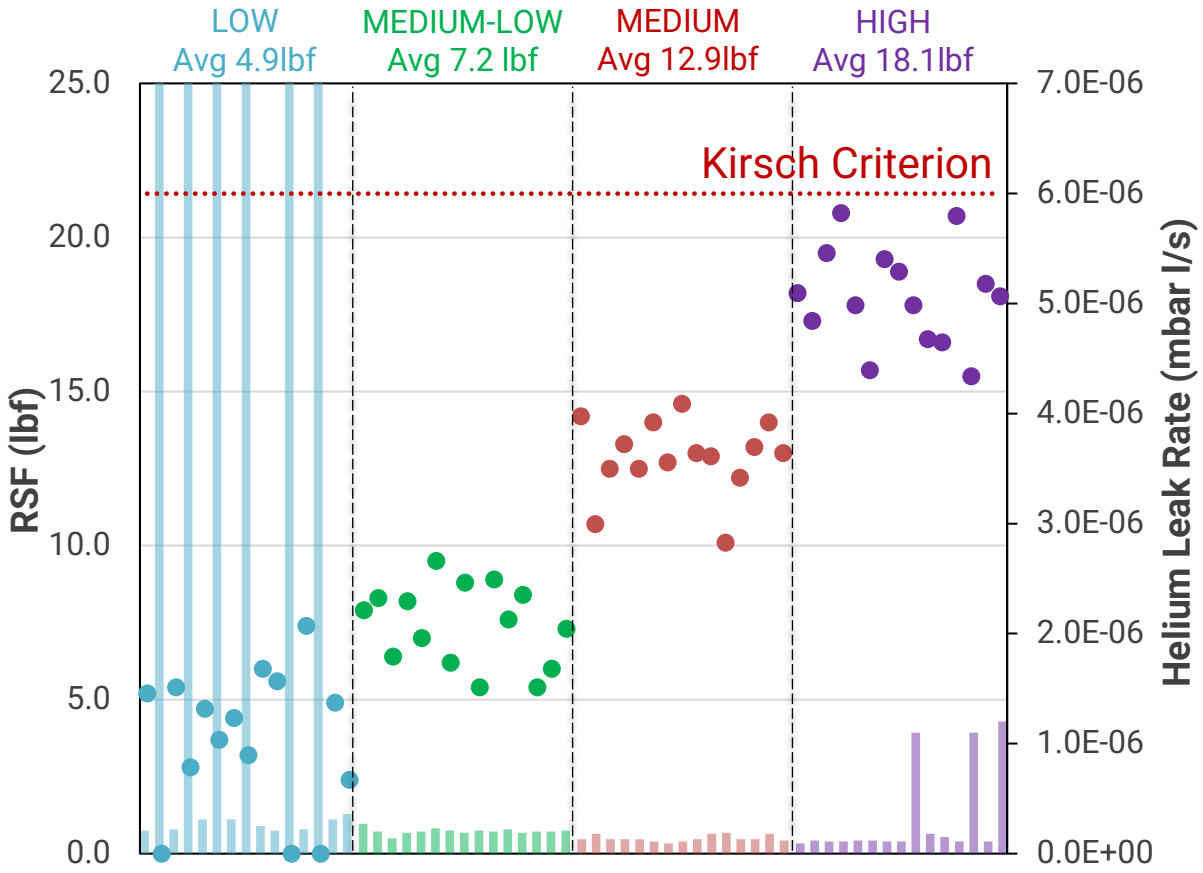
Correlation - RSF to Compression

- CCS:
  - 10R Vial
  - 20 mm Serum Soft Stopper
- Sealing parameters:
  - Four (4) crimping pressures / RSF targets (Low, Medium-Low, Medium, High)
- Compression, RSF and He leak



