

# Residual Seal Force: A Powerful Vial Seal Quality Test

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PDA  
TRAINING

# Agenda

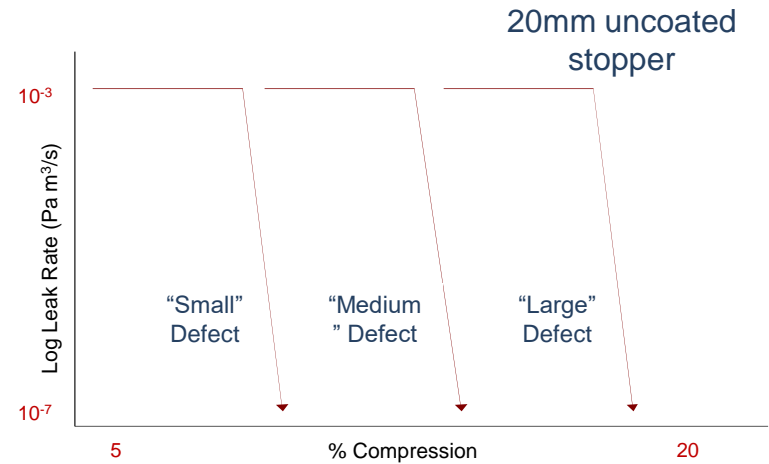
1. Seal quality tests
2. Characterizing a “well-sealed” vial
3. RSF
  - a) Concept
  - b) Basis of RSF testing – Methodology
  - c) RSF Variability considerations
  - d) Significance and use of RSF
4. Case Studies
5. Summary

# 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

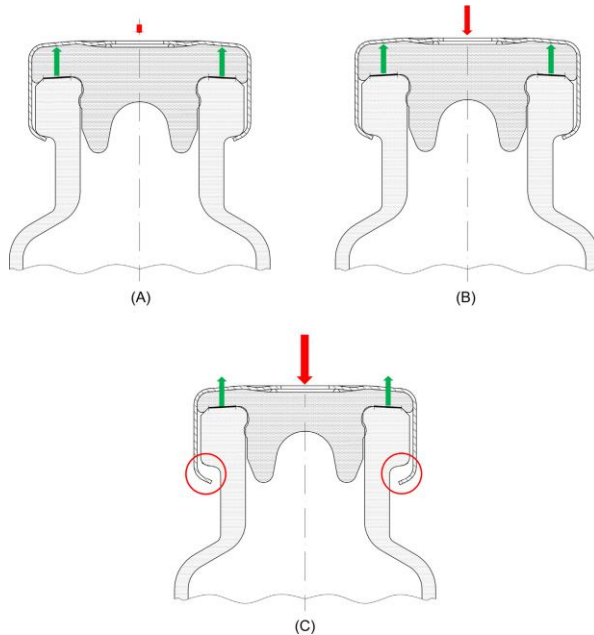
2016



2020

Genesis launched 2<sup>nd</sup> Gen RSF tester *Vera*

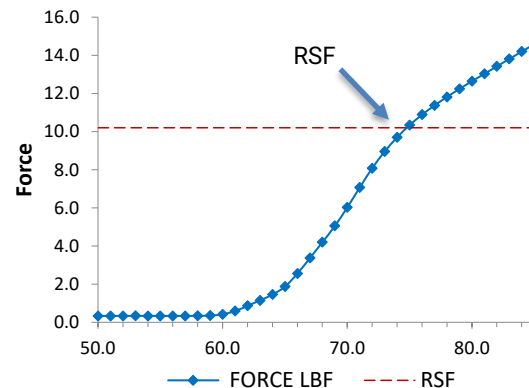
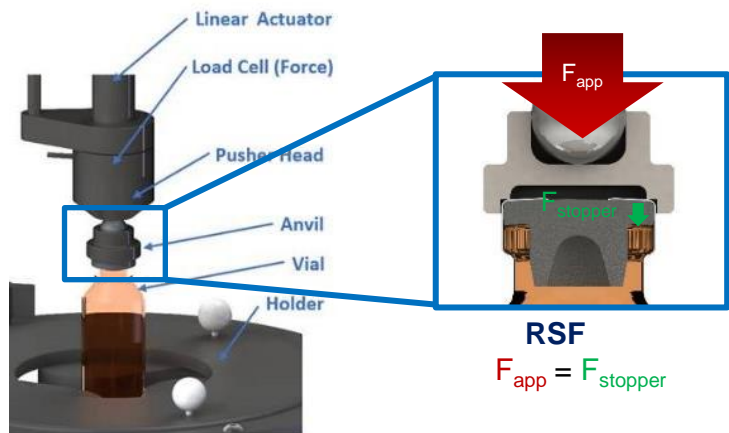
# Basis of RSF Testing



