Residual Seal Force: A Powerful Vial Seal Quality Test

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Agenda

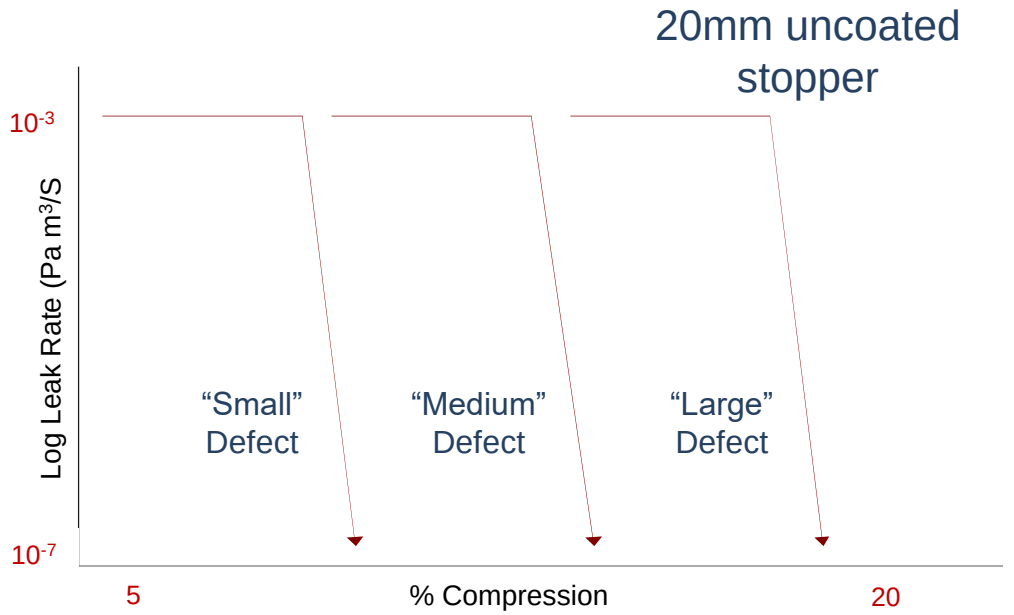
- Seal quality tests
- Characterizing a “well-sealed” vial
- Residual Seal Force
  - What is it?
  - Method concept
  - Basis of Testing
  - Significance and use
- Correlation RSF vs. CCITs
- Importance and use of RSF
- Conclusions

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. The cross section of the component(s)
  2. The 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 (inducing a surface stress) a compressed elastomeric rubber stopper flange continues to exert on the vial crown sealing surface (land area) 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 first develop as an indirect measure of compression

1980's

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

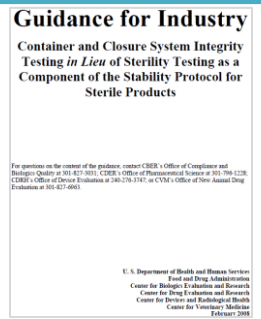
1990's

Instron introduced stress / strain testers

2001

Genesis launched the RSF tester – AWG 1.0

2008



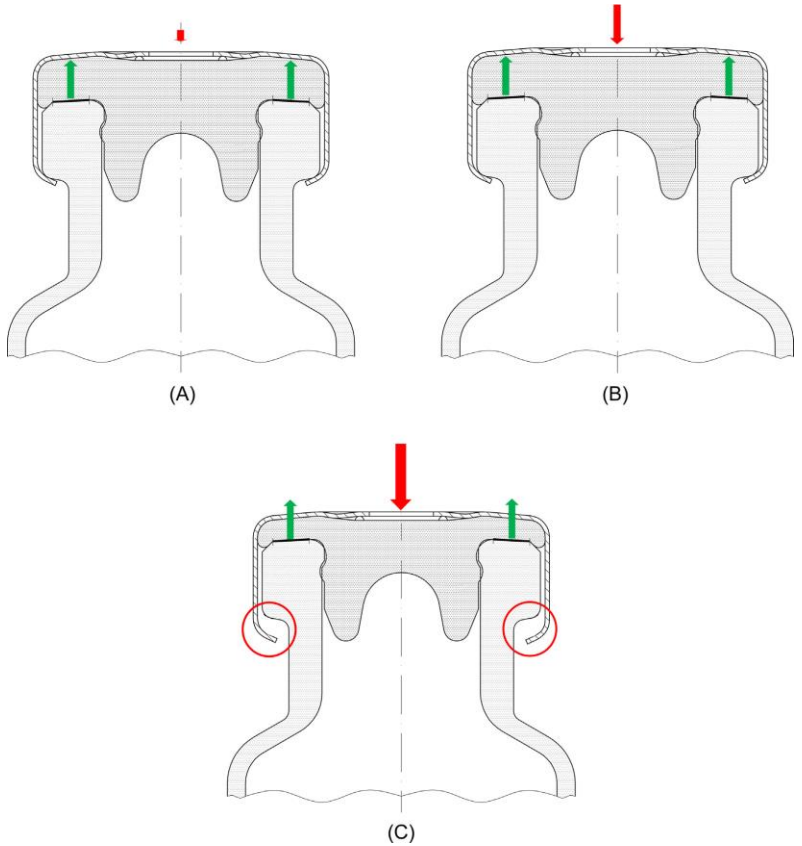
2016

<1207> PACKAGE INTEGRITY EVALUATION – STERILE PRODUCTS
<1207.3> Package Seal Quality Test Methods

