Residual Seal Force
A Powerful Vial Seal Quality Test

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With Significant Contributions from Roger Asselta, Genesis Packaging Technologies

Seal Quality Tests

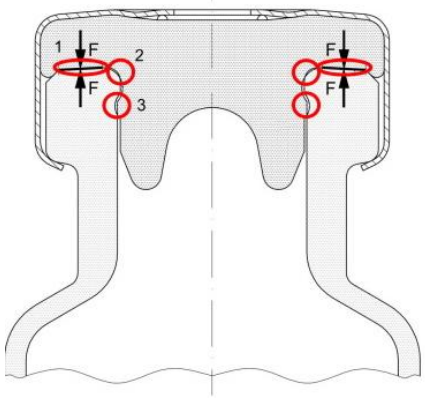
- Tests used to **characterize and monitor** the **quality and consistency** of a **seal parameter** providing some assurance of the package's ability to remain integral.
- **Parameters monitored** may include
  - Seal quality or characteristic
  - Package materials
  - Package components
  - Sealing process
- **SQT are <u>not</u> leak tests**
- RSF is the Stress A Compressed Elastomeric Closure Flange Continues to Exert on A Vial Land Sealing Surface after Application of an Aluminum Seal (Crimping).
- USP <1207.3> Seal Quality Test
- Quantifying the RSF is a Test Method for the Indirect Estimation of Elastomeric Closure Compression.
- Sufficient Compression is Essential to Seal Integrity.

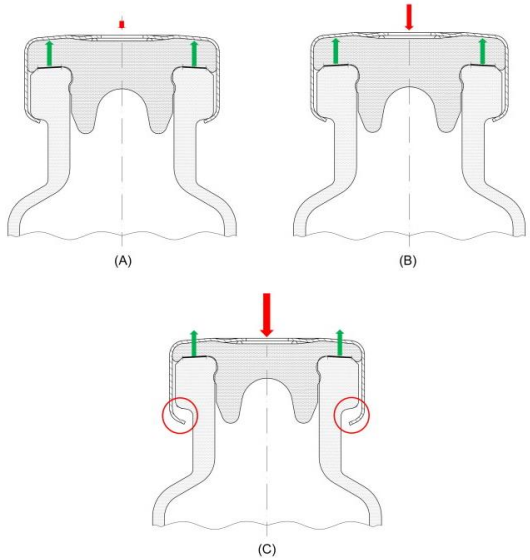
RSF Test Method Concept

- There is an Optimum Window of Closure Compression
  - Too Little versus Too Much Force
- Poor Compression Cannot be Visually Detected
  - RSF Testing is an Indirect Measure of Compression
- RSF testing is recognized in the recently revised USP <1207> *Sterile Product Packaging – Integrity Evaluation* in section <1207.3> *Package Seal Quality Test Methods*

Basis of RSF Testing

- Upon Capping the Closure Flange is Compressed Against the Vial Land Sealing Surface
- The Closure Acts Like a “Compressed Spring”
- The Tester Exerts Force on the Cap/Stopper
- When the Tester Force Exceeds the Closure Compression Force, Graphically the Stress-Strain Slope (Rate of Change) Drops
- This “Knee” in the Curve Equals the RSF
- >Applied Force at Capping > Closure Compression > RSF

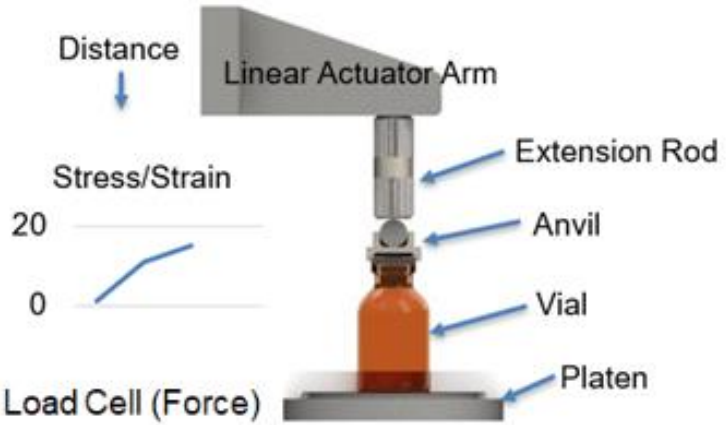




“The pharmaceutical vial capping process: Container closure systems, capping equipment, regulatory framework, and seal quality tests”. Mathaes *et al*, Eur J. Pharm. Biopharm, doi: 10.1016/j.ejpb.2015.11.016.

