Parenteral Vial Sealing and Integrity

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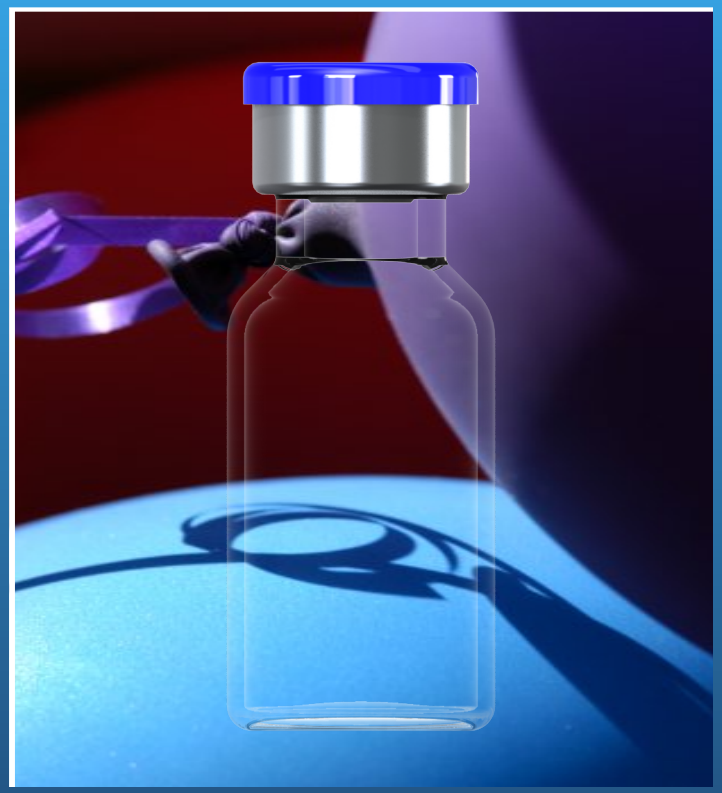
Genesis Packaging Technologies
a division of R-V Industries, Inc.

Everything Leaks

"Leakage is a Rate and Therefore a Continuum"



SENSITIVITY	Rate (Pa m^3/S)
Audible	10^{1}
Visible	10^{0}
Ultrasonic	10^{-3}
Liquid, Microbes	10^{-6}
Gases	10^{-9}
Helium	10^{-12}

Morton, Dana "Package Integrity Testing", Chapter 4, *Parenteral Quality Control*. 3rd ed., Marcel Dekker, NYC (2003)

Definitions

- **Leak:** a hole, crack or porosity through a component of the CCS, or a gap at an interface of the components capable of allowing a gas or liquid ingress or egress the CCS
- **Leakage:** the movement of the liquid or gas through the leak
- **Leak Rate Cut-Off:** point where the measurable leakage is below the test method detection limit, becomes lower as the leak size decreases
- **Maximum Allowable Leakage Limit (MALL):** the smallest gap (leak) or leak rate that puts product quality at risk (sometimes called the 'critical leak')
- **Inherent Package Integrity**: The leakage rate of ***a well-assembled (sealed)*** container/closure system using ***defect-free**** components

*Conform to specifications

Selection and Utilization of Parenteral Container Closure Systems

- Container Closure Systems for Packaging Human Drugs and Biologics (USFDA Guidance 1999)
  - Suitability for the Intended Use
    - Protection (Sterility, Stability)
    - Compatibility (Non reactive, E&L)
    - Safety
    - Performance

Inherent Package Integrity

- The leakage rate of *a **well-assembled (sealed)*** container/closure system using ***defect-free*** components
- Deviations from inherent package integrity
  - Aberrant components- out-of-specification, defective
  - Poorly assembled, inadequately sealed packages
  - Damage to assembled packages
  - Exposure to harm conditions post assembly that affect the seal, component materials (including there properties) and/or component fit

Life Cycle Approach to CCI

- Package Development
  - Component Design and Selection
  - Matching of Components
- Component Assembly
  - Attributes of a “well-sealed” vial
  - Identification of potential defects
- Manufacturing Process Development
  - Equipment Selection
  - Sealing Optimization
    - Identify Critical Process Parameters
  - Validation
- Manufacturing
  - Defects
  - Deviations
- Shelf-Life Assessments
  - Time to expiry
  - Storage Conditions
  - Transportation Challenges

- Specification Reviews (Dimensions and Tolerances)
- Tolerance Stack-up Analysis
- Interference Fit
- Visualization Techniques
- FEA
- Trial Assemblies by Hand

- Compression Analysis
- RSF
- X-ray Tomography
- Helium Leak Correlation
- Experimental Design (understand variation)

- RSF
- Headspace Analysis (HSA)
- 100% Inspection Techniques
  - HVLD
  - Vacuum/Pressure Decay
  - HSA

A Parenteral Package must be Suitable for its Intended Use

- USP <1207> states:
  - "…the maximum allowable leakage into and out of intact packages should be so minimal that there is no impact on product safety, and no consequential impact on the product's physicochemical stability."
  - CCI or package integrity is defined as "the absence of package leakage greater than the product package **maximum allowable leakage limit (MALL)**."
  - An "Integral Package" must:
    - Prevent microbial ingress (ensure sterility)
    - Maintain drug quality
      - Limit loss of product contents
      - Prevent entry of debris or detrimental gasses

Became official August 2016

CCI is proven when…

The ***Inherent Package Integrity package*** is demonstrated to be greater than the

Maximum Allowable Leakage Limit that is necessary to ensure product critical quality attributes of sterility and physicochemical stability through expiry (manufacturing, storage transportation, use).

Those package requirements include:

Sterility preservation

Formulation loss prevention

Critical gas headspace preservation

Vacuum, Low O_2, Low H_2O vapor

Aspects of Container Closure Integrity

- Permeation
  - Migration
- Leakage
  - Through Defect
    - Crack, Hole, Split, Tear, Incomplete Component
  - Through Seal *(Seal Integrity)*
    - Insufficient Compression
    - Failure to Maintain Compression

Pharmaceutical Quality by Design (QbD)

- Recently, the USFDA has implemented the concepts of QbD into its pre-market assessments. “The focus of this concept is that quality should be built into a product with an understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks.”
- The USFDA’s QbD initiative attempts to provide guidance on pharmaceutical development to facilitate design of products and processes that maximizes the product's efficacy and safety profile while enhancing product manufacturability.