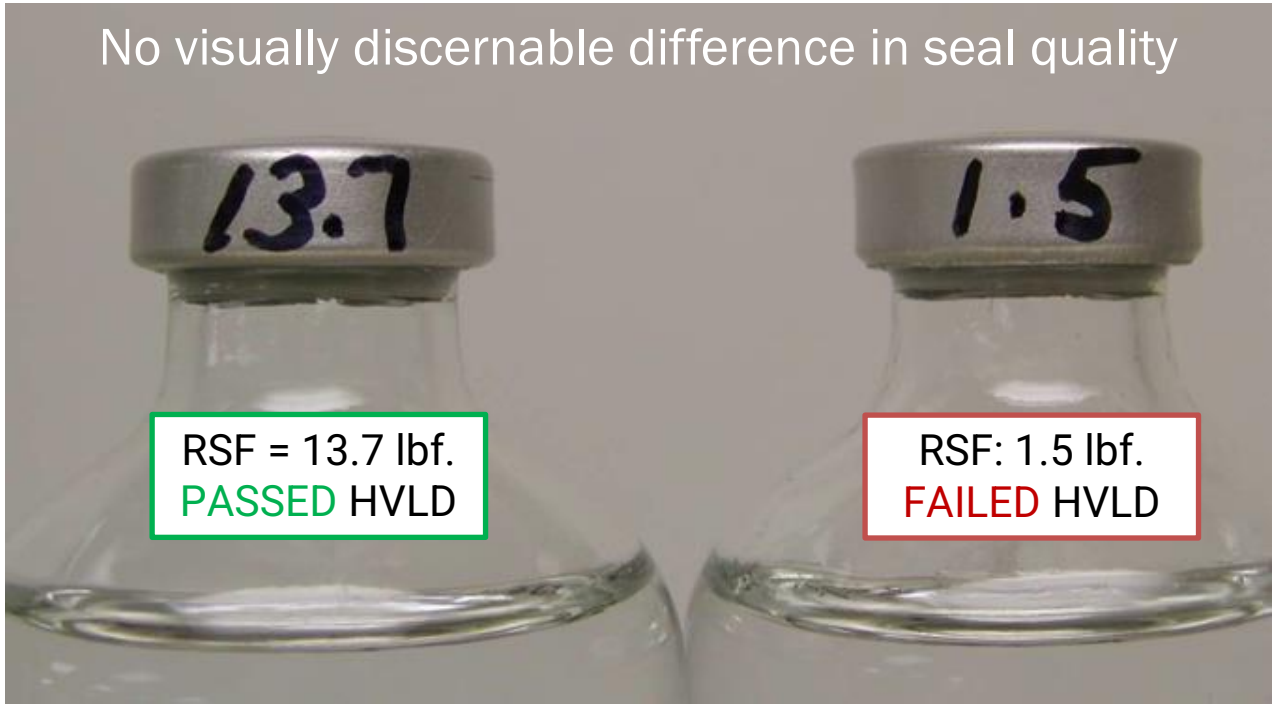
Correlation - RSF to He Leak Rate

- 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



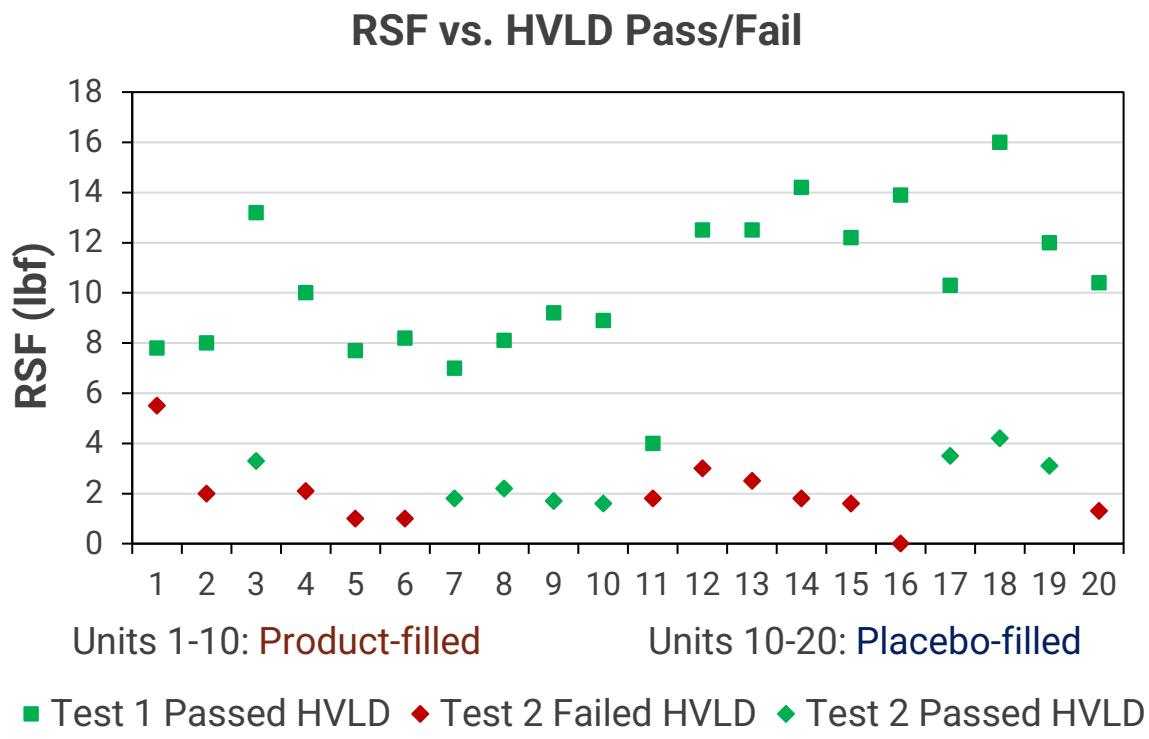
*Kirsch, L et al. "Pharmaceutical container/closure integrity II: The relationship between microbial ingress and helium leak rates in rubber-stoppered glass vials" *PDA J of Pharm Sci and Technol 51* (5) 195-202 (1997)

