Preventative Studies:
Critical Dimensions and Capping

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PDA Container Closure Integrity Testing – Basic Course
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Agenda

- Potential causes and impacts of leakage
- Vial seal anatomy
- Impact of component dimension on seal quality
- Preventative CCI studies: a well-characterized seal
  - Dimensional variation
  - Compression analysis
  - Residual seal force (RSF)
  - Leak testing (CCIT)

Considerations for Leakage

- All packages leak
- Leakage is a continuum
- Permeation
- Leakage
  - Through Defect
    - Cracks, pinholes, tear, defective component
  - Through Seal Areas

What affects the quality of a seal?

– Leakage at a seal is influenced by many factors, including:

- Dimensional tolerances of components
- Crimping variables
- Temperature
- Debris / Component Cleanliness
- Innate package materials (inherent)
- Processing and manufacturing variables
  - Ex: Gamma irradiation

How can a poor seal affect the product?

Potential product failure modes include:

- Loss of product
- Loss of sterility
- Loss of potency
- Increase in concentration (solvent loss)
- Lyo cake deterioration
- Lyo cake moisture absorption
- Oxidation of API from O_2 ingress
- pH shift of solution from CO_2 ingress
- Loss of partial vacuum
  - Leads to overpressure
- And likely more

How do issues arise?

Component Level

- Defective components
- Poorly designed components
- Components with poor dimensional specifications
- Poor quality control

System Level

- Poor equipment quality or operation
- Lack of process validation
  - Capping variables, etc
- Component incompatibility

Deficiency in package or process development.

Test Approach Limitations

Dye ingress and the “twist test” are not suitable to determine seal integrity.

They lack sensitivity to evaluate the impact of subtle differences such as dimensional tolerance

They lack sensitivity to reach critical leak detection.

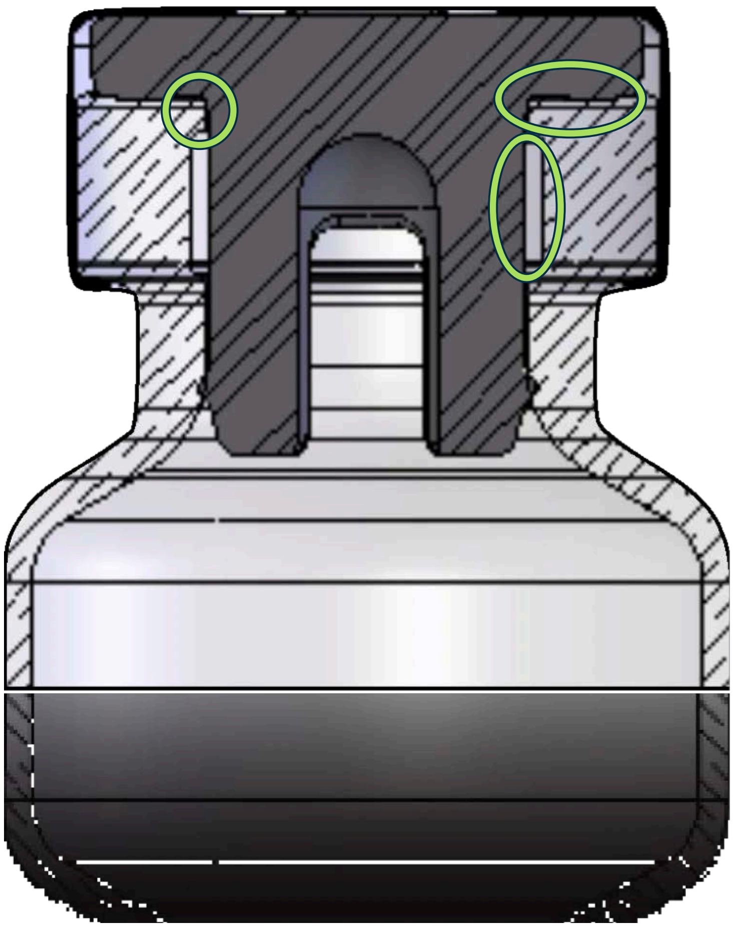
Elements of a Well-Characterized Seal

1. Considerations for dimensional tolerances and fit for sealing components.
2. Evaluation of stopper compression.
3. Evaluation of residual seal force.
4. Evaluation of leakage by a sensitive method (helium / headspace analysis)