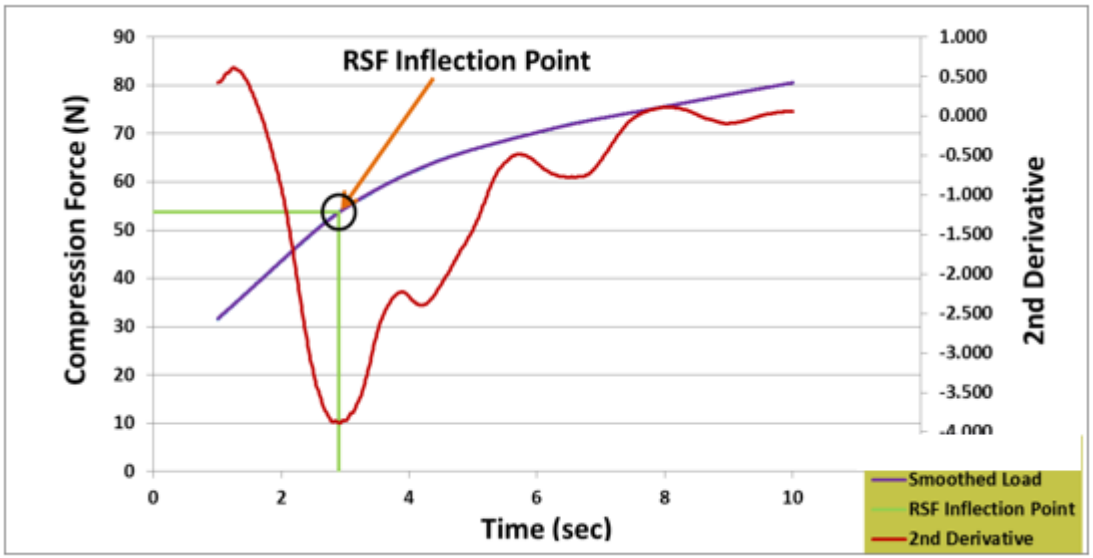
RSF Testers

RSF Tester and Methodology



- Remove flip off cap (CS#1) – destructive technique.
- Measure at a similar time after capping (CS#2) - challenges in manufacturing setting.

Signal Analysis



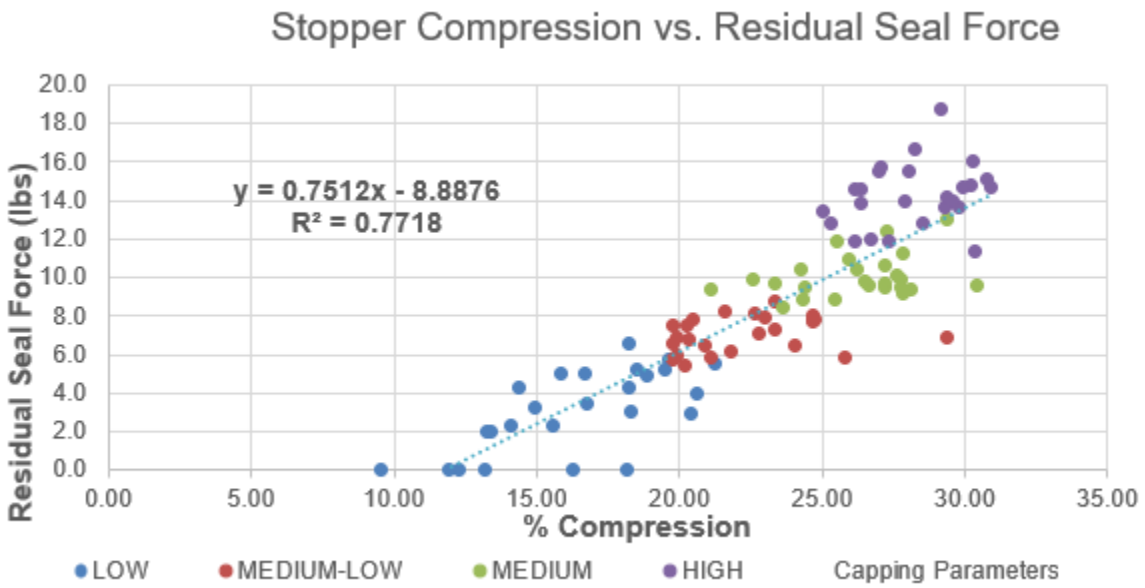
The compression curve (purple) is a combination of the viscous and elastic responses to the stress from tester load. Beyond "the knee"(green), is the compression of the elastomer. An algorithm is applied, using the 1st and 2nd (red) derivatives to accurately identify that knee.

Ludwig, J. D., *et al*., "Automated method for determining Instron residual seal force of glass vial/rubber closure systems", PDA J Pharm Sci Tech, 47. 211-253 (**1993**).

Significance and Use of RSF Test Method

- Package Development
  - Determine Effects 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 of RSF to Compression



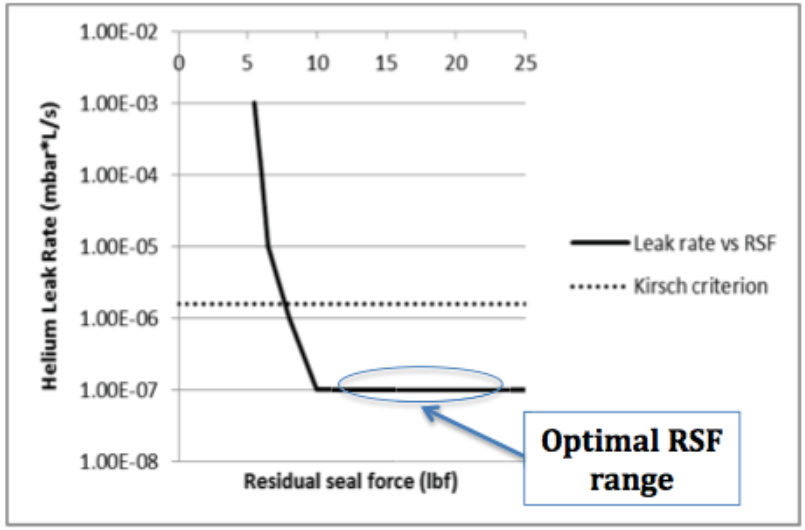
Example: 20 mm Serum Soft Stopper

Correlation of RSF to Leak Rate

Tracer gas leakage rate (ASTM F2391) vs Residual seal force

Optimal RSF resulted in consistent leak rates well below the rate predicted for a 0.2µm hole