Correlation - RSF to HVLD



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

Correlation - RSF to HVLD



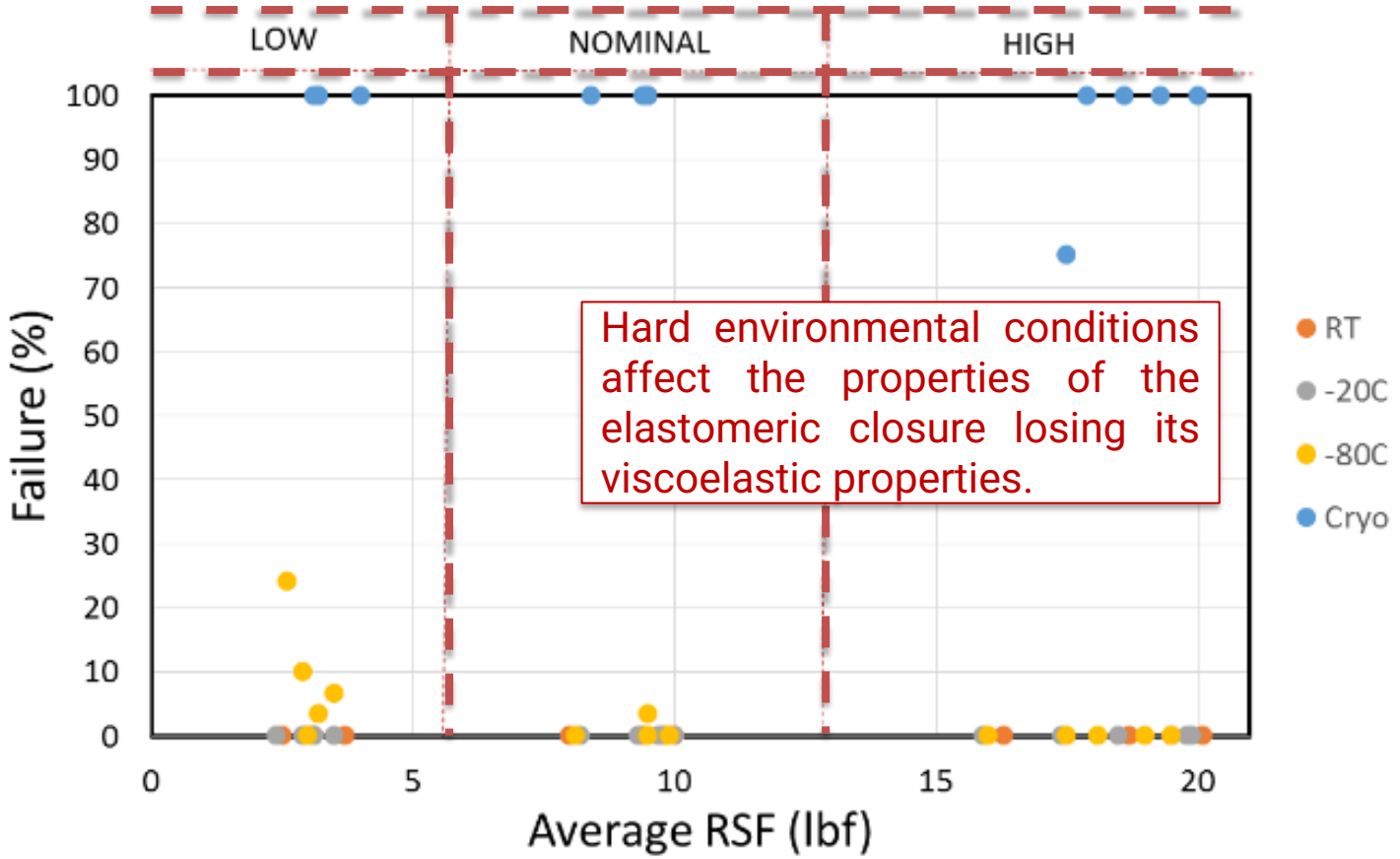
Avg. RSF: 10.3 lbf.
0% Failures

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

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 (Low, Nominal, High)