- 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

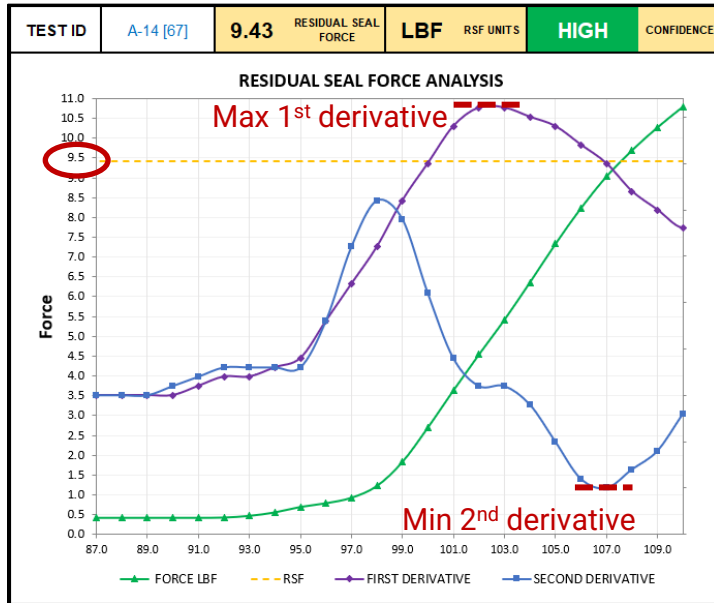
R. Mathaes et al. “The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests” *European Journal of Pharmaceutics and Biopharmaceutics* 99 (2016) 54–64

# RSF Tester and Methodology





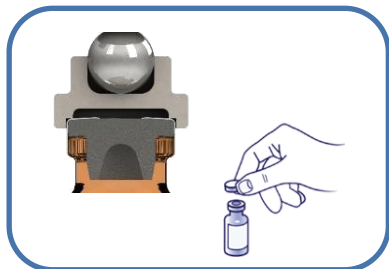
# Determining RSF



- 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 1<sup>st</sup> (purple) and 2<sup>nd</sup> (blue) derivatives to accurately identify that knee

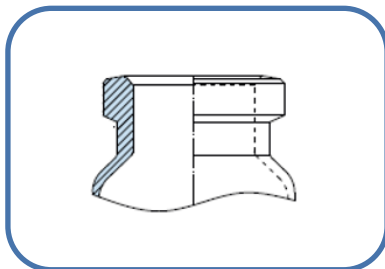
\* Ludwig J, Nolan P, Davis C, Automated method for determining Instron residual seal force of glass vial/rubber stopper closure systems, *PDA J of Pharm Sci and Technol* 1993, 47 (5) 211-253