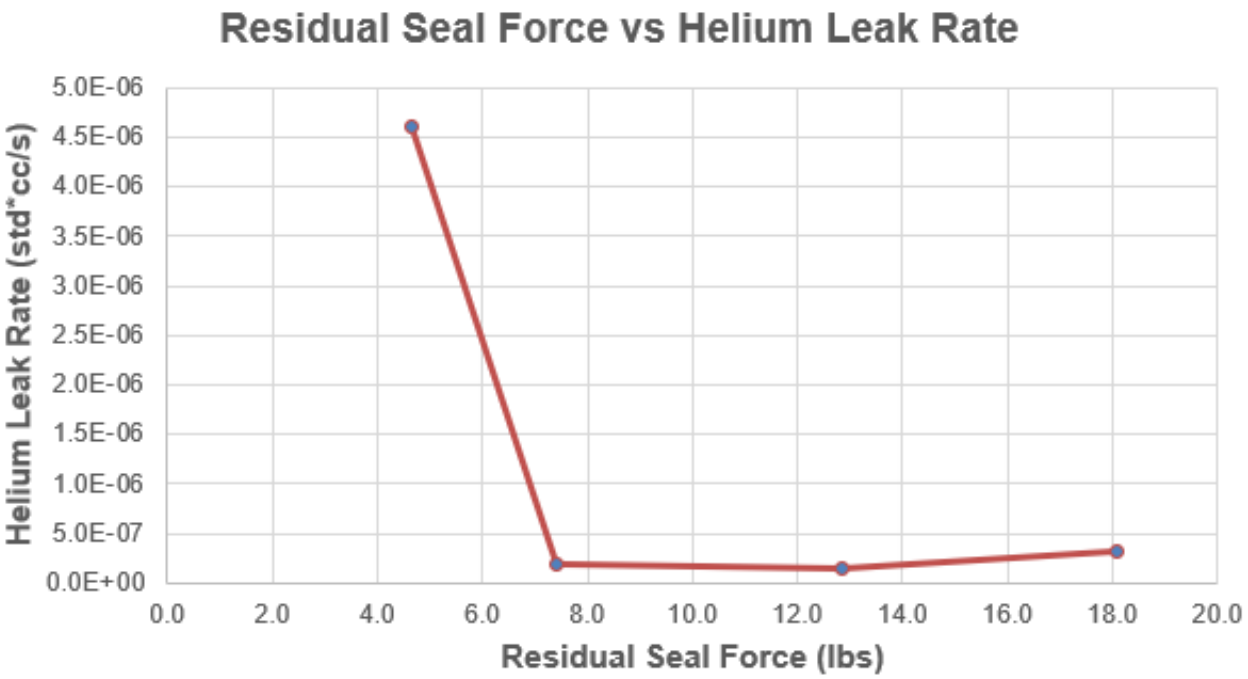
Ref. L Kirsch, L Nguyen, C Moeckly, R Gerth, *Pharmaceutical container/closure integrity II: The relationship between microbial ingress and helium leak rates in rubber-stoppered glass vials,* PDA J Pharm Sci & Tech 51, 1997, 195 – 202