Planning

If you've waited until production batches, it is too late

Considering Vial Seal Points



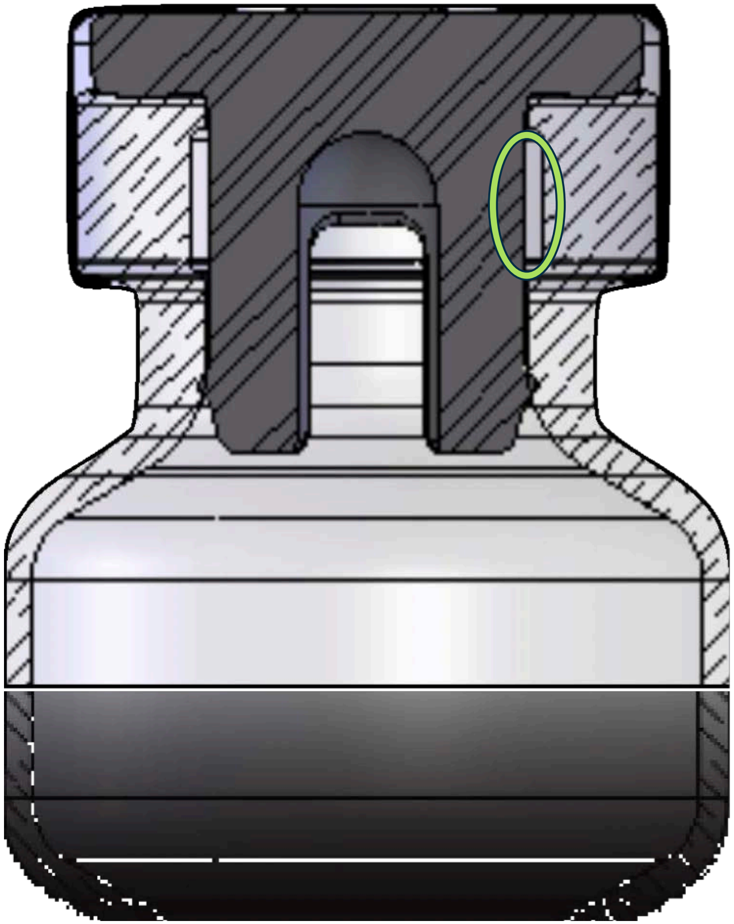
Components

1. Vial
2. Stopper
3. Crimp

Seals

1. Valve
2. Transition
3. Land

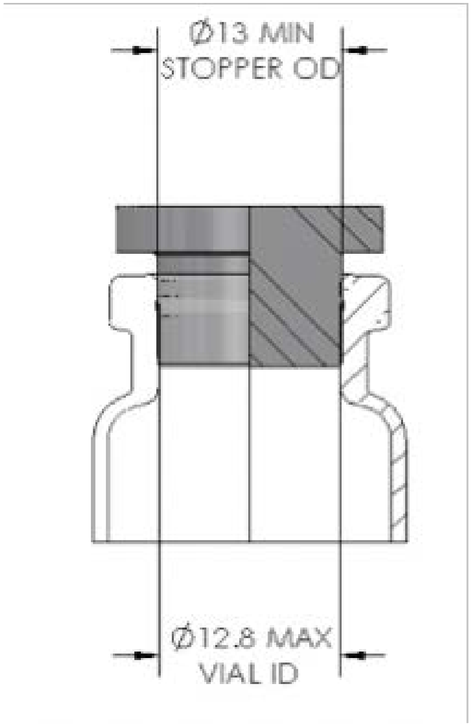
Valve / Plug Seals



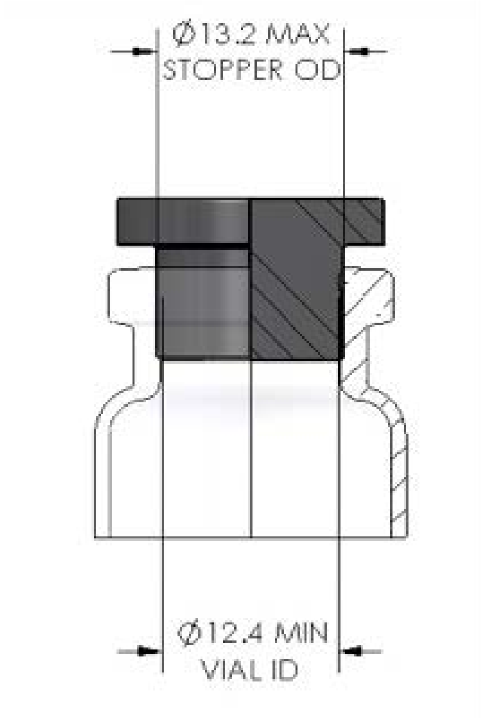
- Key Functions
  - Position closure into container
  - Provide integrity prior to crimp application