# Variability Considerations



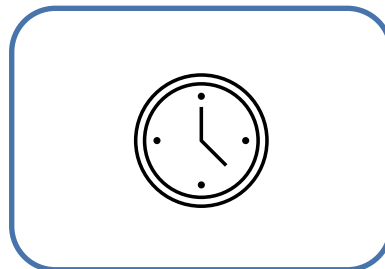
## Methodology

- Anvil design
- Button Removal



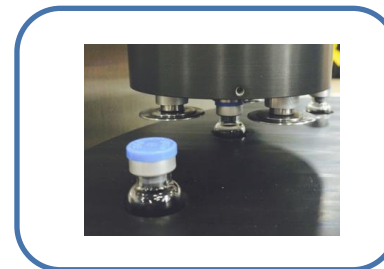
## Components Variation

- 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

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

## Package Development



- Establish optimum capping parameters
- Evaluate variation

## Validation



- Verify capping equipment set-up
- Capping process monitor

## Production



# 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”

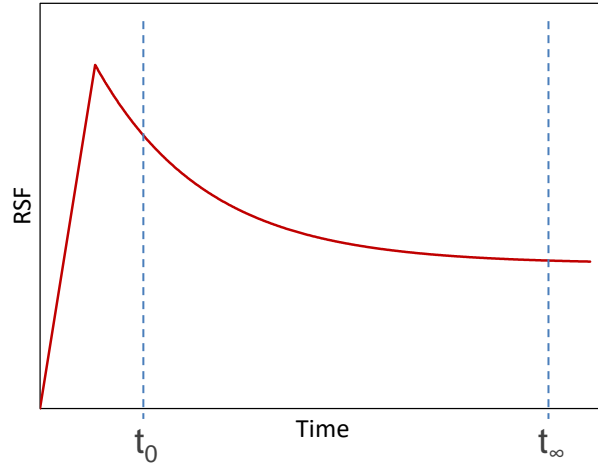
Ovadia, R; Streubel, A; et al. “Quantifying the Vial Capping Process: Residual Seal Force and Container Closure Integrity” PDA Journal of Parenteral Science and Technology 73 (2019)

# Case Study 1

## Effect of Time

# Influence of Elastomer Relaxation

Maxwell-Weichert  
Degeneration Curve

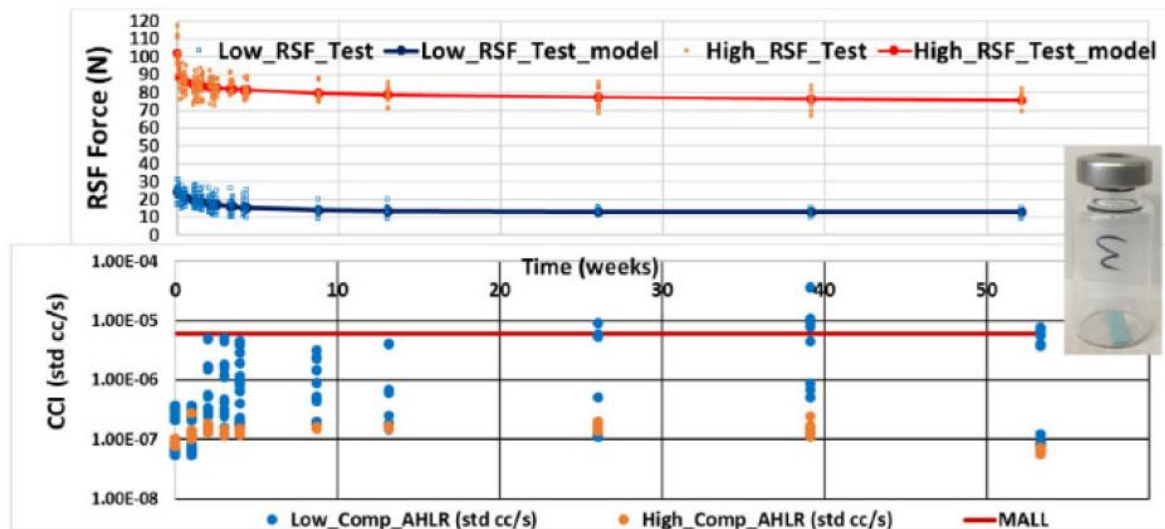


- Elastomer is the base material of the stopper
- Exhibit viscoelastic behavior
- Relaxes over time → RSF decay over time