D. Guazzo, RxPax, LLC

Fictional data for illustration only

Residual Seal Force vs Helium Leak Rate

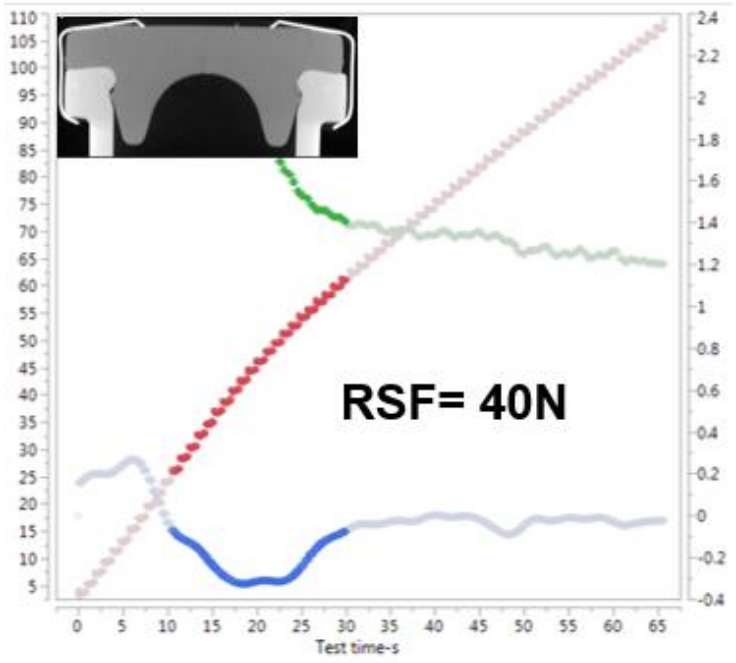


Case Study # 1

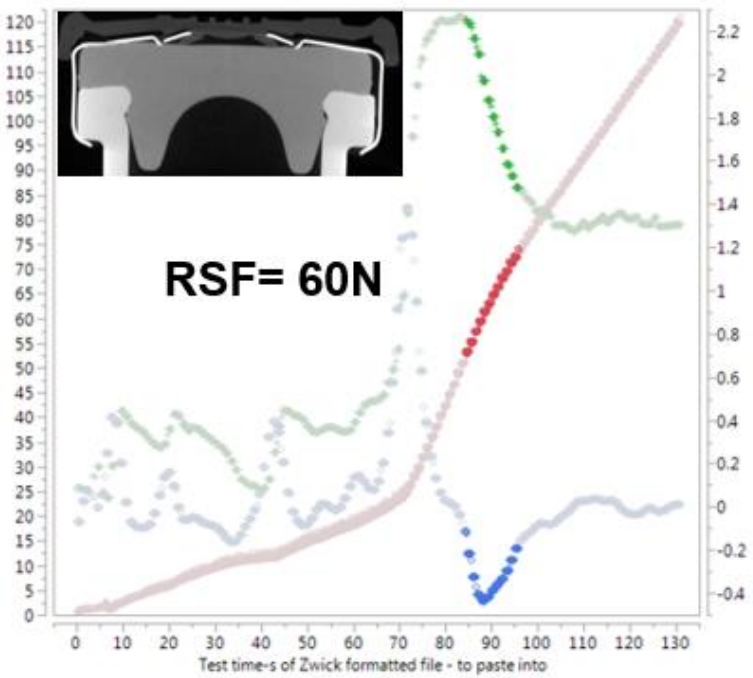
Effect of Flip-off Cap

Case Study #1, Flip-off cap impact

Flip-off Cap Off



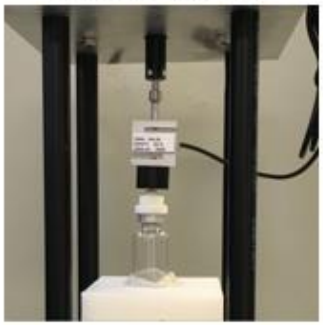
Flip-off Cap On



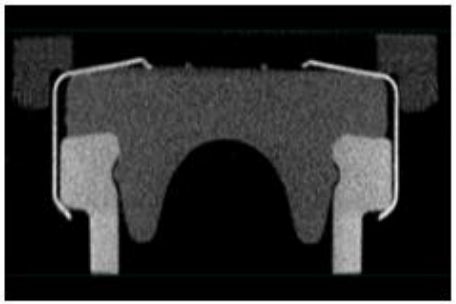
- Flip-off cap on presents a more complex and noisier signal than flip-off cap off, and longer time to run.
- Which signal is valid?

RSF Testing with 4D X-ray CT

Motor driven compression with load cell

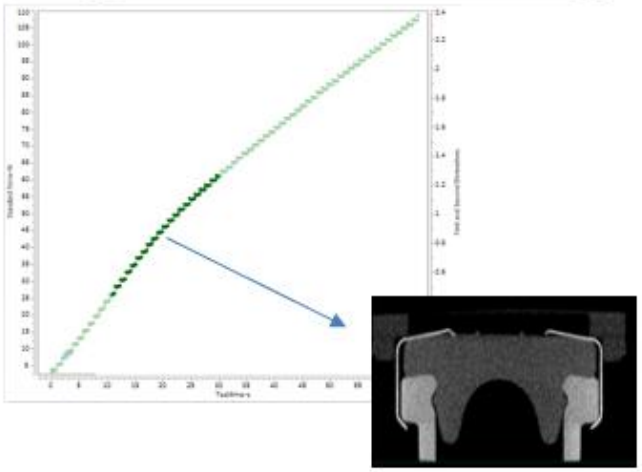


X-Ray Computed Tomography

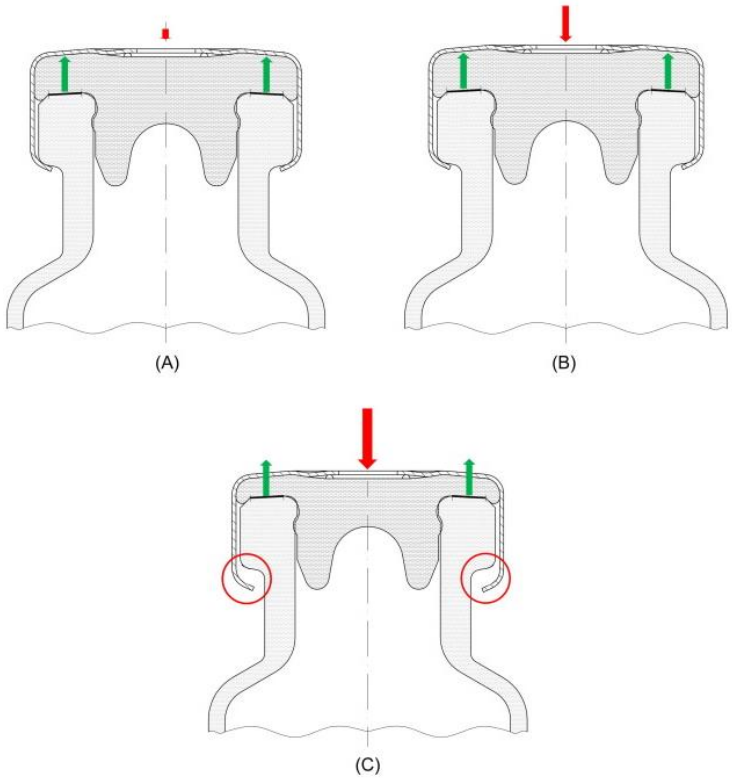


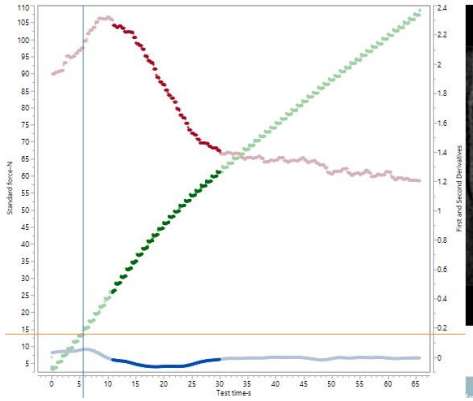
4D Representation of the CCS upon compression

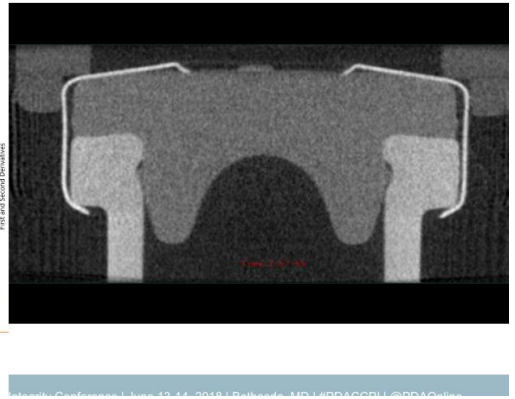
- Visualization of compression on CCS
- Relation between RSF and CCS state at each point of the response curve