Pharmaceutical Quality for the 21st Century: A Risk-Based Approach
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm128080.htm

Parenteral Drug Stability Failures Due to CCI Issues

- Loss of Potency
- Potency Rise, Increase in Concentration
- Increase in Moisture Content of Lyo Cake
- Deterioration of Cake Quality
- Oxidation of API due to Changes in Headspace
- pH Shift due to CO_2 Ingress
- Gravimetric Change
- Vacuum Loss
- Sterility Failure
- CCI Testing Failure

Root Causes of CCI Failures

- Component Quality
  - Poorly Designed, Specified, Controlled
  - CCS Components Improperly Matched
  - Defective
- Seal Quality
  - Lack of *Sufficient* Process Validation (Understanding of Variation)
  - Suboptimal equipment or operation
  - Improper Equipment Set-Up, Variation in Set-up
  - Lack of Process Monitoring and Control
- CCS Not Sufficiently Robust

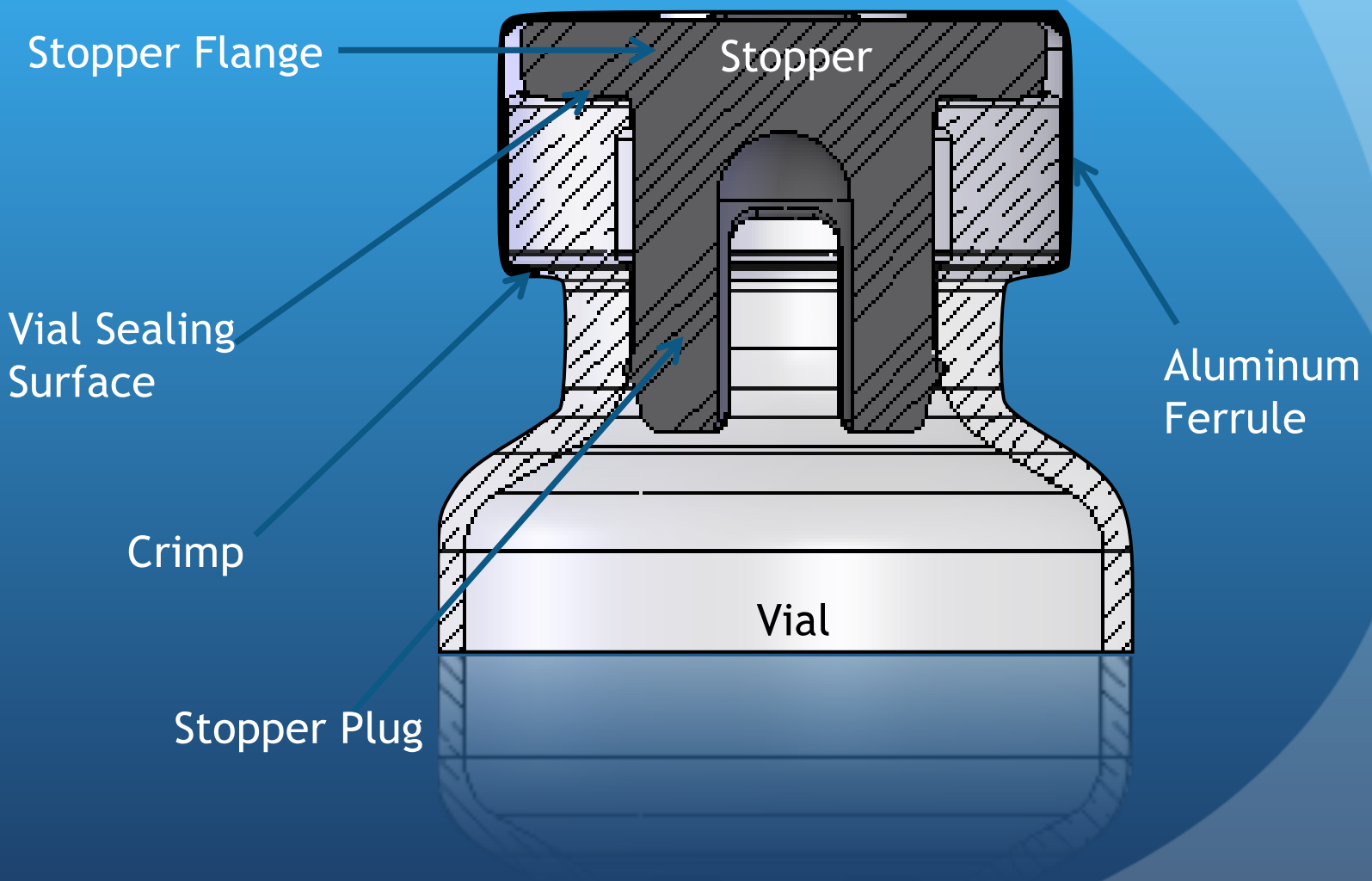
Validation

- A successful validation program depends upon information and knowledge from product (CSS components) and (assembly and sealing) process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes.
- Understand the sources of variation (components and process)
- Detect the presence and degree of variation (within lots, lot-to-lot, overtime)
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

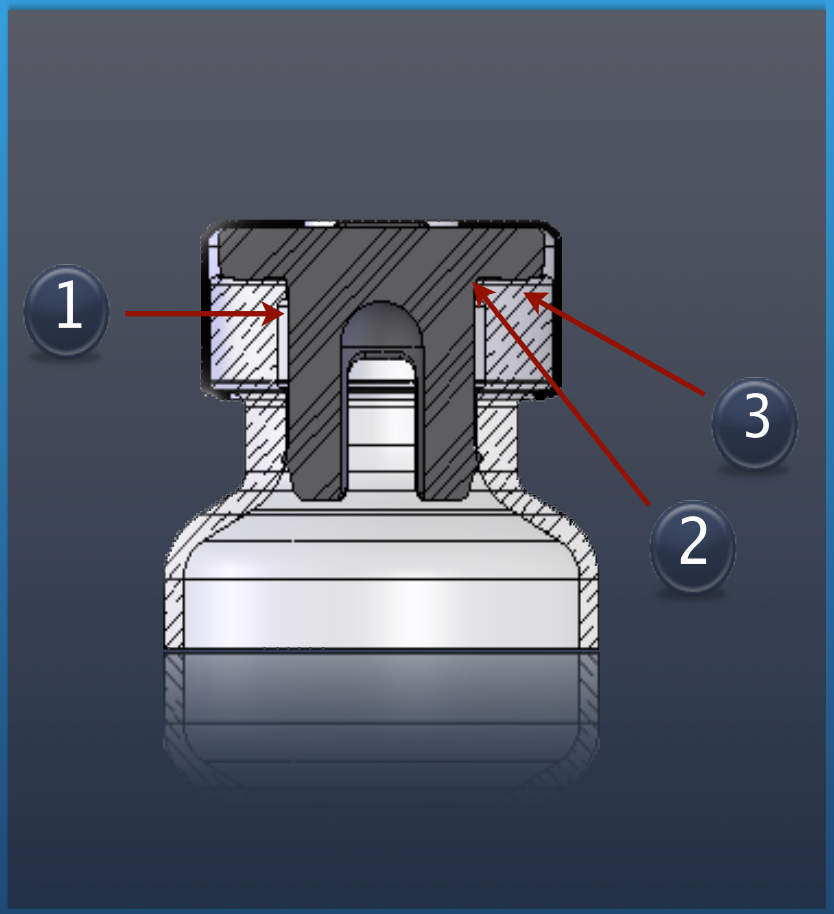
Guidance for Industry Process Validation: General Principles and Practices, USFDA 2011

Evaluation of Container Closure System *Components*

Components of a Vial Seal



Parenteral Vial Seals



- 1 Valve (Plug) Seal
- 2 Transition (Ring) Seal
- 3 Land Seal

Valve Plug Seal

- Closure Plug
  - Positions Closure into Vial Neck
  - Requires Tight Tolerances
    - Little Out-of-Round
  - Not Robust
  - Important to Maintain Integrity Prior to Crimping
  - Is the Primary Seal a Plunger in PF Syringes

Land Compression Seal

- Is the Primary Seal
- Achieved by Vertical Deformation (Applied Force)
- It is:
  - Reliable
  - Controllable
  - Measurable

EMEA Annex 1: *Manufacture of Sterile Medicinal Products*
118: The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be preformed as soon as possible after stopper insertion.