2020

RSF tester AWG 2.0

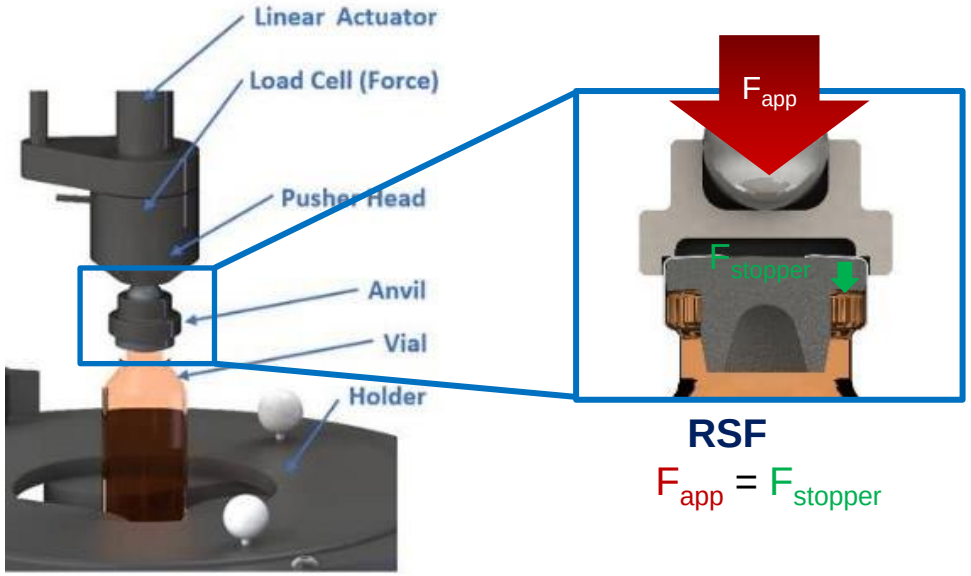
Basis of RSF Testing



- 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

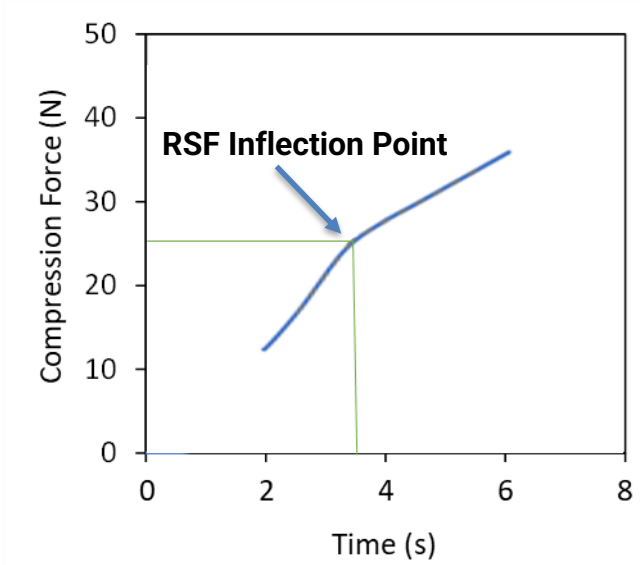
R. Mathaes et al. “The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests” *European Journal of Pharmaceutics and Biopharmaceutics* 99 (2016) 54–64