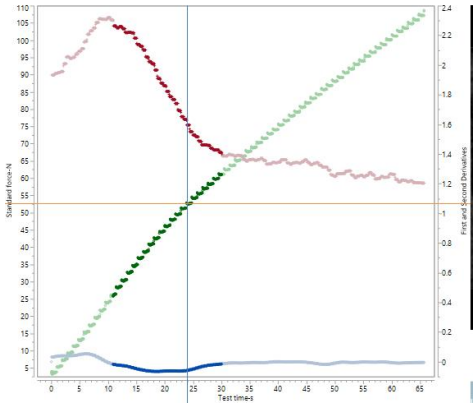


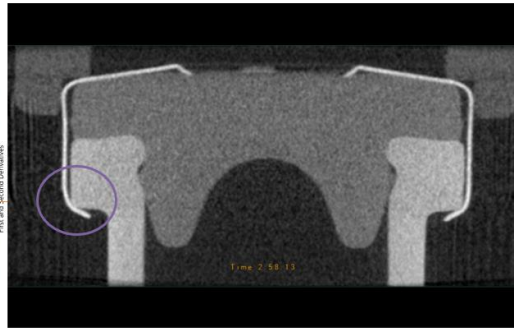
How to visualize RSF?



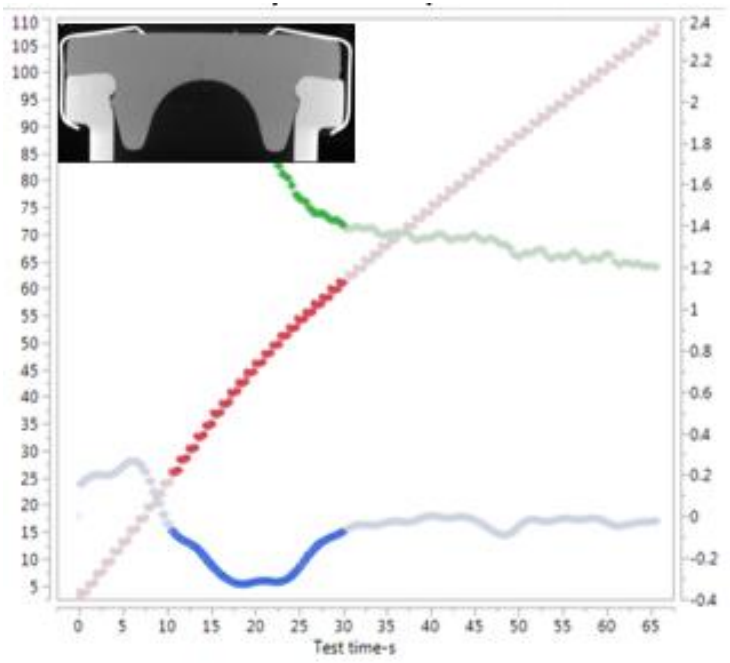




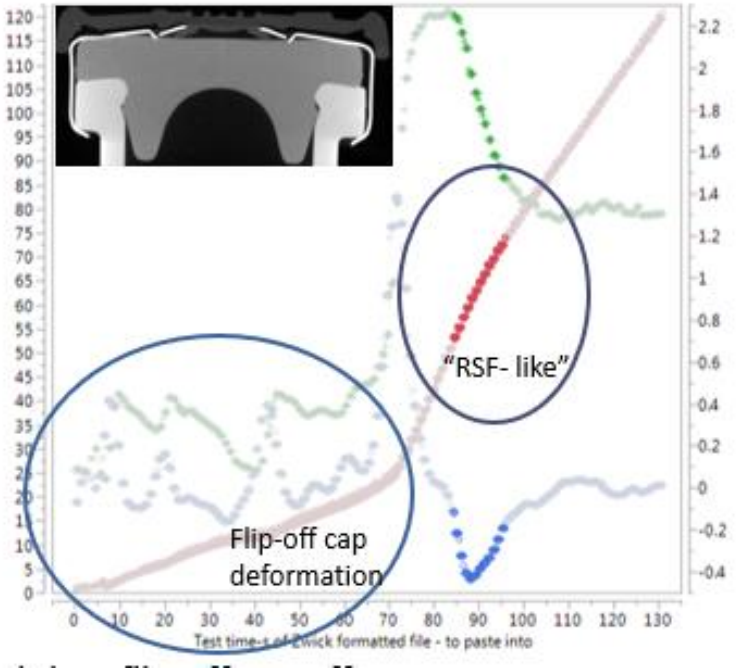




Flip-off Cap Off



Flip-off Cap On



- Flip-off cap on presents a more complex and noisier signal than flip-off cap off
- While region is "RSF-like", question of true value of RSF due to entire cap pressing inconsistently on the stopper