- Storage:
  - Four (4) storage temperatures: Room temperature (RT), -20°C, -80°C, Cryo (~ -150°C)

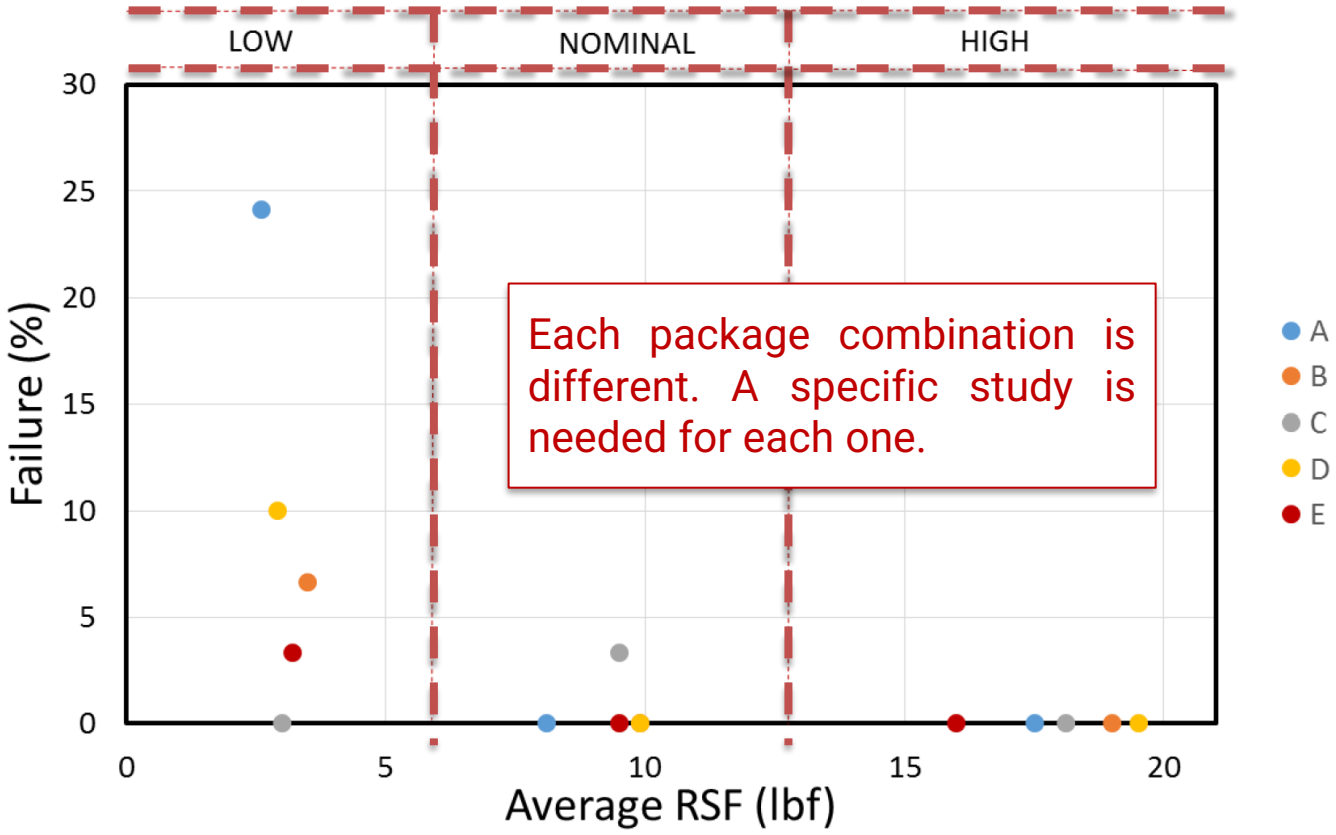


Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of PDA Parenteral Packaging Conference, Frankfurt, Germany; (2015)