RSF Tester and Methodology

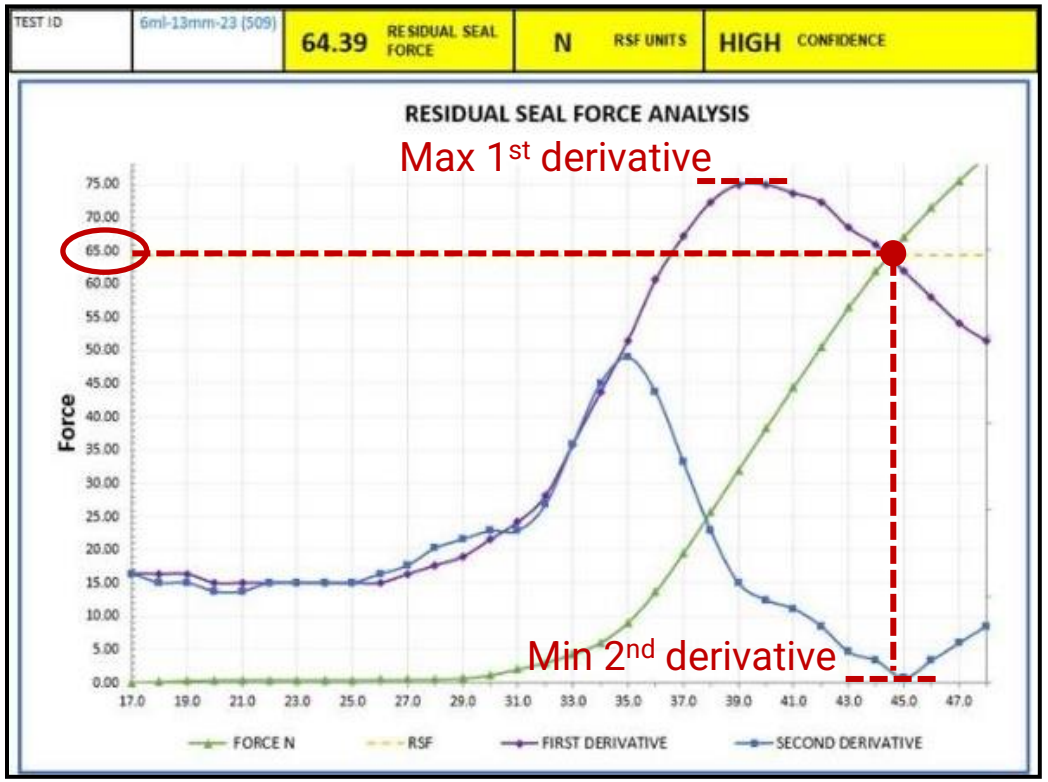


RSF

$F_{app} = F_{stopper}$



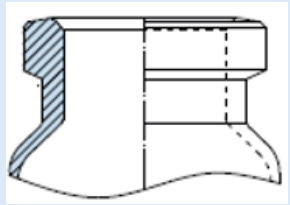
Determining RSF

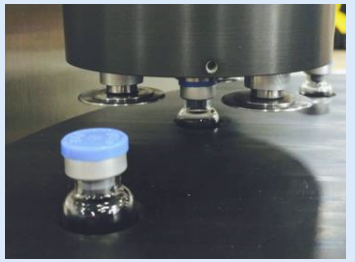


- Stress-strain curve (green) is a combination of the viscous and elastic response to the stress from tester load
- RSF is determined using the stress-strain curve: the "knee" (yellow)
- An algorithm* is applied, using the 1st (purple) and 2nd (blue) derivatives to accurately identify that knee

*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





RSF Tester

- Anvil design
- Button Removal
- Orientation

Components Variation

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

Time

- Elastomer relaxation
- Greater variability at <10min
- Greater decrease with higher crimping forces

Capping Process

- Type of capper
- Optimization of setting

RSF Testers

Genesis AWG 2.0

Fixtures for Instron®

Fixtures for Zwick®

Significance & Use of RSF Method

Package Development

- Determine impact of CCS component variables
  - Dimensional tolerances, durometer, cure, processing, etc.
  - Assembled CCS processing, distribution, storage