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 Dependence

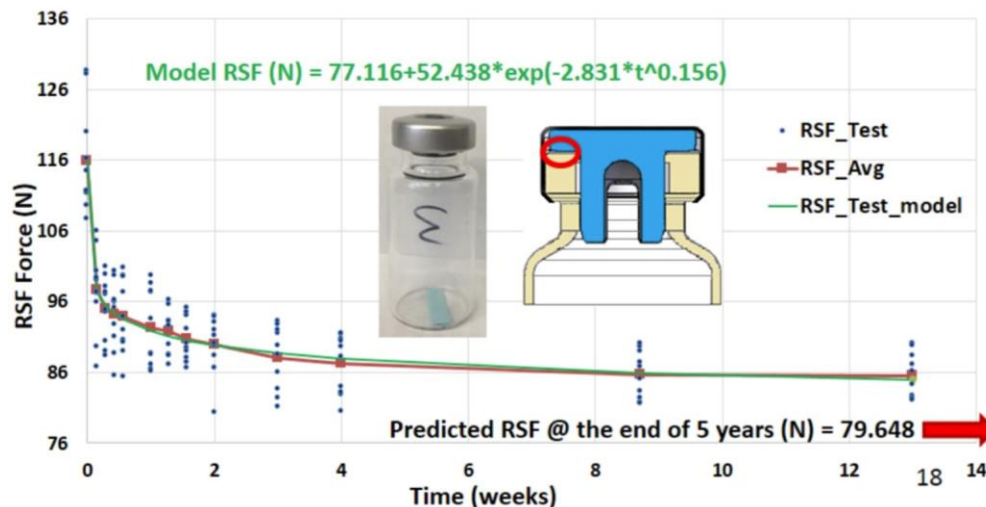
**Figure 1:** RSF and helium leak testing data for vial CCS using a 20 mm butyl elastomer stopper and a 10 mL glass vial fully filled with helium at ambient pressure, tested at ambient temperature through a vacuum chamber [8, 9].



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

Time dependent RSF testing at ambient conditions and modeling fit  
(20mm serum stopper, seal, & vial)



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	<b>8.7</b>	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

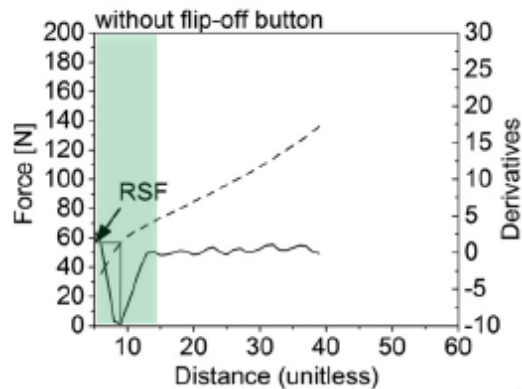
# Case Study 1 – Conclusions

- 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

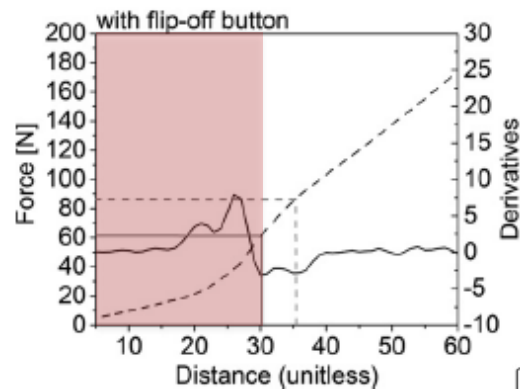
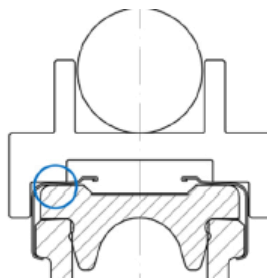
# Case Study 2