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



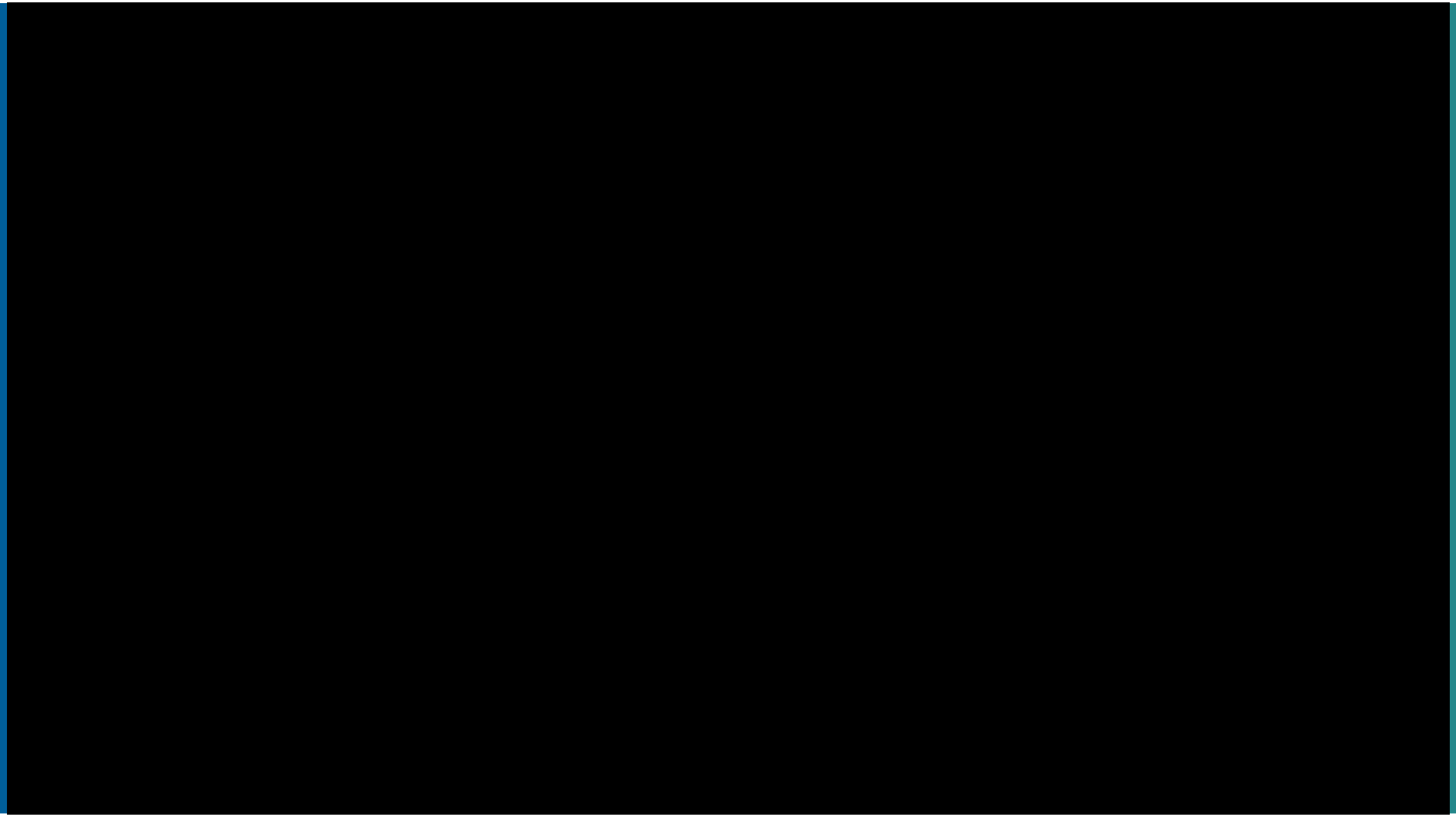
Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of PDA Parenteral Packaging Conference, Frankfurt, Germany; (2015)

Case Study 3 – Conclusions

- 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
- 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



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

Address:
373 Poplar Road
Honey Brook, PA 19344