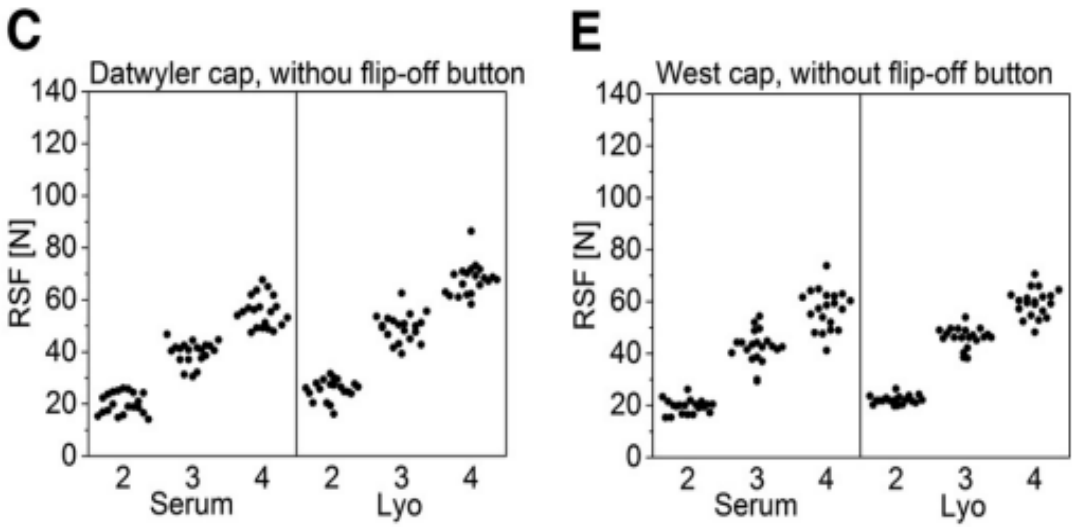
Case Study #1 Conclusions

- Need to take flip-off cap - RSF is a destructive method
- Time when cap is removed does not matter
- Has been proved in “classic” glass / stopper / aluminums skirt, TBD with newer technology press-fit plastic cap

Case Study # 2

Standard Variation & Effect of Time

Standard Variation



- Standard Variation around RSF values
  - ~ ± 7 N for RSF = 20N
  - ~ ± 17N for RSF = 60N
- Standard Variation
  - Size of the components (vials, stoppers)
  - Capping (# of capper heads, plunger height / plunger pressure)

"Impact of Vial Capping on Residual Seal Force and Container Closure Integrity", Mathaes *et al*, PDA Pharm. Sci. and Tech. doi:10.5731/pdajpst.2015.005876

Influence of Elastomer Relaxation

Rubber will relax with time, decreasing the RSF:

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

TABLE II

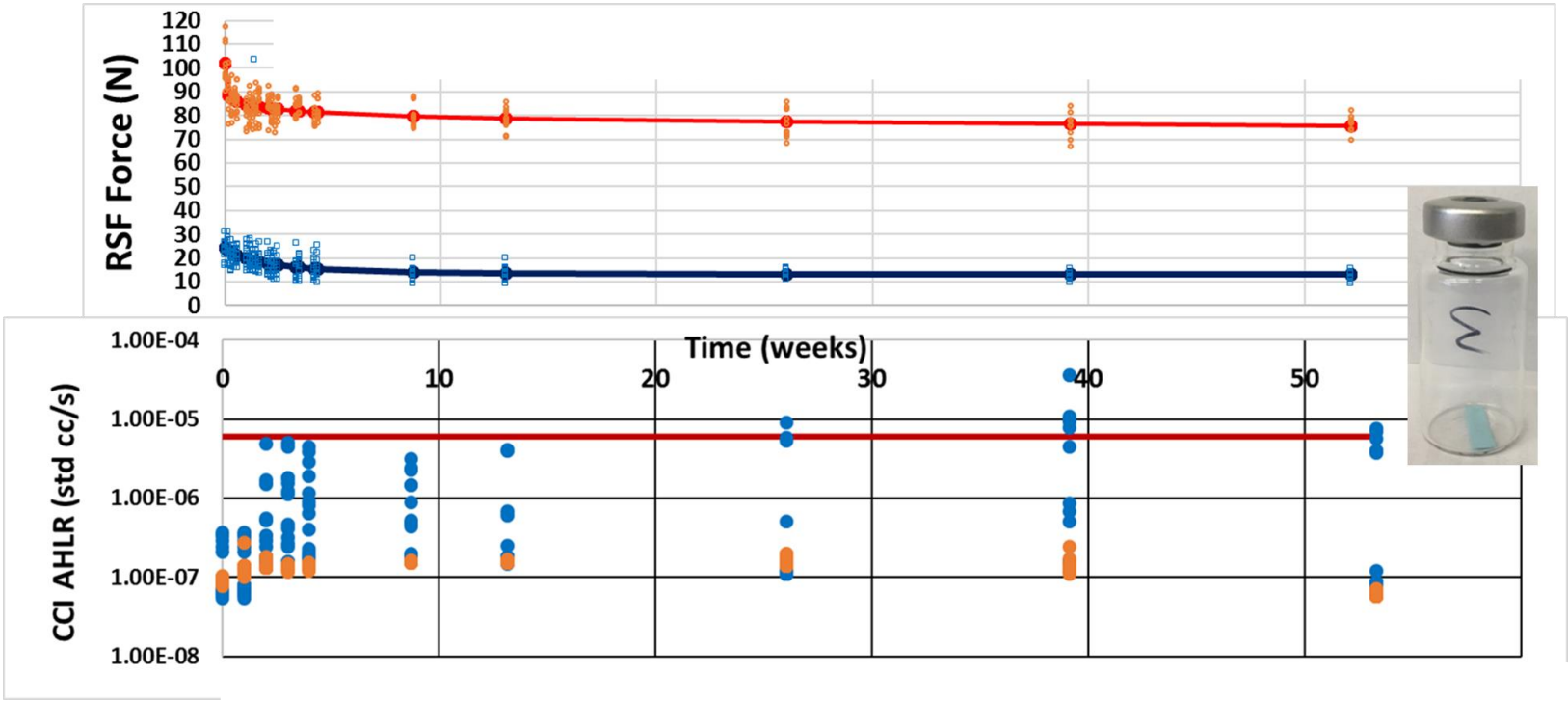
Statistical Data Generated of 20 vials from the RSF Time Course

Time	Mean RSF (N)	RSD (%)
1 minute	62.7	9.9
10 minutes	54.0	11.0
90 minutes	53.1	7.0
1 day	52.1	9.6
7 days	51.0	11.1
21 days	50.5	10.2

"Quantifying the Vial Capping Process: Residual Seal Force and Container Closure Integrity" Ovaldia *et al*, PDA Pharm. Sci. and Tech, doi: 10.5731/pdajpst.2018.008797.