Validation

- Establish optimum capping parameters
- Evaluate variation

Production

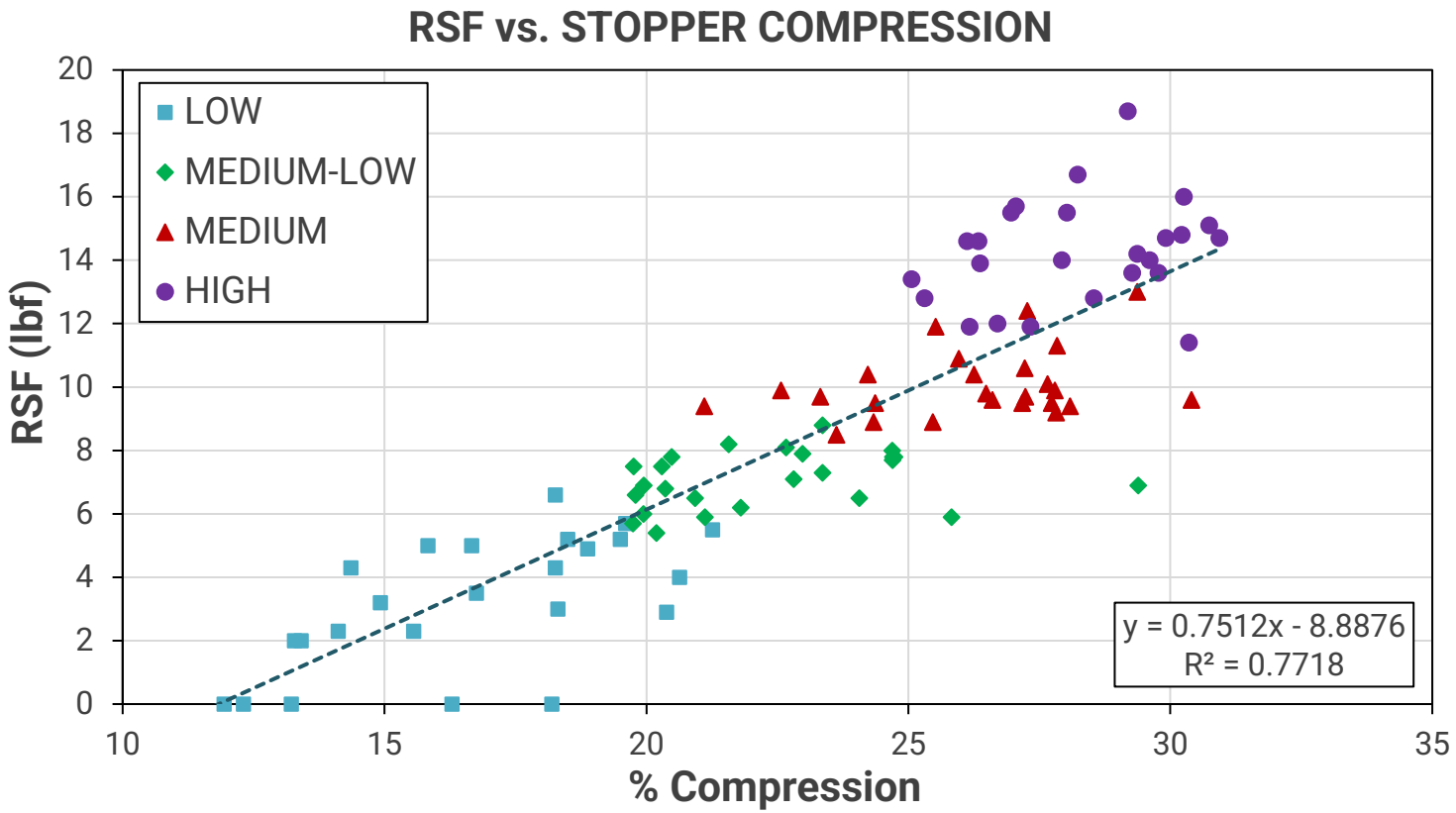
- Verify capping equipment set-up
- Capping process monitor