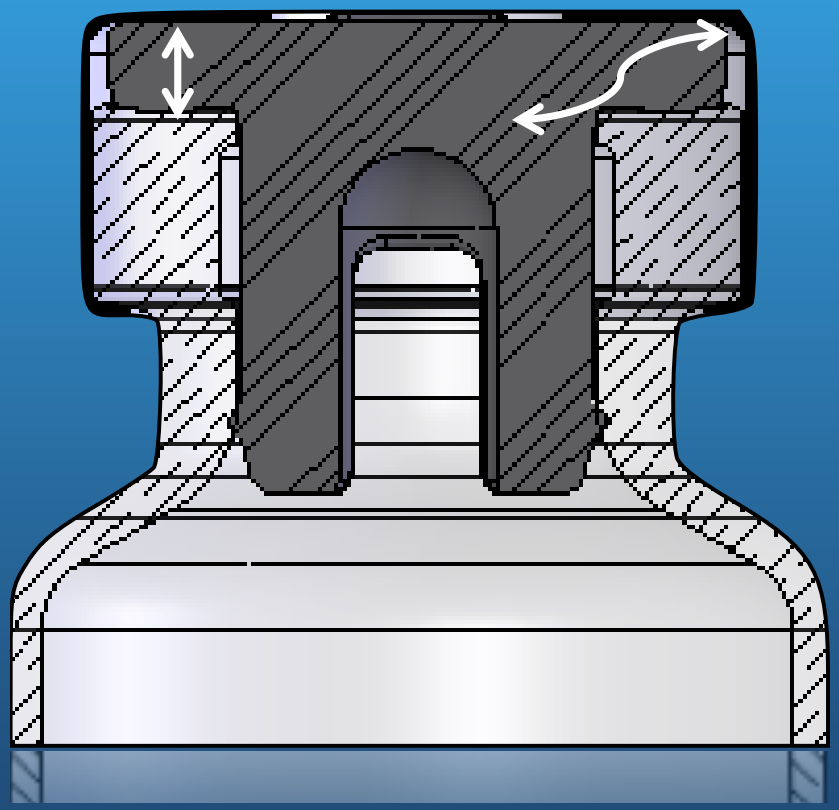
Elastomeric Closure

- Elastomer Interchangeable with the Term Rubber
  - Rubber more properly used for vulcanized (cross-linked) elastomers
- Elastomers are amorphous polymers that exist above their Glass Transition Temperature (Tg) and exhibit viscoelastic behavior. Rubber Formulations for closures to seal pharmaceutical containers have Tg s that are usually below -50° C.
- Viscoelastic Properties in response to an applied energy (force)
  - Elastic in that it can store energy.
  - Viscous in that it dissipates energy

Elastomeric Closure (continued)

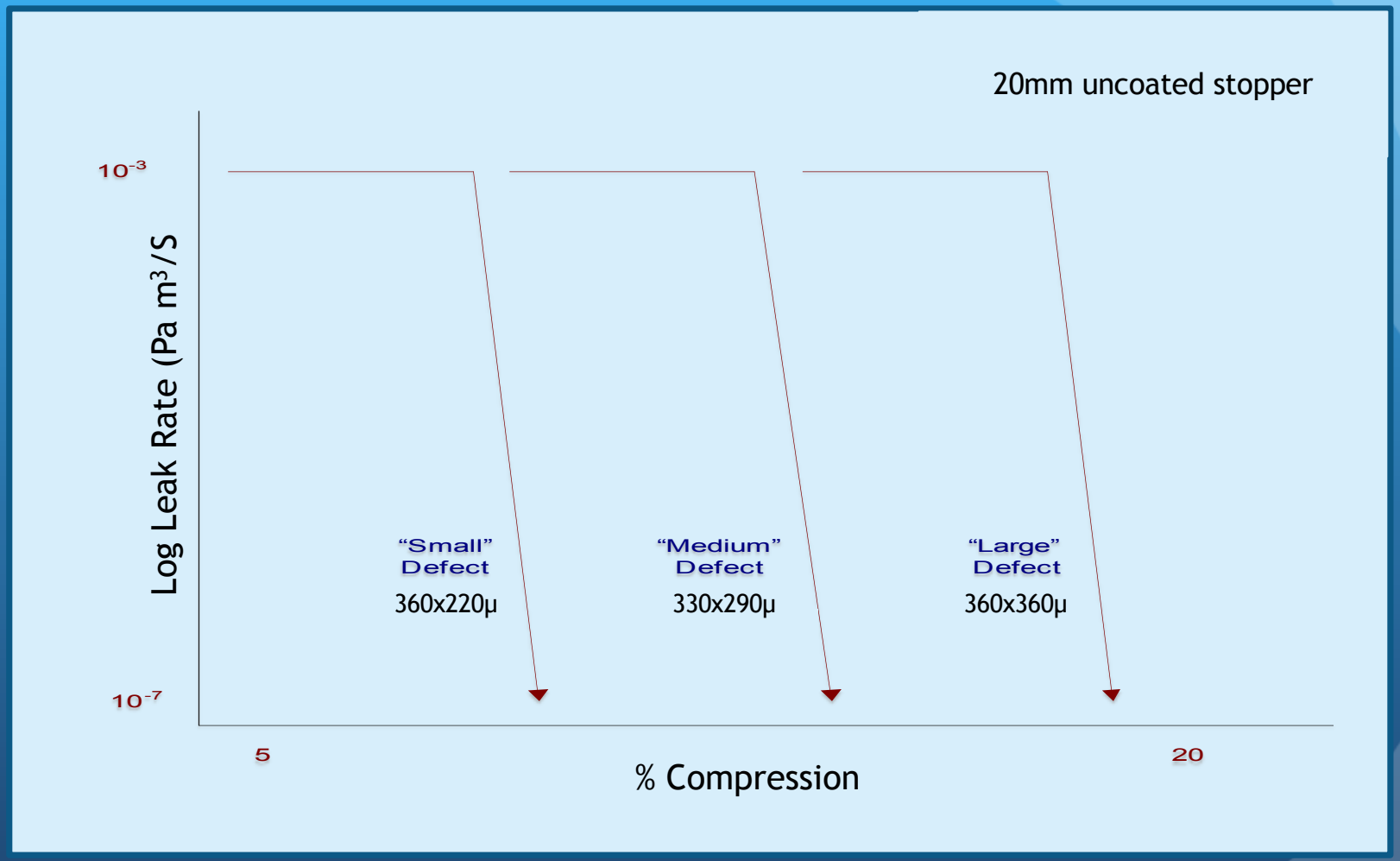
- In sealing rubber components, the elastic property is the more important. An applied stress (sealing force) induces a corresponding strain which creates a contact stress. This stored internal energy is the Residual Seal Force (RSF).
  - As the polymer chains rearrange to reduce this internal energy, stress relaxation occurs with a reduction in RSF.
- The viscous property of rubber, too, is important. It allows considerable segmental motion or flow. This movement can fill gaps and voids in the sealing surface.