Time-dependance of RSF value

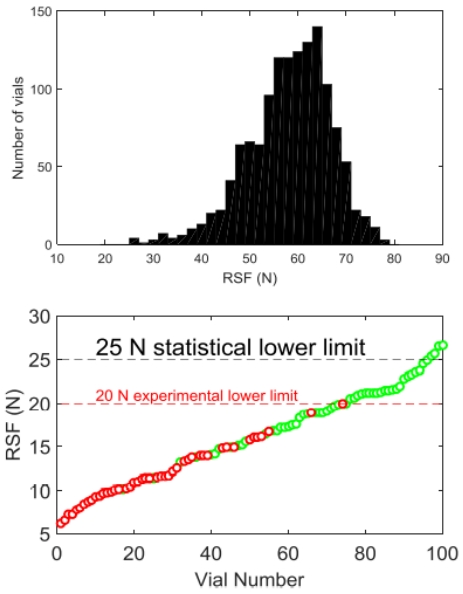
- Vials capped with high crimping force (orange) and low crimping force (blue)
- RSF value and HeLV CCI level were followed as a function of time



Robert Ovadia, Engineer II, Genentech, Inc. A Member of the Roche Group

2018 PDA Europe Conference

Method Development



Statistical Approach Criteria

1. Statistical distribution of manufacturing RSF data of a desired configuration
2. Use a 95/99 Lower Bound Tolerance Interval (LBTI)
3. Lower bound RSF limit based on the correlation of RSF to CCI
4. Desired sample size to be tested during capper setup

Case Study # 2, Conclusions

- Method development
  - Understand standard variation for your CCS
  - Understand effect of time : Real life data / modeling
  - Understand effect lower RSF bound to maintain CCI both at T=0 and T=shelf time

Case Study # 3

Machine Set-Up

Q: With new CCS, what are the best capping parameters?