Correlation RSF vs. CCITs

Case Study 1 – RSF vs. He Leak

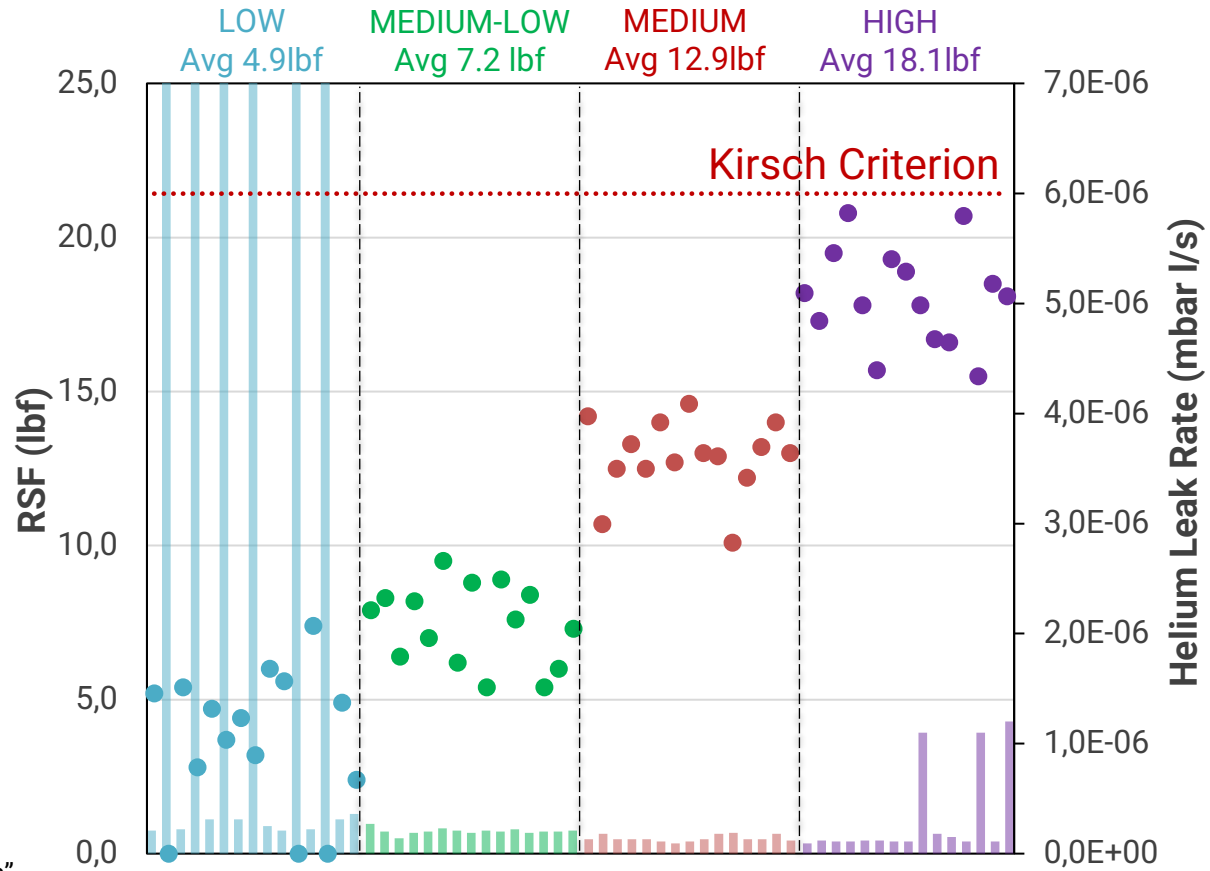
Case Study 1 – RSF vs. He Leak

- 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



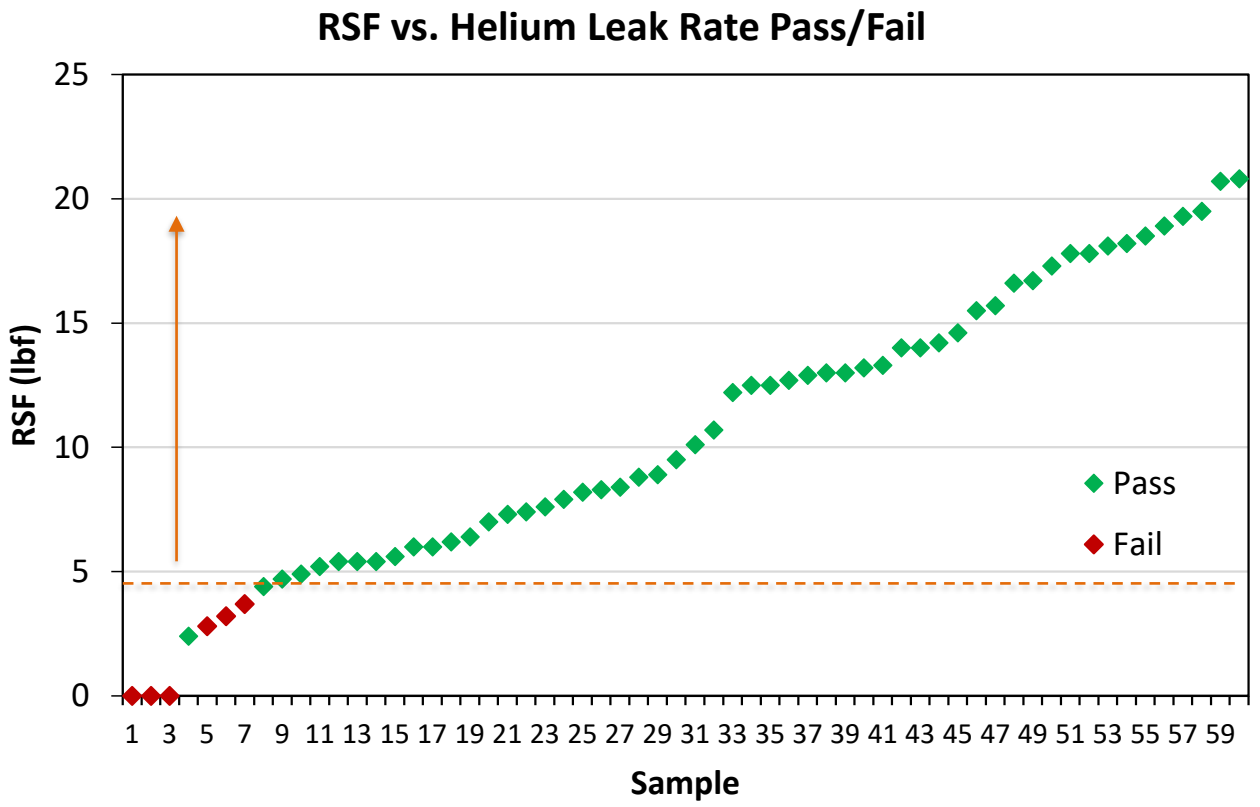
Case Study 1 – RSF vs. He Leak

- 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)