    - Especially relevant for lyo
- Key Considerations
  - Require tight tolerances
  - Typically not robust

Valve Seal Critical Dimensions – Interference Fit

Will this min overlap create a seal?



Minimum 0.2 mm

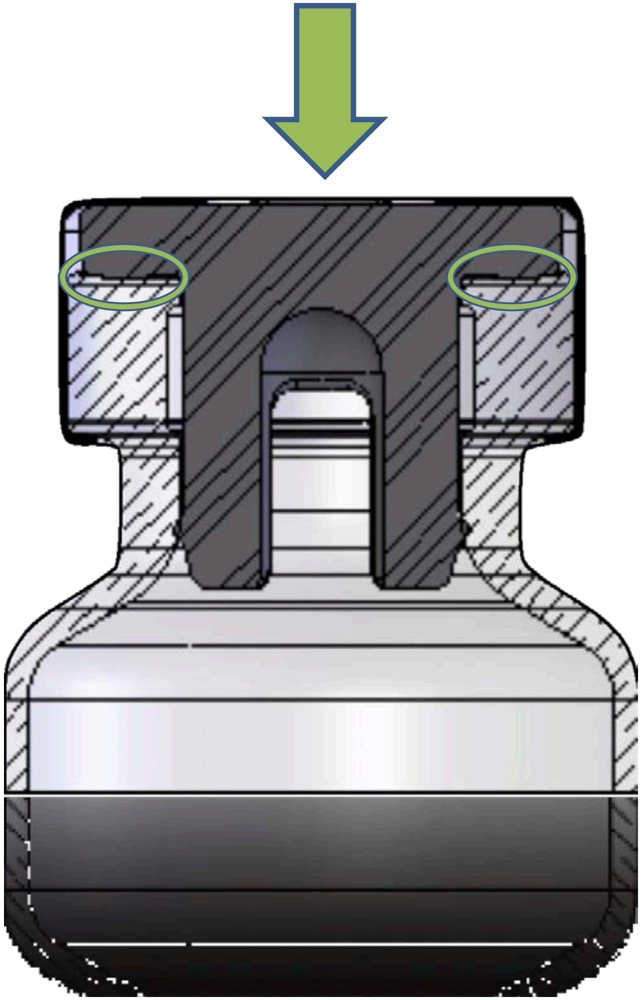


Maximum 0.8 mm

Will this max overlap cause pop up?

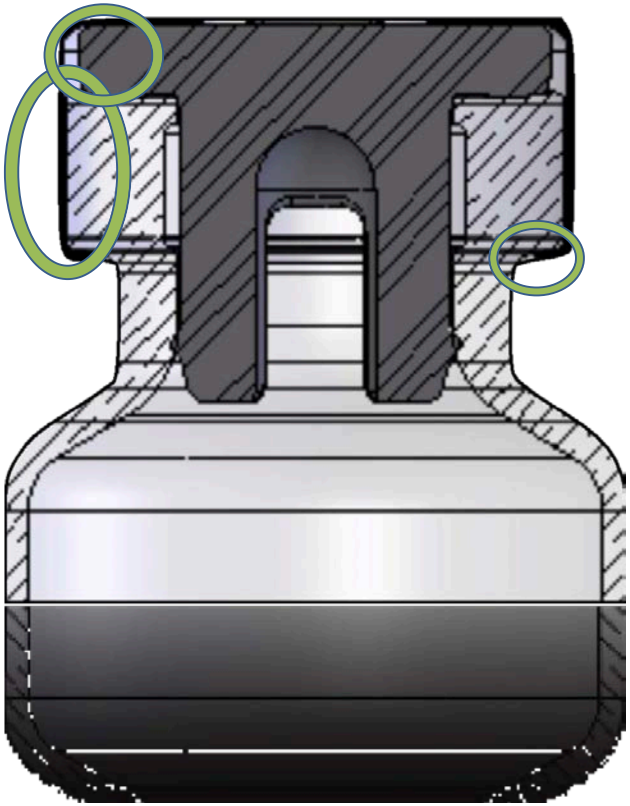
Source:
Asselta, R. "Parenteral Vial Sealing and Integrity"; (2017)