Viscoelastic Deformation (Compression) Seal



- **Closure Compression:** the extent to which the elastomeric stopper flange is vertically deformed (visco-elastic deformation) against the vial sealing (land) surface by the applied aluminum seal
- **Elasticity** Provides Continuous Pressure Between the Finish Surface and the Ferrule
- **Viscosity** allows for Flow of Rubber into Gaps and Voids

Compression & Leak Rate Cut Off



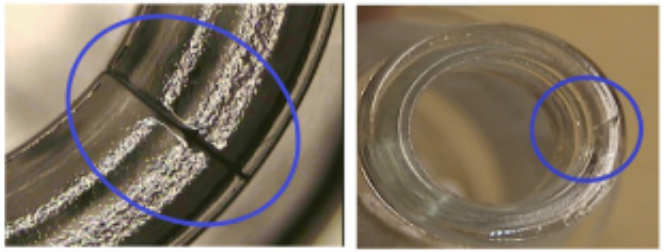
Morton, Dana K. "Container/Closure Integrity of Parenteral Vials." *PDA Journal of Parenteral Science and Technology* 43 (1989)

Examples of Sealing Surface Defects (PDA TR43)

Line Over Finish

Location: Seal Surface

Class: Critical if seal integrity compromised; Major A if line over is >50% of seal surface.



A channel that can extend partially or completely across the sealing surface of the finish.

Rough Finish

Location: Finish

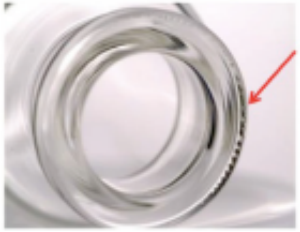
Class: Critical if seal integrity is compromised; Minor if seal integrity is intact (Limit Sample*)

A finish that has minute imperfections causing a rough surface.

Crizzle

Location: Finish/Neck

Class: Critical if it affects seal or container integrity; Minor (Limit Sample*) or N/A

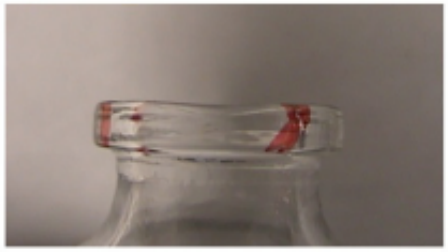


A finish or neck that has a multitude of fine surface marks.

Unfilled-Malformed

Location: Finish

Class: Critical if Seal integrity is compromised; Major B if seal integrity is intact (Limit Sample*)



Finish profile is incomplete.

Stopper Compression

- Compression of Stopper Flange by an Applied Force
  - The force required to achieve proper seal is the result of three main factors:
    1. The cross section of the component(s)
    2. The durometer (hardness) of the rubber
    3. The per cent of compression required to achieve leak rate cut-off

Dimensional Relationships

- Components are Independently Developed by Suppliers
- Dimensions and Tolerances Developed Long Ago
  - Based on Suppliers' Manufacturing Capability, Not Necessarily Fit and Functionality
- Standards Vague, Allow for Poor Fit
- Differing Dimensional Measurement Techniques
- Formulation Development Does Not Necessarily Focus on Physical Properties, Recent Focus more on E & L

Mismatch of Components

- Machinability Challenges
- Raised Stopper Issues
- Failure to Achieve CCI
- Failure to Maintain CCI (Robustness)
  - Under Ambient Conditions
  - Under Stressed Conditions (e.g. very low storage temperatures)

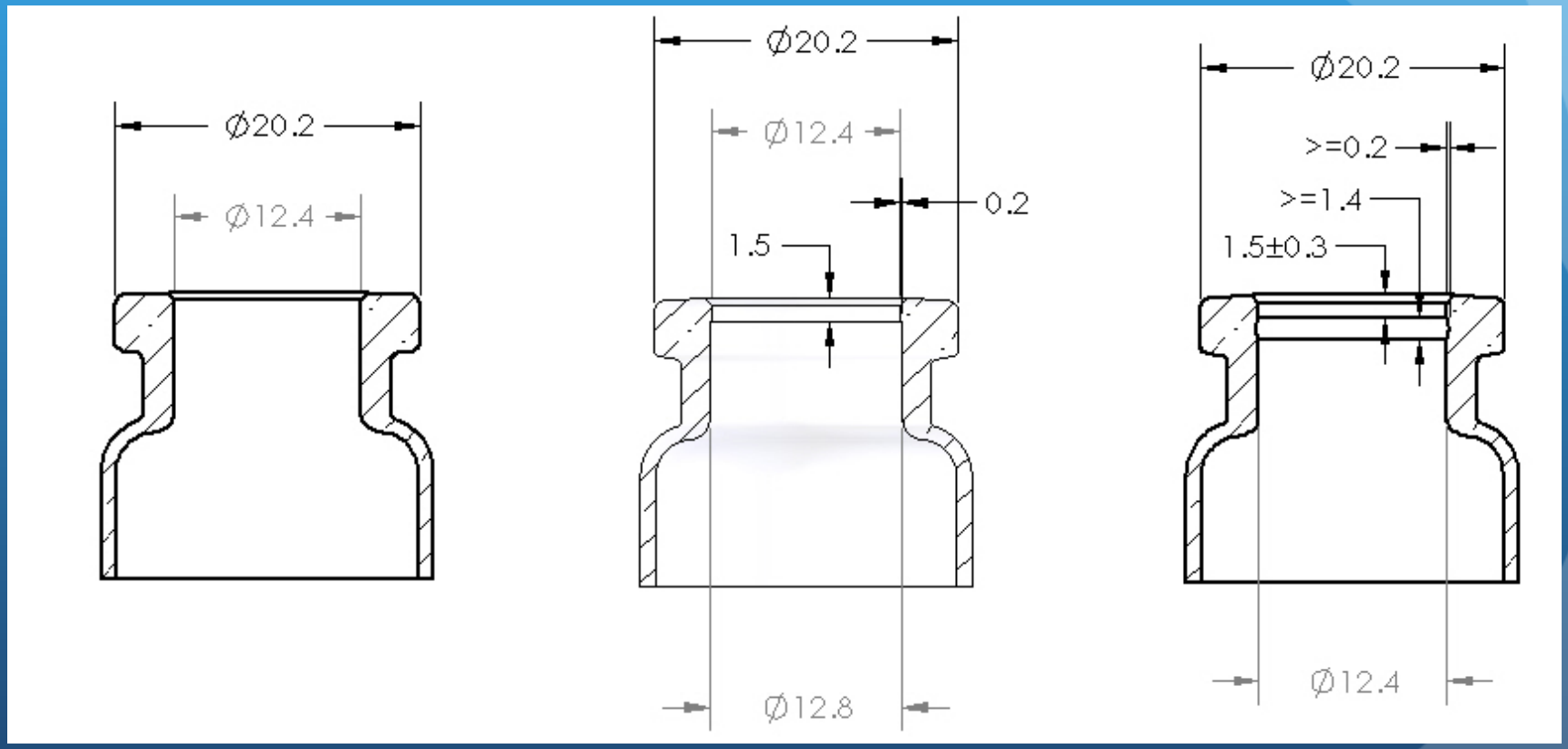
Points to Consider

- "Critical factors for the maintenance of CCI included appropriate design of the vial and stopper plug, relative dimensions … giving a tight fit, as well as an appropriately tight capping and crimping process."
- "Dimensional variation … as well as (manufacturer's) different specifications … motivates a careful selection of packaging components for storage at -80°C".