Case Study 1 – RSF vs. He Leak

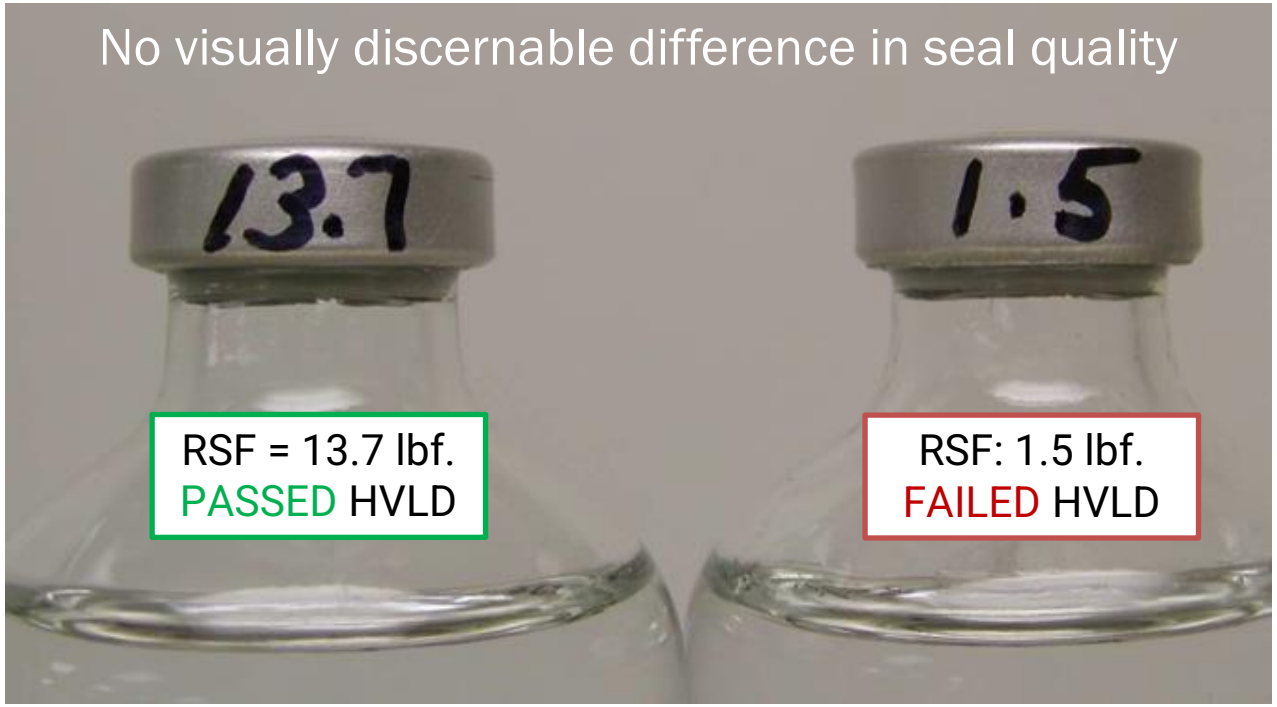


Pass/Fail criterion: $6x10^{-6}$ std cc/s

Correlation RSF vs. CCITs

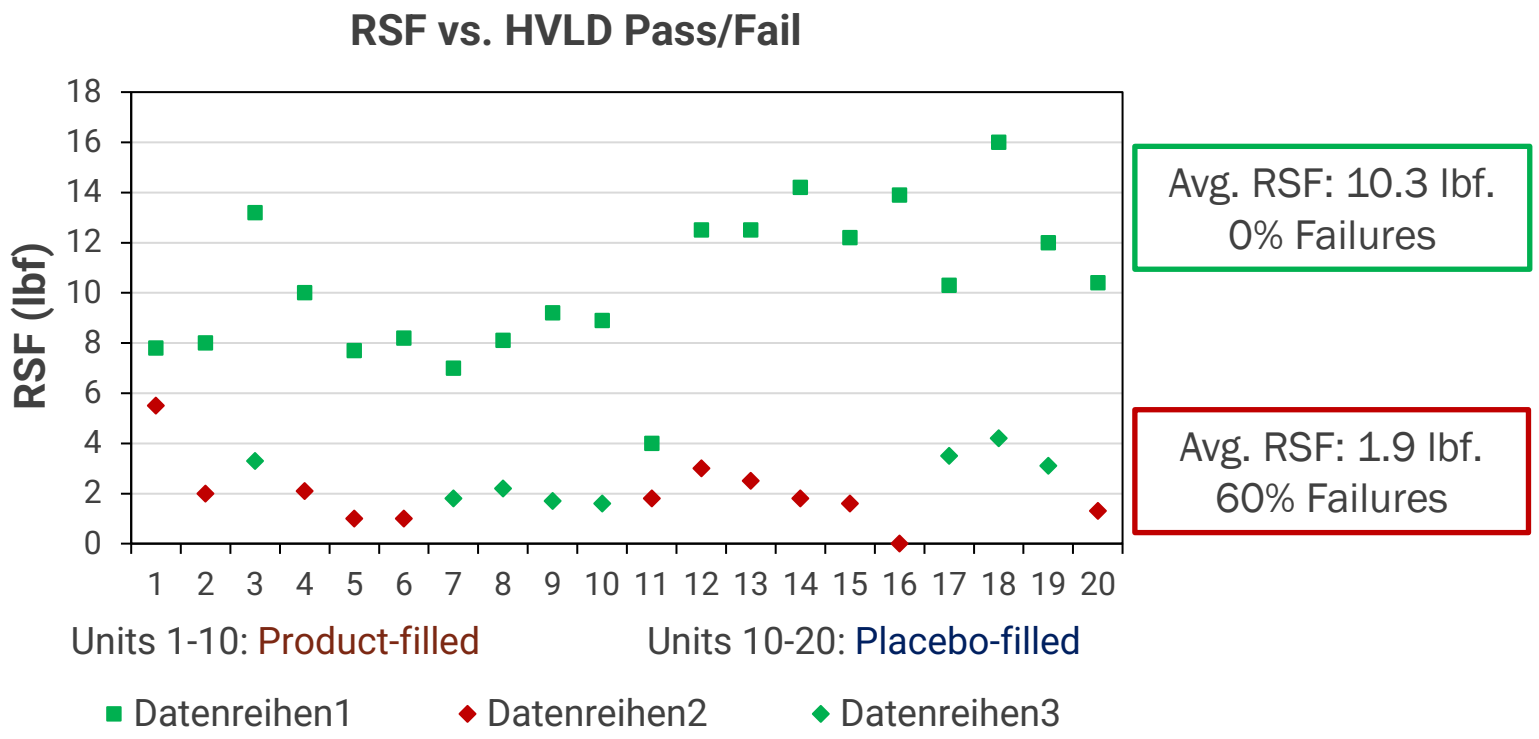
Case Study 2 – RSF vs. HVLD