Land Seals



- Key Functions
  - Achieves primary seal
  - Primarily responsible for maintenance of CCI
- Key Considerations
  - Result of applying a crimp seal (vertical compression)
  - Results from a process
    - Controllable
    - Measurable
    - Predictable

Land Seal Critical Dimensions – Stack-up



- Dimensions will impact compression and therefore sealing
- Stopper
  - Flange thickness
- Vial
  - Flange thickness
  - Neck diameter
- Aluminum Crimp Seal
  - Skirt length (pre-crimp)

Land Seal Critical Dimensions – Stack-up

Source:
Asselta, R. "Parenteral Vial Sealing and Integrity";
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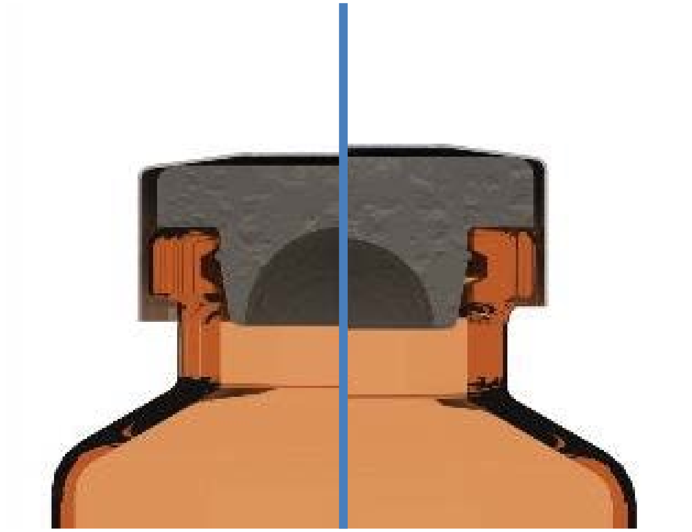


Min	Stopper Flange Thickness	Max
Min	Vial Flange Thickness	Max
Max	Vial Neck Diameter	Min
Max	Seal Skirt Length	Min

- There exists combinations that are NOT compatible
  - Issues can occur at the extremes
- Minimum Stack-up
  - Compression too low - leakage
  - Skirt may hit vial neck
- Maximum Stack-up
  - Compression too high – cracks, deformation
  - Skirt may be too short to "grab" vial

Understanding Dimensional Impacts

Lack of consideration for dimensional extremes can lead to CCI issues

These issues can exist even if a validated, deterministic is used for routine testing of final production samples

Dimensions should be built into capping optimization and validation

Elements of a Well-Characterized Seal

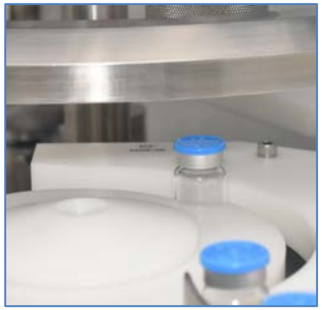
1. Considerations for dimensional tolerances and fit for sealing components.
2. Evaluation of stopper compression.
3. Evaluation of residual seal force.
4. Evaluation of leakage by a sensitive method (helium / headspace analysis)

Capping Study Samples

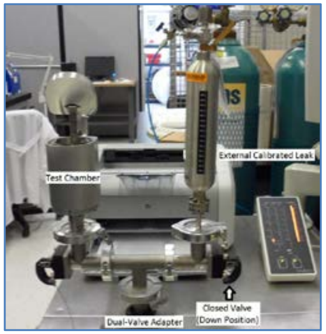
Group #	Vial – Stopper – Seal Combo	
	Sample IDs	**Capping Force**
1	A1 - A30	Very Low
2	A31 - A60	Low
3	A61 - A90	Nominal
4	A91 - A120	High
5	A121 - A150	Very High