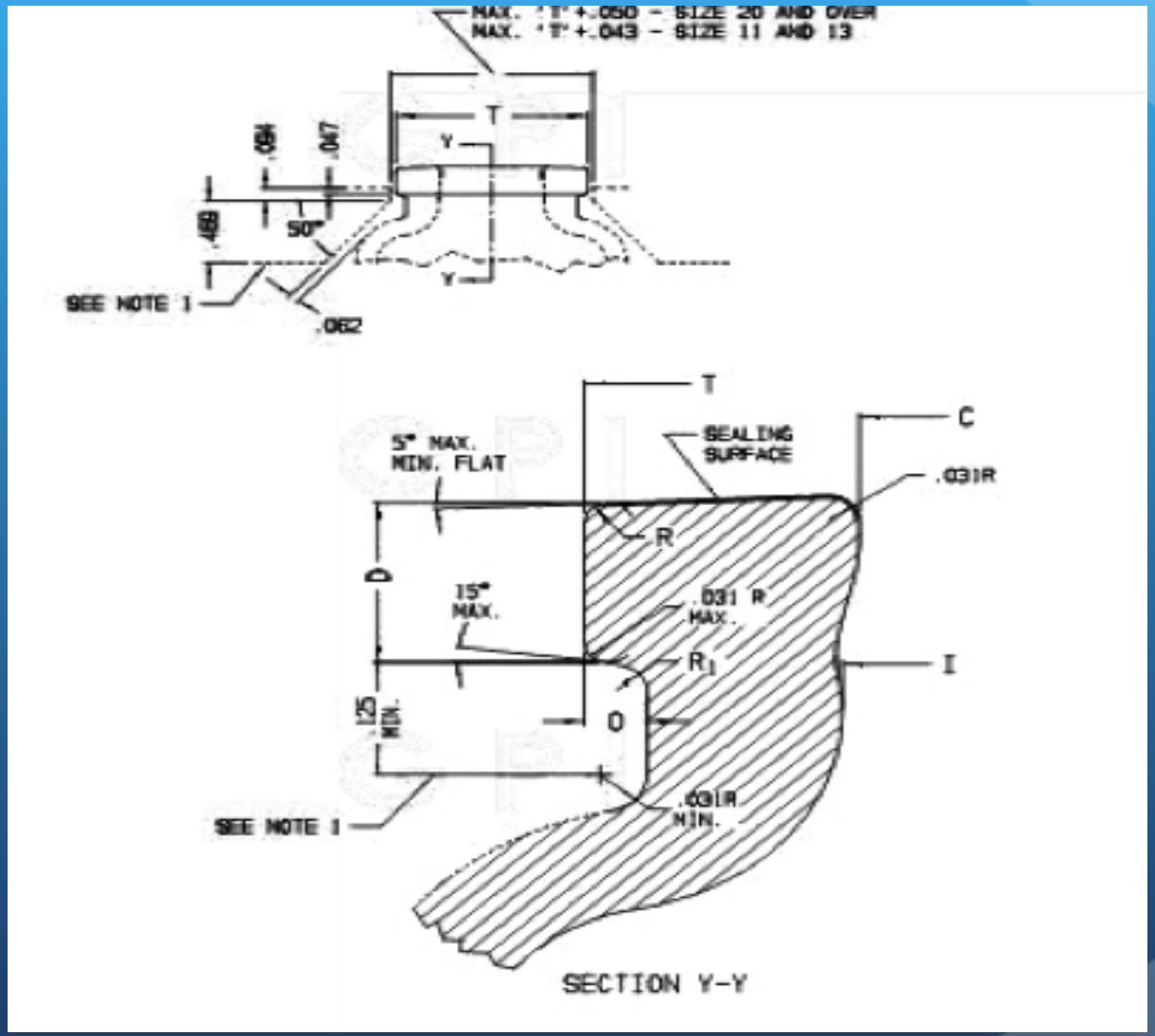
Brigitte Zuleger, et al. "Container/Closure Integrity Testing and the Identification of a Suitable Vial/Stopper Combination for Low-Temperature Storage at -80°C"; *PDA J Pharm Sci and Tech, 2012*

Stopper Varieties

ISO 8362-1 Blowback Variation



GPI 2710


MAX. 'T'+.050 - SIZE 20 AND OVER
MAX. 'T'+.043 - SIZE 11 AND 13
T
Y
.484
.047
.488
50°
SEE NOTE 1
.062
T
C
SEALING SURFACE
5° MAX. MIN. FLAT
.031R
R
D
15° MAX.
.031 R MAX.
R_1
I
.125 MIN.
O
.031R MIN.
SEE NOTE 1
SECTION Y-Y

Visualization Techniques for Assessing Design Factors That Affect the Interaction between Pharmaceutical Vials and Stoppers