Case Study 2 – RSF vs. HVLD



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

Case Study 2 – RSF vs. HVLD



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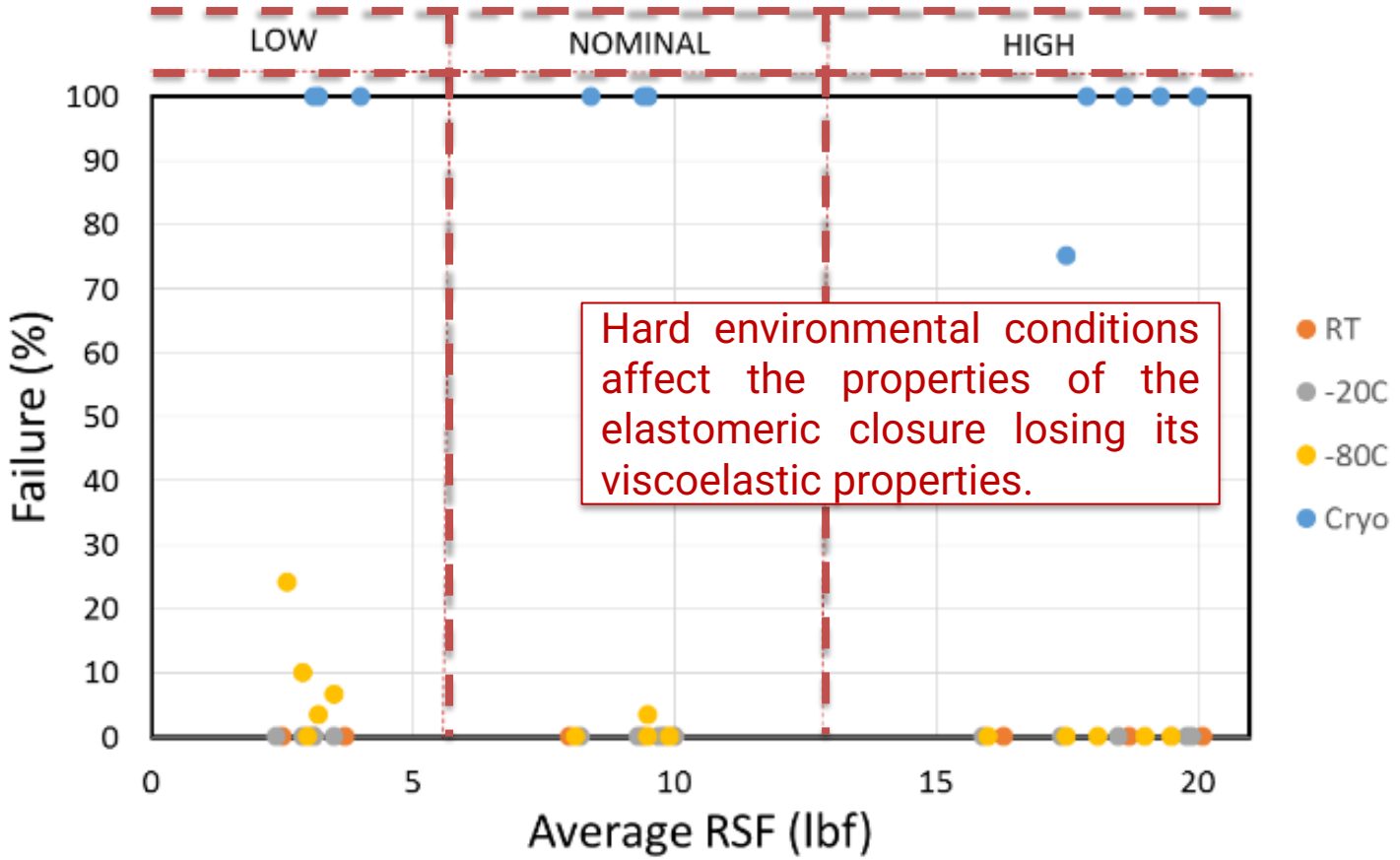
Correlation RSF vs. CCITs