Elements of a Capping Study

- Capping Study Incorporating
  - Dimensional Variation
  - Capping Settings
  - Percent Compression
  - Residual Seal Force (RSF)
  - Leak Detection (HeLD / Headspace)
- Yields
  - Quantitative Data
  - Correlations between capping settings, % C, RSF, and leakage
  - Provides feedback or confirmation of the assembly process wrt CCI

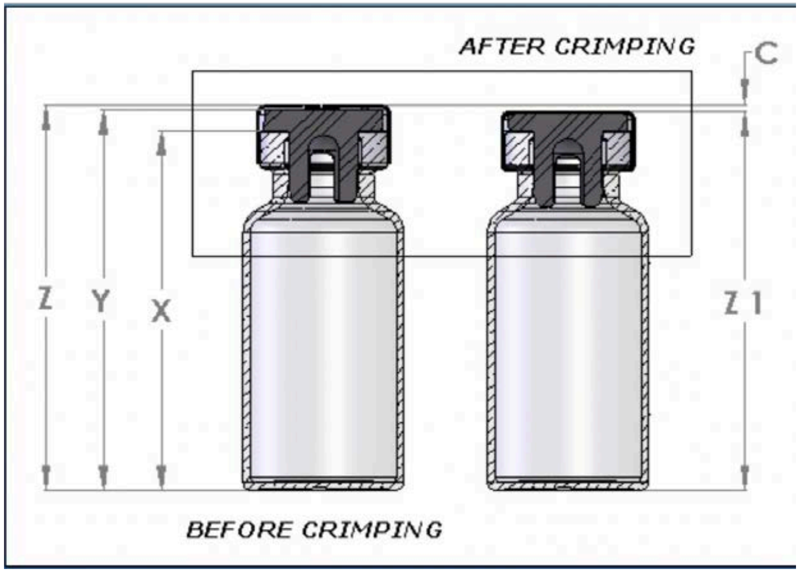

Vial Capping


RSF



HeLD

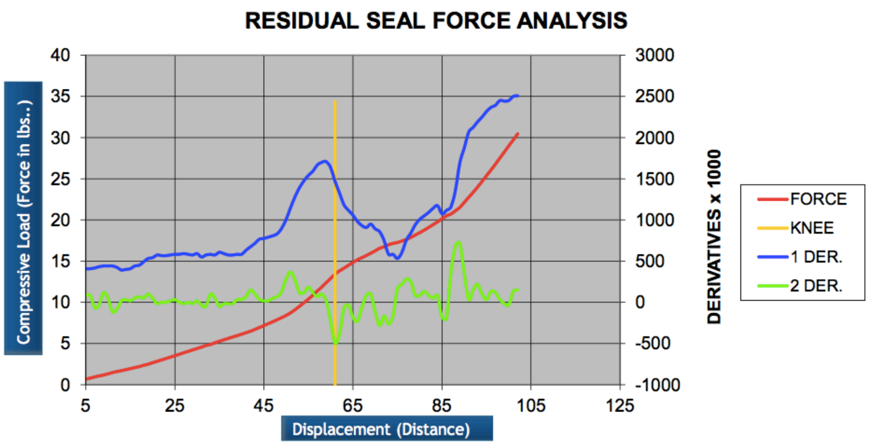
Stopper Compression



$$Z - Z_1 / Y - X$$

Photo credit: Roger Asselta, Genesis Packaging Technologies