Philippe Lam and Al Stern

PDA J Pharm Sci and Tech **2010**, *64* 182-187

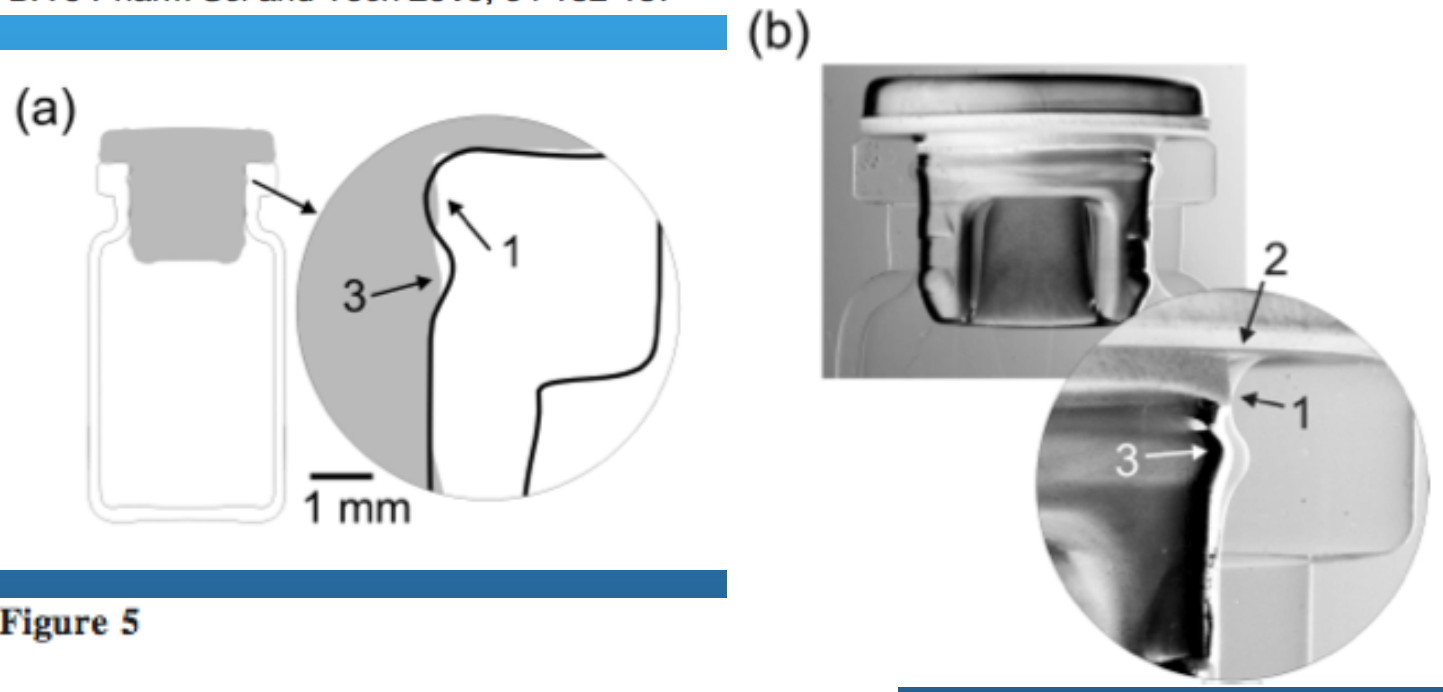
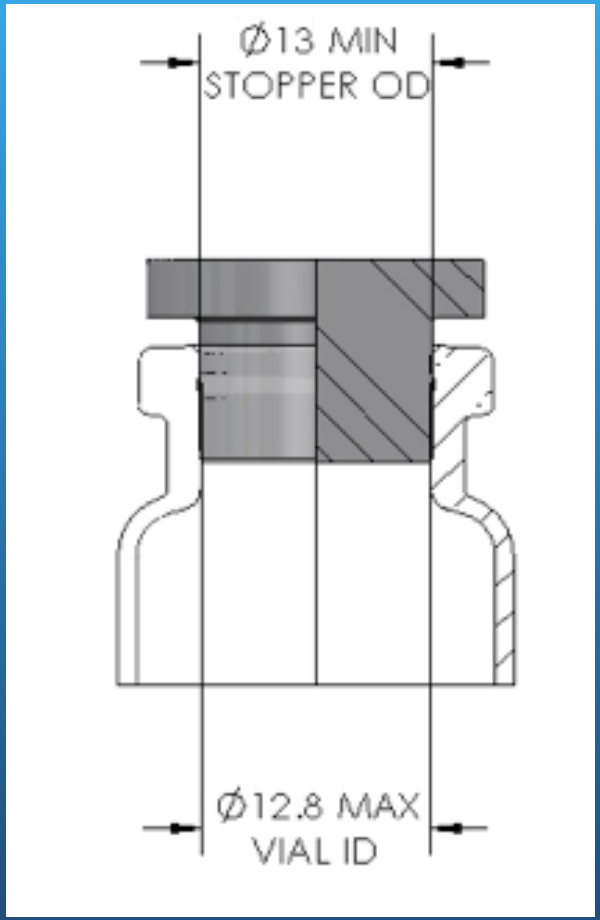


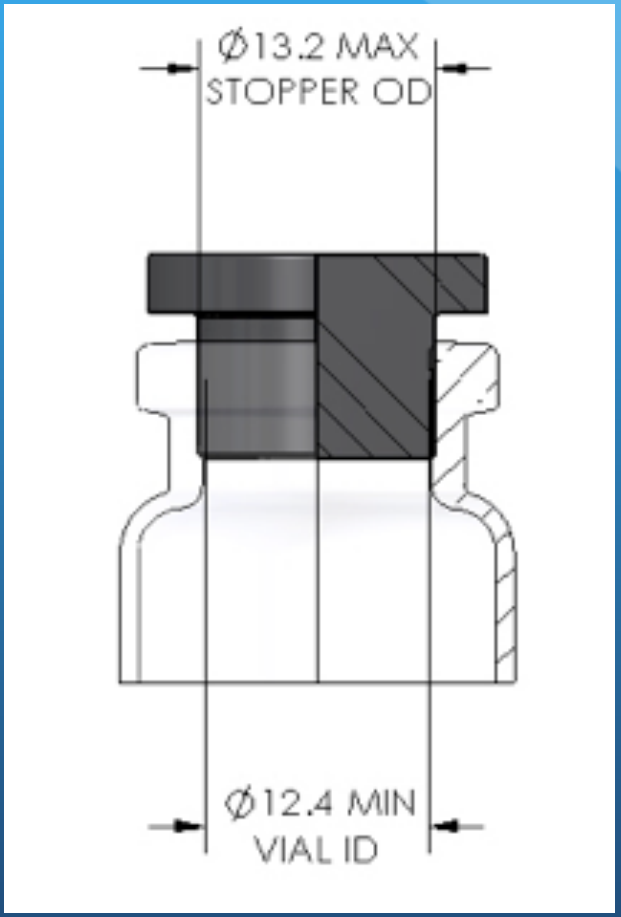
Figure 5

Lyophilization components that frequently loose vacuum. (a) Superimposed profiles of an igloo-style lyophilization stopper and a vial with an American blowback; (b) Photograph of the assembled vial and stopper. 1, interference fit; 2, poor mating region; 3, stopper no-pop feature.