Case Study 3 – RSF vs. HSA

Case Study 3 – 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 (Low, Nominal, High)
- Storage:
  - Four (4) storage temperatures: Room temperature (RT), -20°C, -80°C, Cryo (~ -150°C)

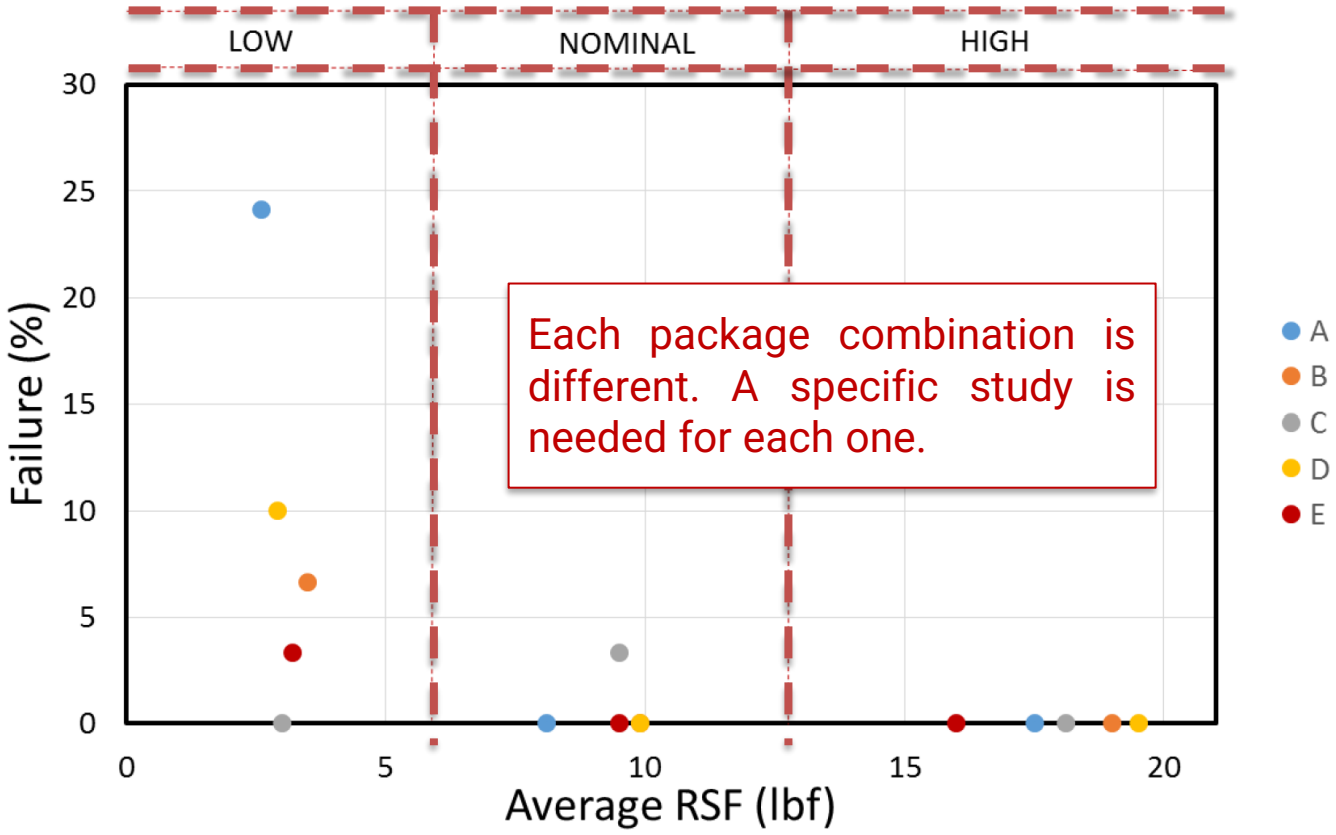


Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of PDA Parenteral Packaging Conference, Frankfurt, Germany; (2015)

Case Study 3 – 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



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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)

Conclusions

- 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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