Residual Seal Force Testing



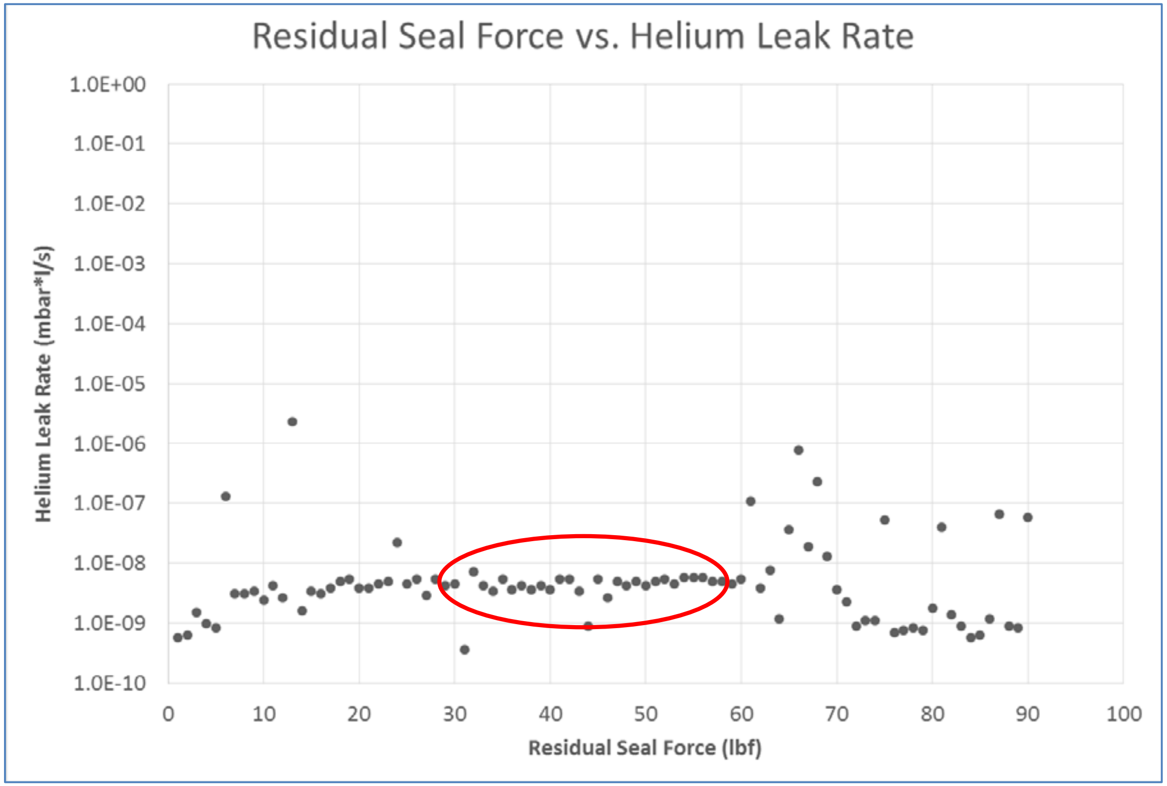
The compression curve (red) is a combination of the viscous and elastic responses to the stress from tester load. "The knee"(yellow) is where additional deformation occurs. An algorithm is applied, using the 1st (blue) and 2nd (green) derivatives to accurately identify that knee.

Ludwig J, Nolan P, Davis C, Automated method for determining Instron residual seal force of glass vial/rubber stopper closure systems, *PDA J Pharm Sci & Technol* 47, (1993) 211 – 218