Stopper Plug/Vial Interference Fit

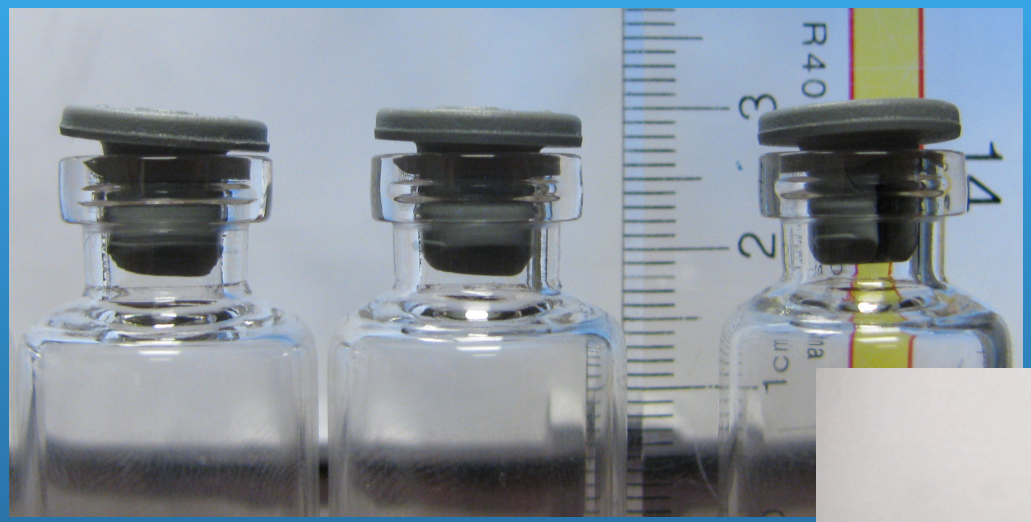


Minimum Interference
0.2mm

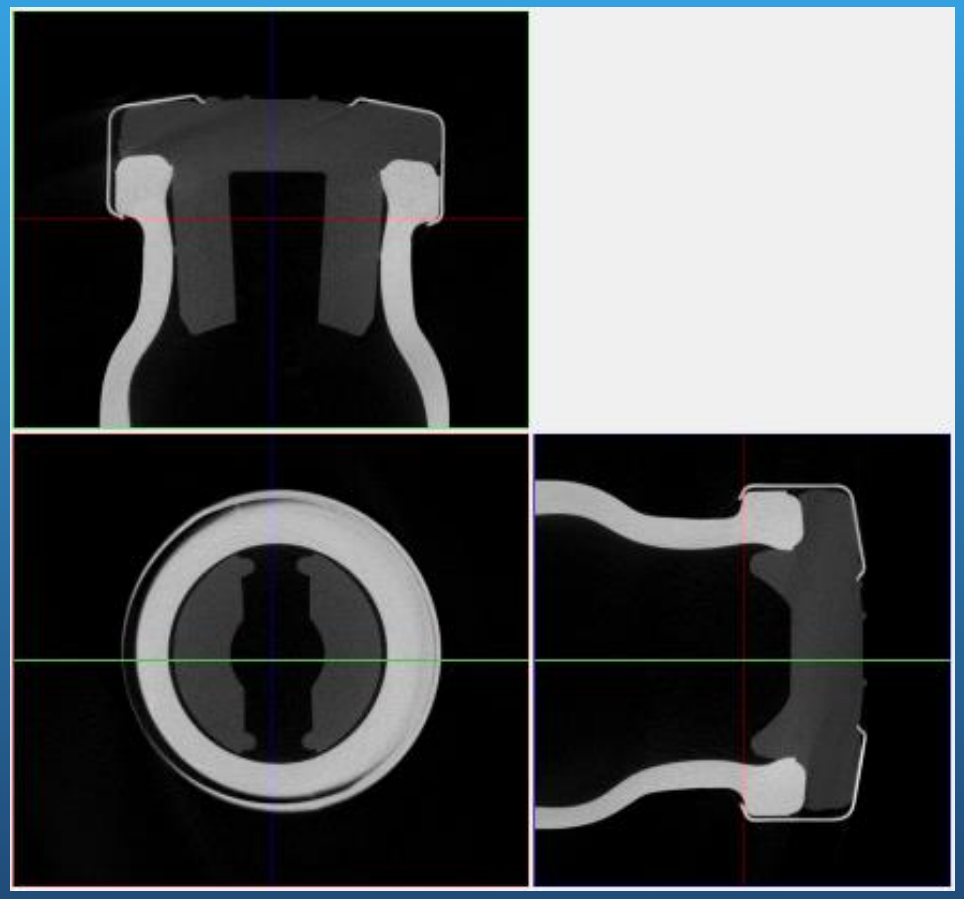


Maximum Interference
0.8mm

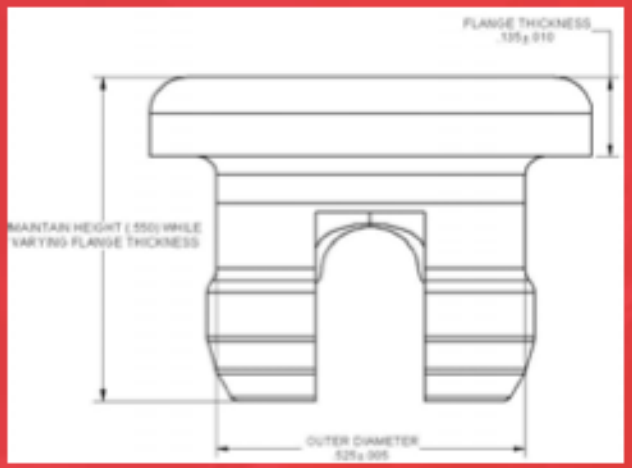
Raised Stoppers



Interference Fit of Lyo Stopper

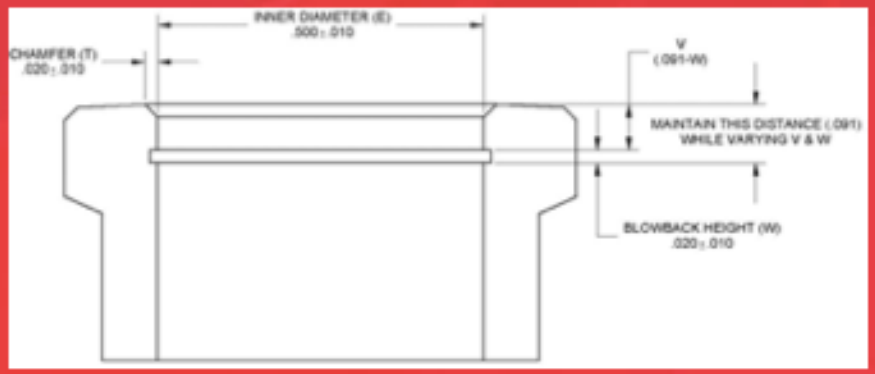


Finite Element Analysis



Parameters Varied:

- Stopper / Vial Interference
- Stopper Flange Height
- Vial Blowback Height
- Vial Crown Chamfer
- Stopper Material Stiffness



Combined FEA and statistical Design of Experiments approaches

Considerations

- "Critical factors for the maintenance of CCI included appropriate design of the vial and stopper plug, relative dimensions … giving a tight fit, as well as an appropriately tight capping and crimping process."
- "Dimensional variation … as well as (manufacturer's) different specifications … motivates a careful selection of packaging components for storage at -80°C".