## Effect of Flip-Off Cap

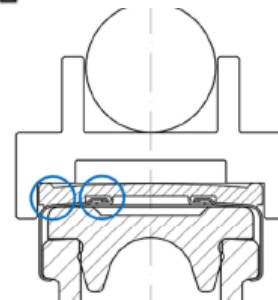
# Flip-Off Cap Impact



One clear minimum on 2<sup>nd</sup> derivative

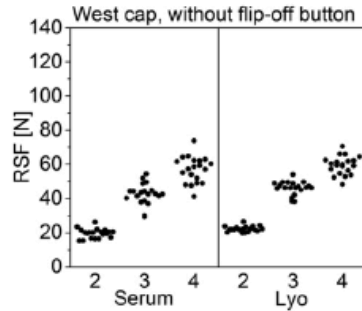
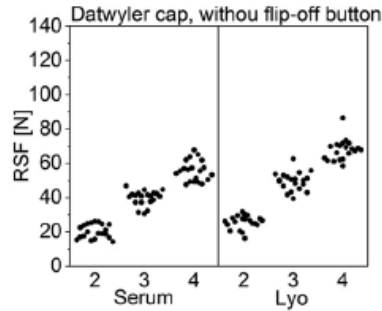


More complex and noisier signal

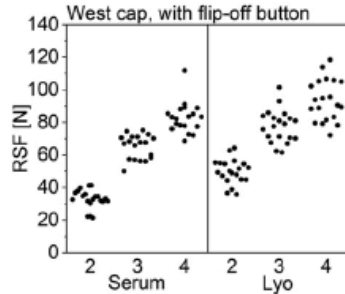
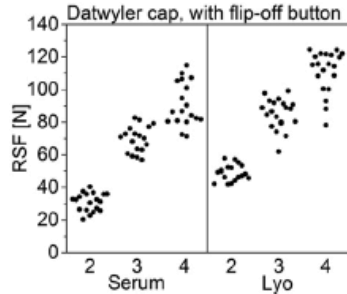


R. Mathaes et al. "Impact of Vial Capping on Residual Seal force and Container Closure Integrity" *PDA J Pharm Sci and Tech* 2016, 70 12-29

# 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

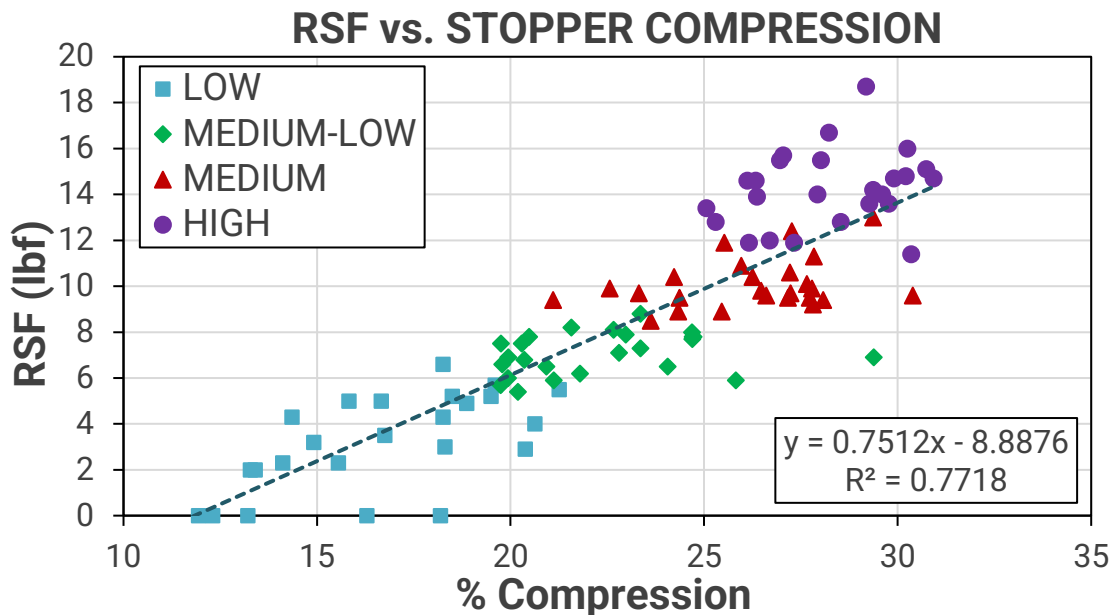
- The flip-off button adds complexity to the system, preventing a clean transition of the force applied by the RSF tester
  - The stress-strain curve is more complex – sometimes with 2 minima
  - Higher variability
- More reliable results without the flip-off button → Destructive