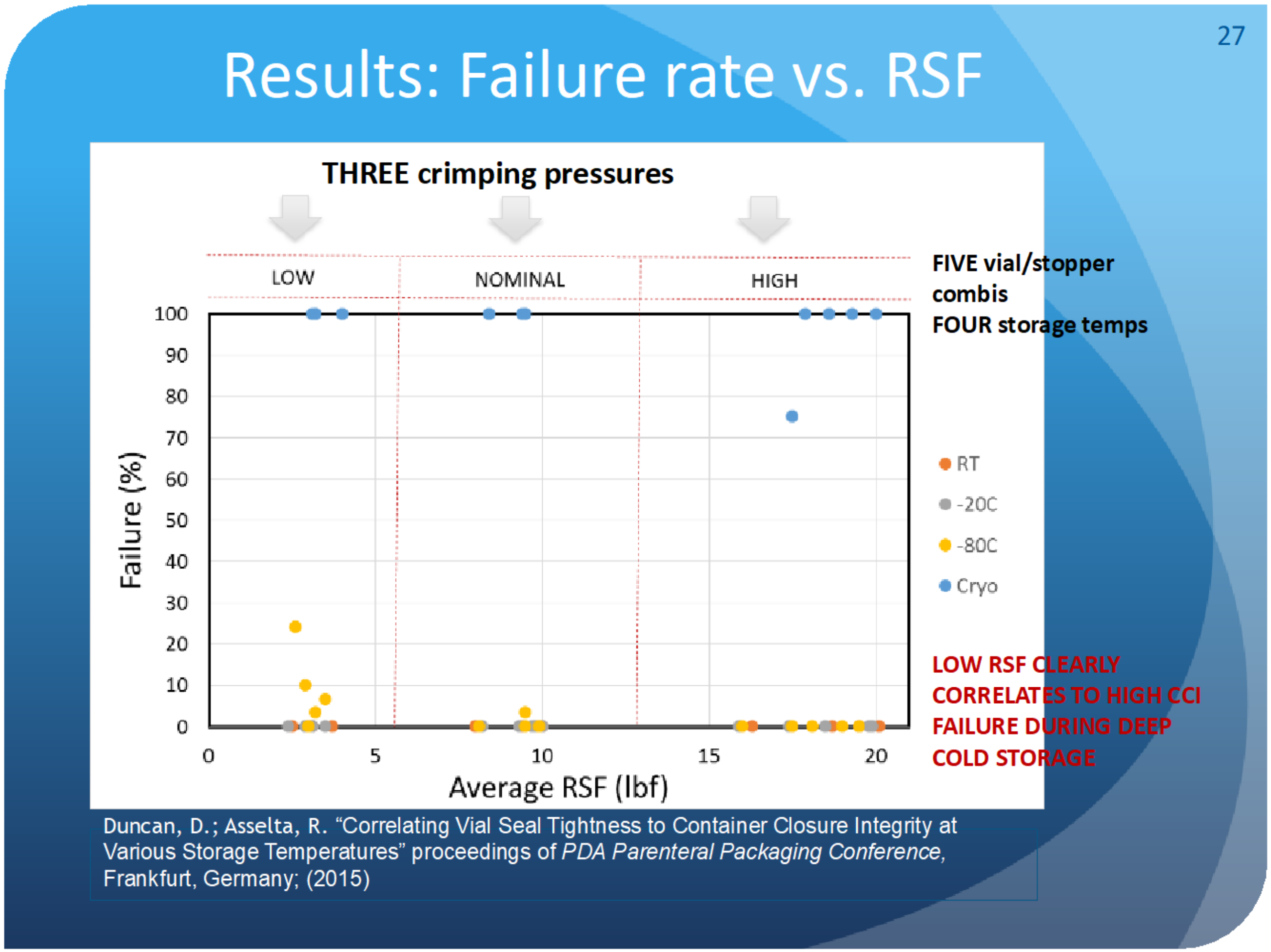
Photo Credit: Roger Asselta, Genesis Packaging Technologies

- Can be thought of as an indirect measure of stopper force on a vial
- Influenced by stopper compression
- Is an offline test, can be performed "anywhere"
- Can be correlated to leakage, enabling
  - In process capping check
  - Capping setting check for additional or changed sealing lines
  - Enables basis of comparison for a given package system

RSF to Leakage Correlation



RSF can now be checked during manufacturing



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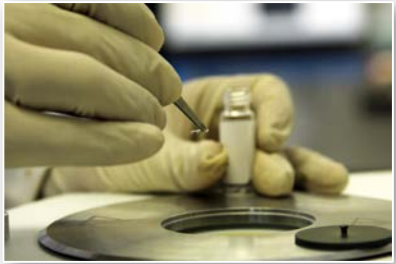
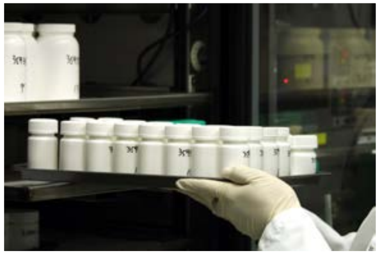
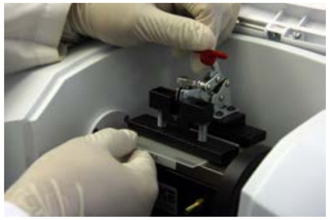
Concluding Statements



- Preventative studies like these reduce risk of CCI failures downstream
- Adjustments to components or processes can be made based on learnings
- Package development studies incorporating extremely sensitive leak tests establish inherent integrity
  - Sensitivity almost certain to detect critical leaks





Thank you!