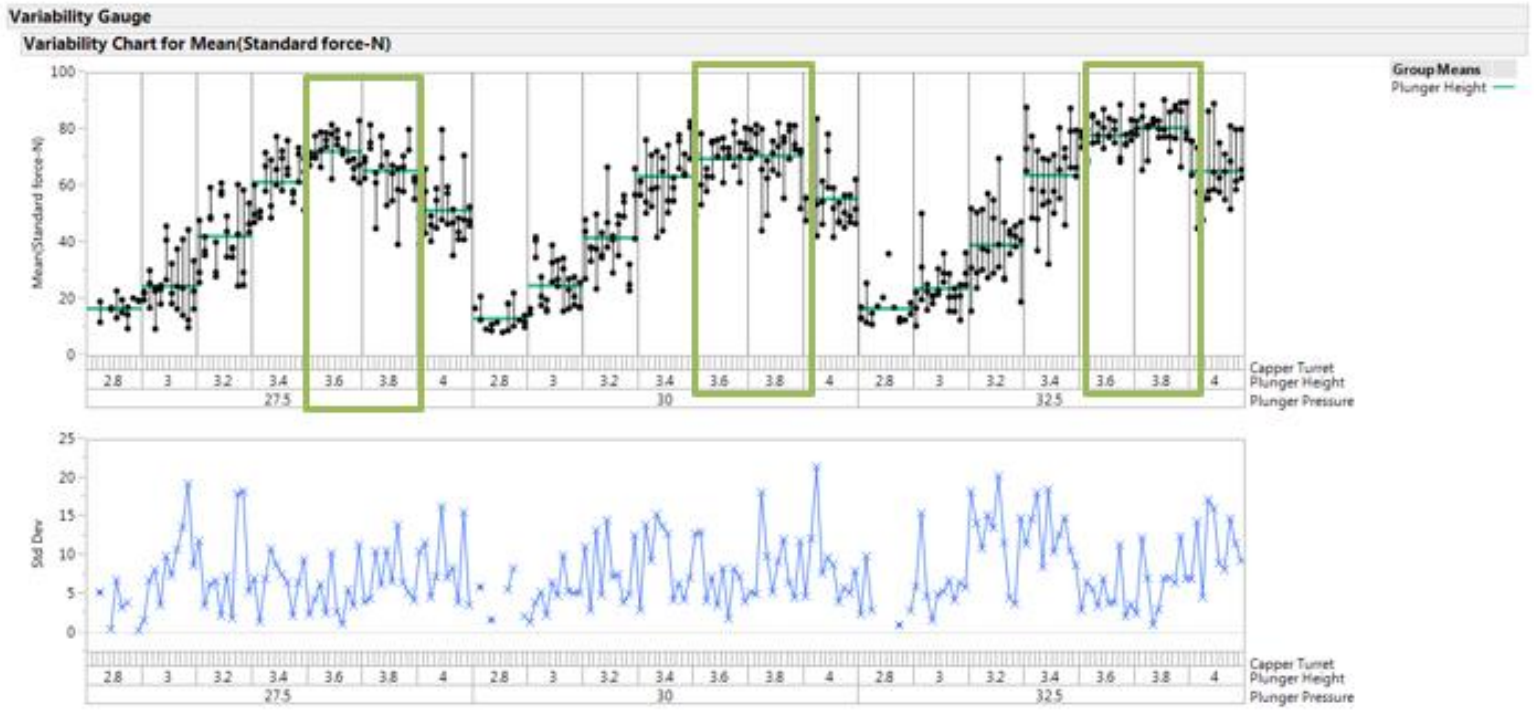
Capper Optimization

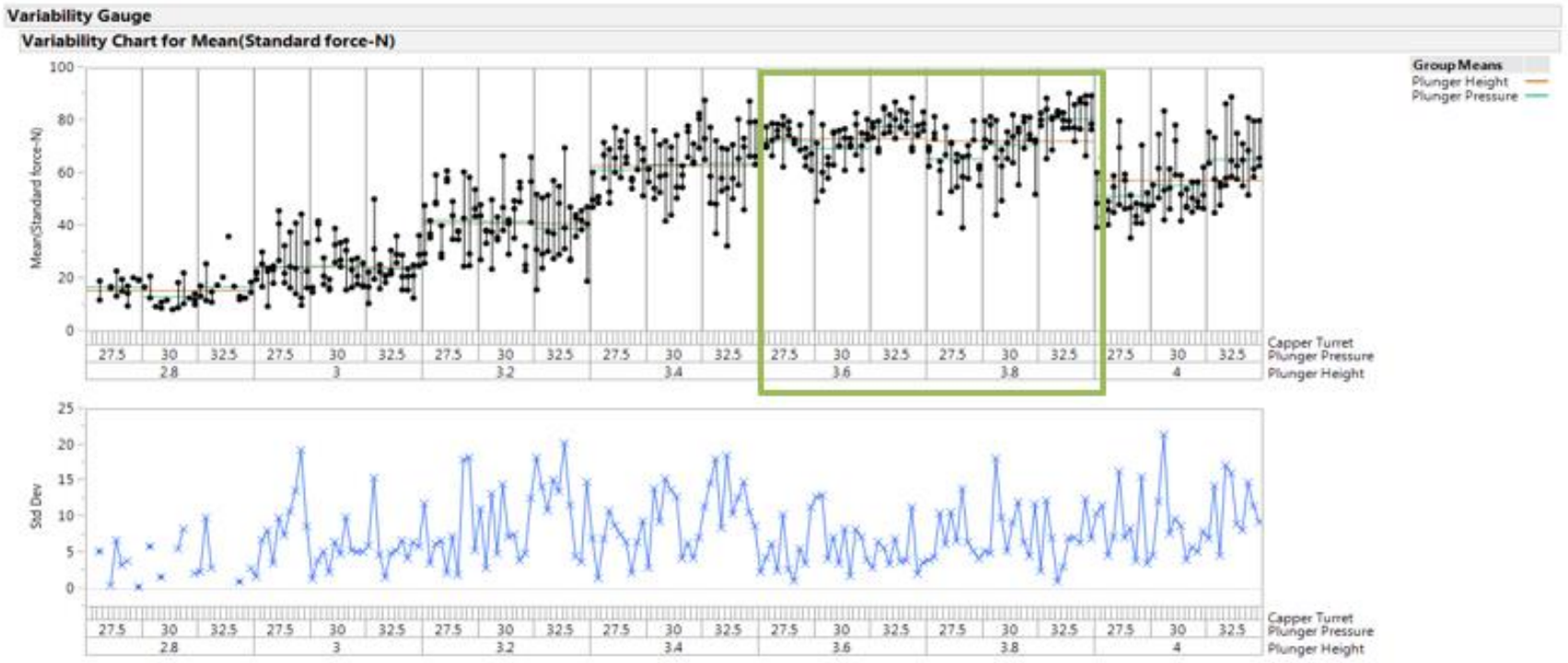
BOTTOM SPRING PRESSURE	TOP SPRING PRESSURE 25	27	30	33	35	38
6	Failure Insufficient Tuck	Failure Low Compression 14.8%	Acceptable Seal Compression at 17.9%	Failure Over-Worked Seal Split Seam	Acceptable Seal Compression at 18.72% Slightly Over-Worked	Failure Over-Worked Seal Split Seam
8	Failure Insufficient Tuck	Acceptable Seal Compression at 17.59%	Acceptable Seal Compression at 17.05%	Acceptable Seal Compression at 18.09% Slightly Over-Worked	Acceptable Seal Compression at 18.63% Slightly Over-Worked	Failure Over-Worked Seal Split Seam
10	Failure Insufficient Tuck	Visual Pass Borderline Compression at 15.94%	Acceptable Seal Compression at 17.15%	Acceptable Seal Compression at 17.31%	Acceptable Seal Compression at 17.63%	Failure Over-Worked Seal Split Seam
12	Failure Insufficient Tuck	Visual Pass Borderline Compression at 15.42%	Acceptable Seal Compression at 16.04%	Acceptable Seal Compression at 16.62%	Acceptable Seal Compression at 16.50%	Failure Over-Worked Seal Split Seam
14	Failure Insufficient Tuck	Failure Insufficient Tuck	Visual Pass Borderline Compression at 15.73%	Acceptable Seal Compression at 17.2%	Acceptable Seal Compression at 16.13%	Failure Over-Worked Seal Split Seam

Currently: Visual & Seal Compression

"Parenteral Vial Sealing and Integrity" R. Asselta, Genesis Seminar, May 3, 2016.

Plunger Pressure / Plunger Height





3.6 to 3.8 is ideal plunger height: high RSF and most consistent, and independent from plunger pressure.

Case Study # 3, Conclusions

- RSF powerful tool
  - Comparing across capping machines & sites
  - Establishing best capping parameters for new CCS
  - Verifying machine is properly set-up when CCS / product change

Conclusions

- RSF is a powerful Seal Quality Method.
- As with all methods, has limitations.
- Not a “black box”, need a rigorous method development.