# Case Study 3

## Correlation with CCIT

# Correlation - RSF to Compression

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

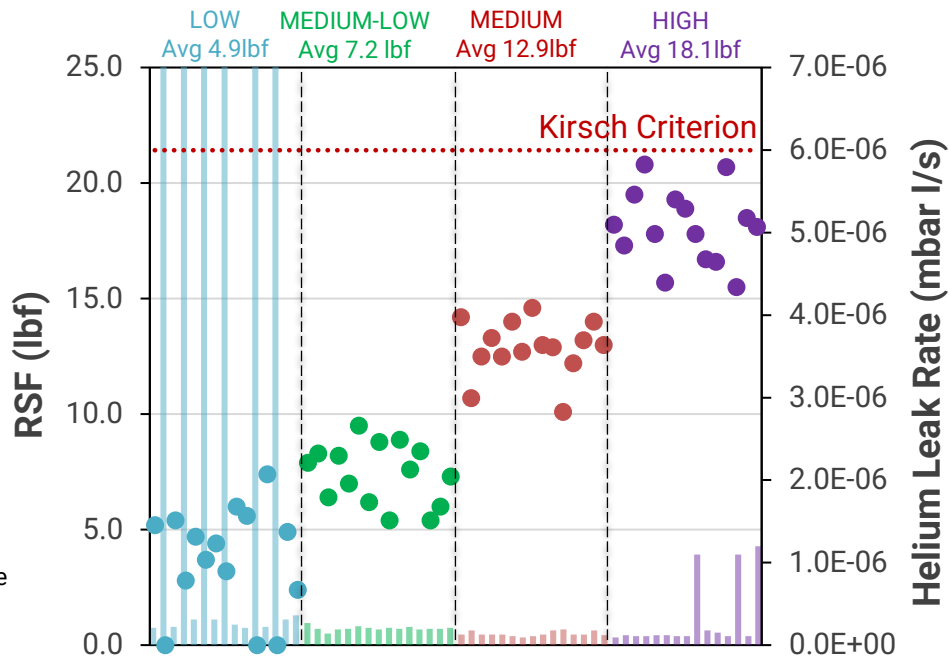




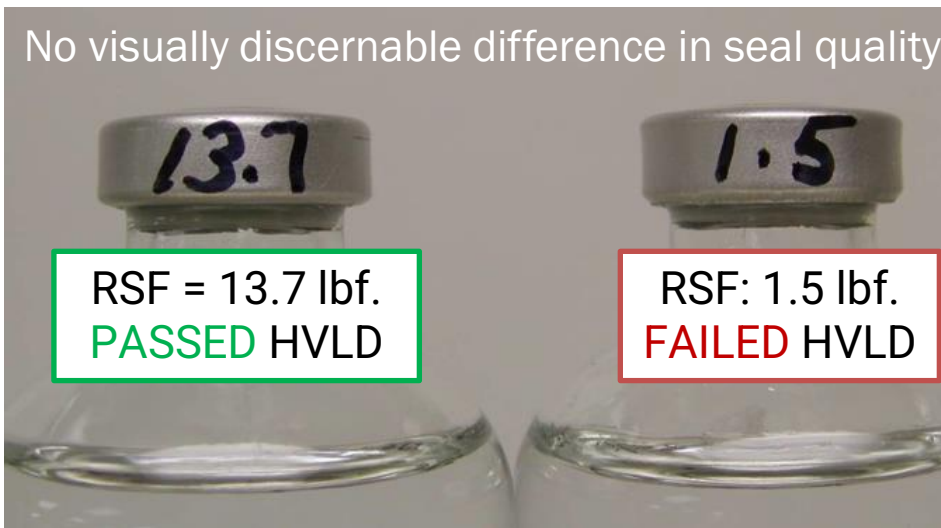
# Correlation - RSF to He Leak Rate

- Kirsch criterion\*: Helium leak rates lower than  $6 \times 10^{-6}$  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)

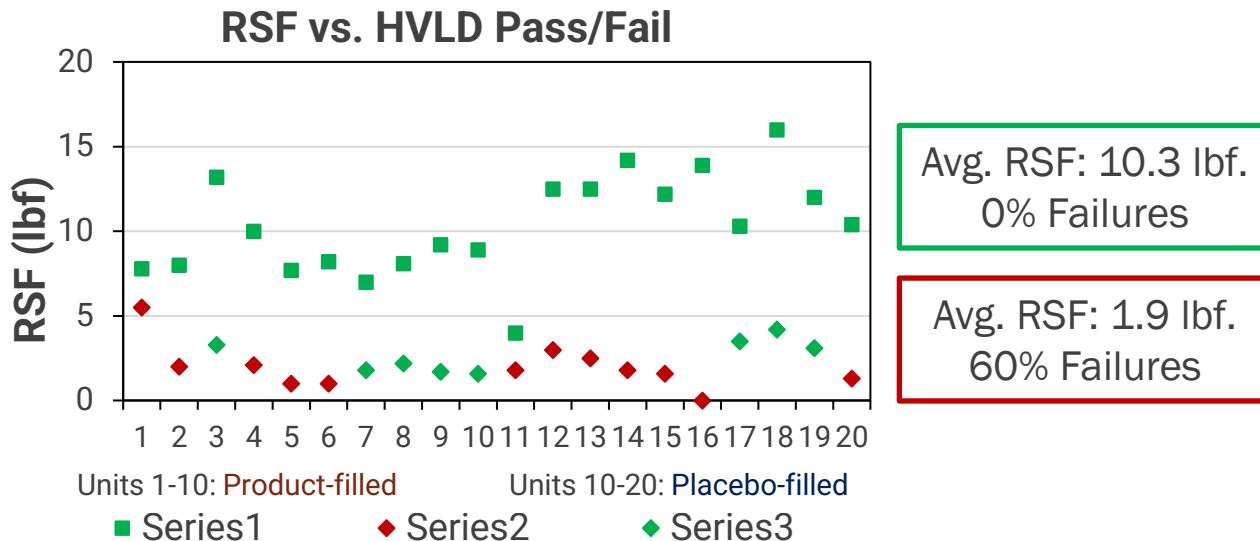


# Correlation - RSF to HVLD



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

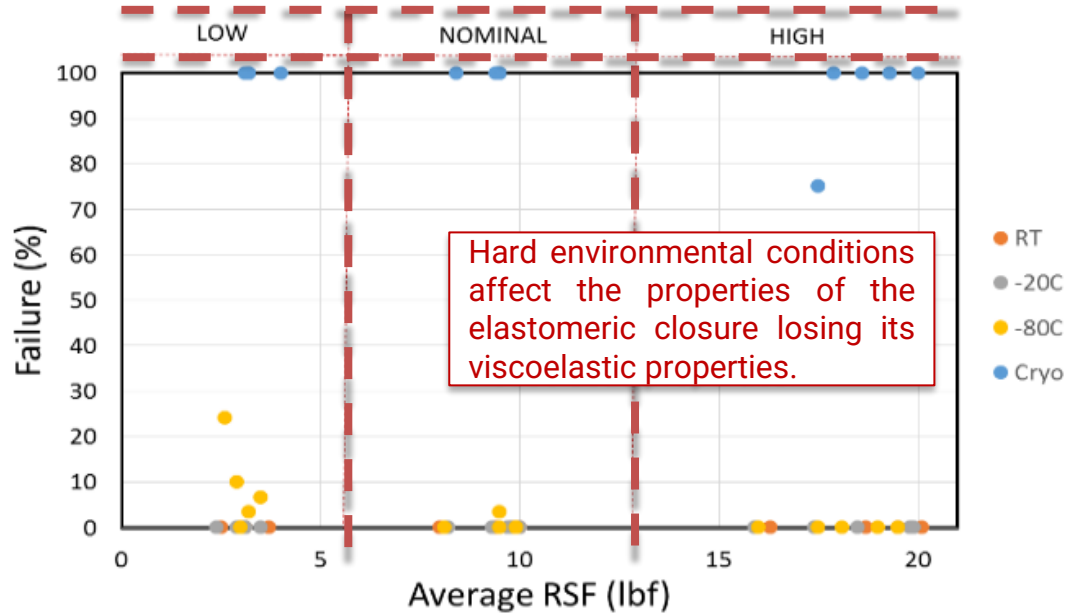
# Correlation - RSF to HVLD



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

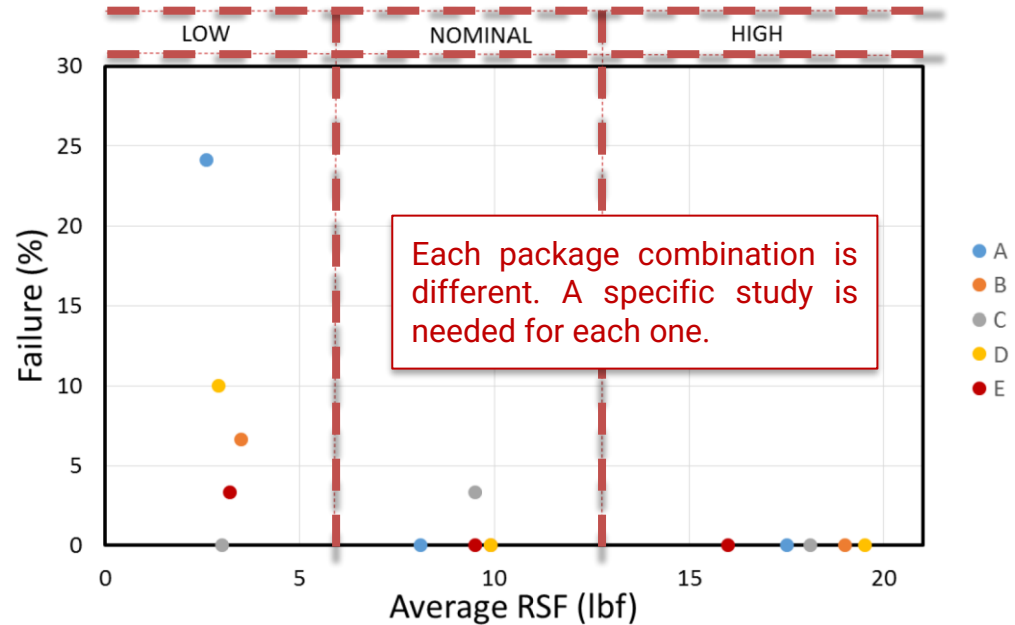


Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of PDA Parenteral Packaging Conference, Frankfurt, Germany; (2015)

# 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



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



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# Thank you!



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