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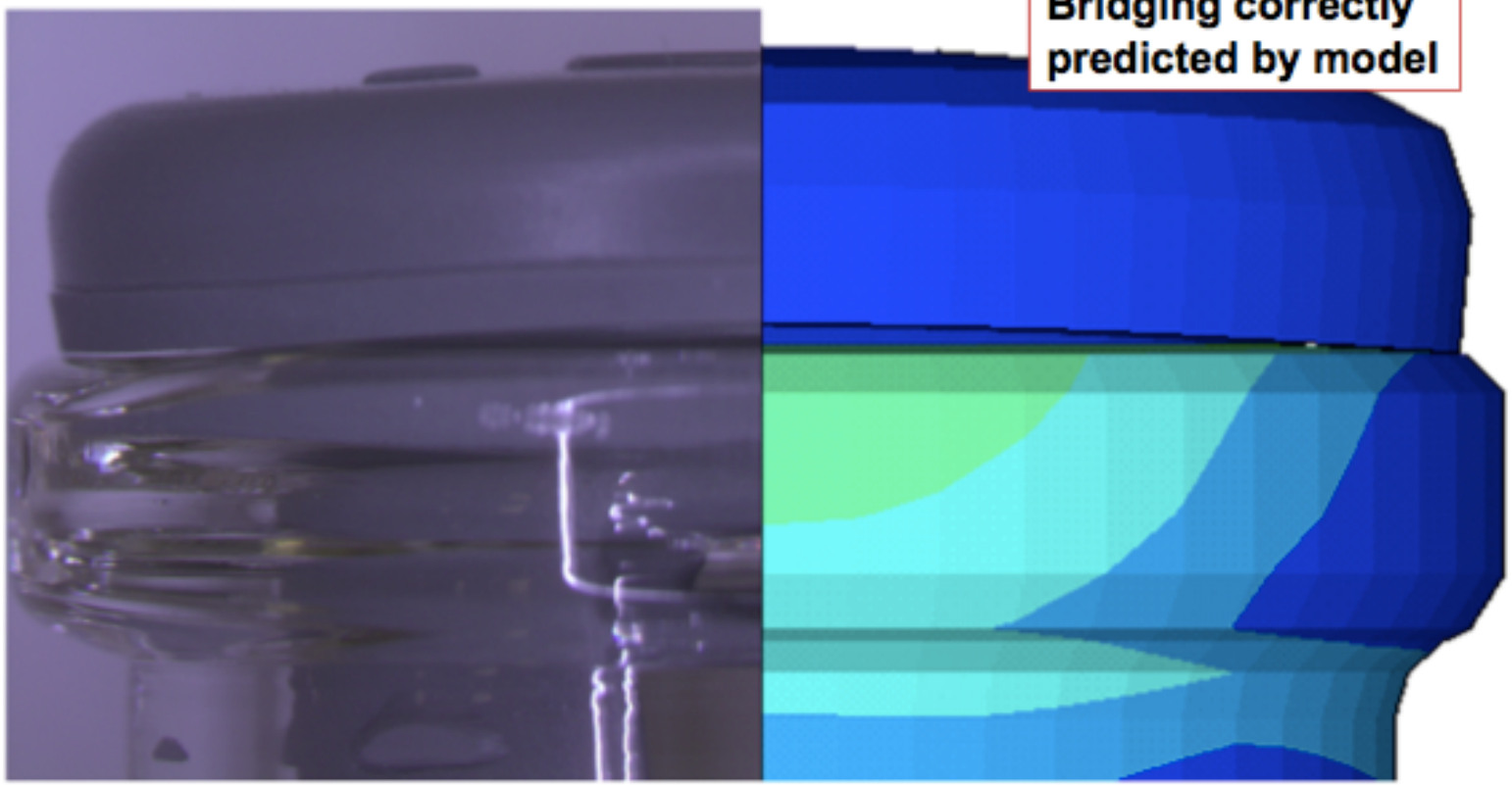
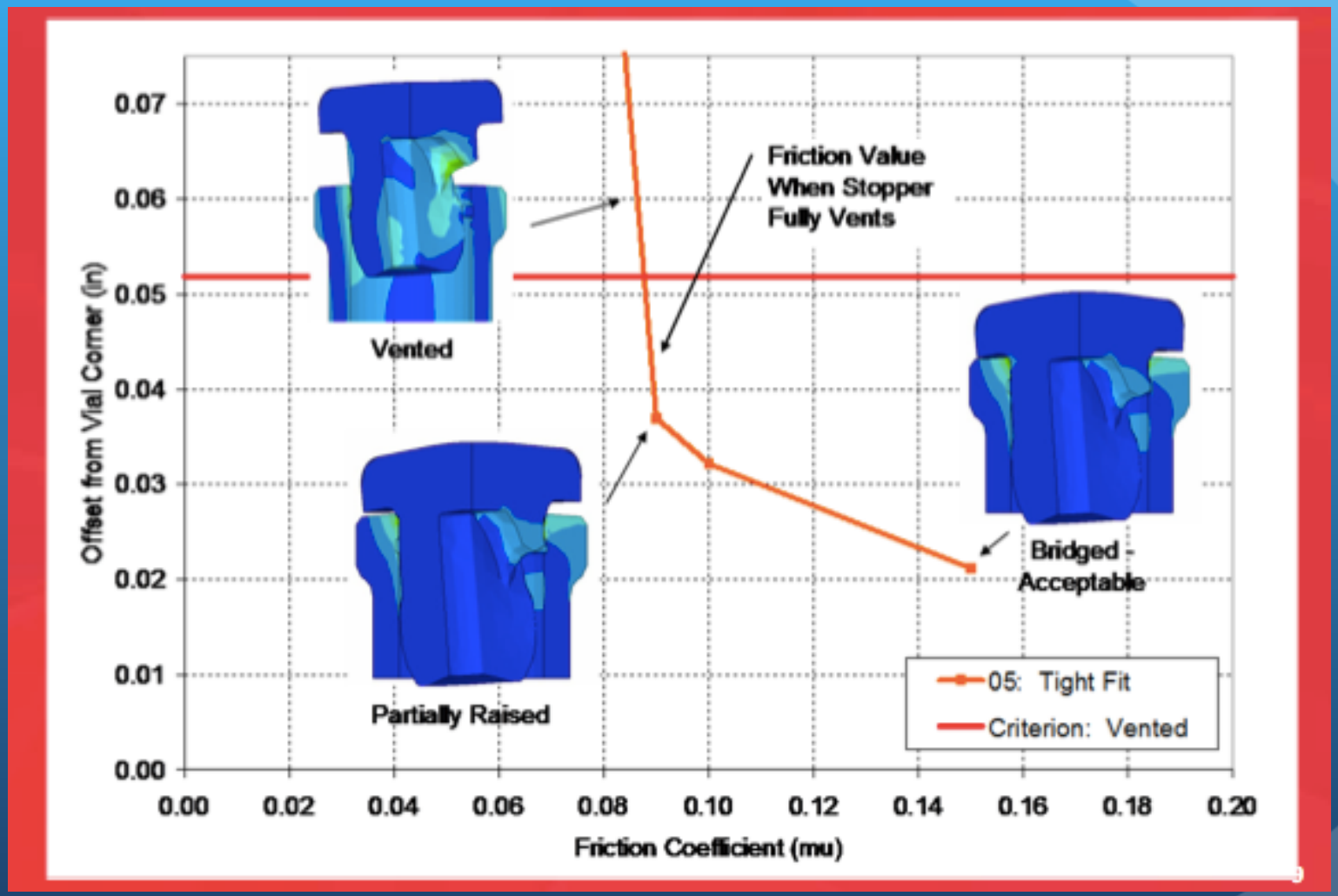
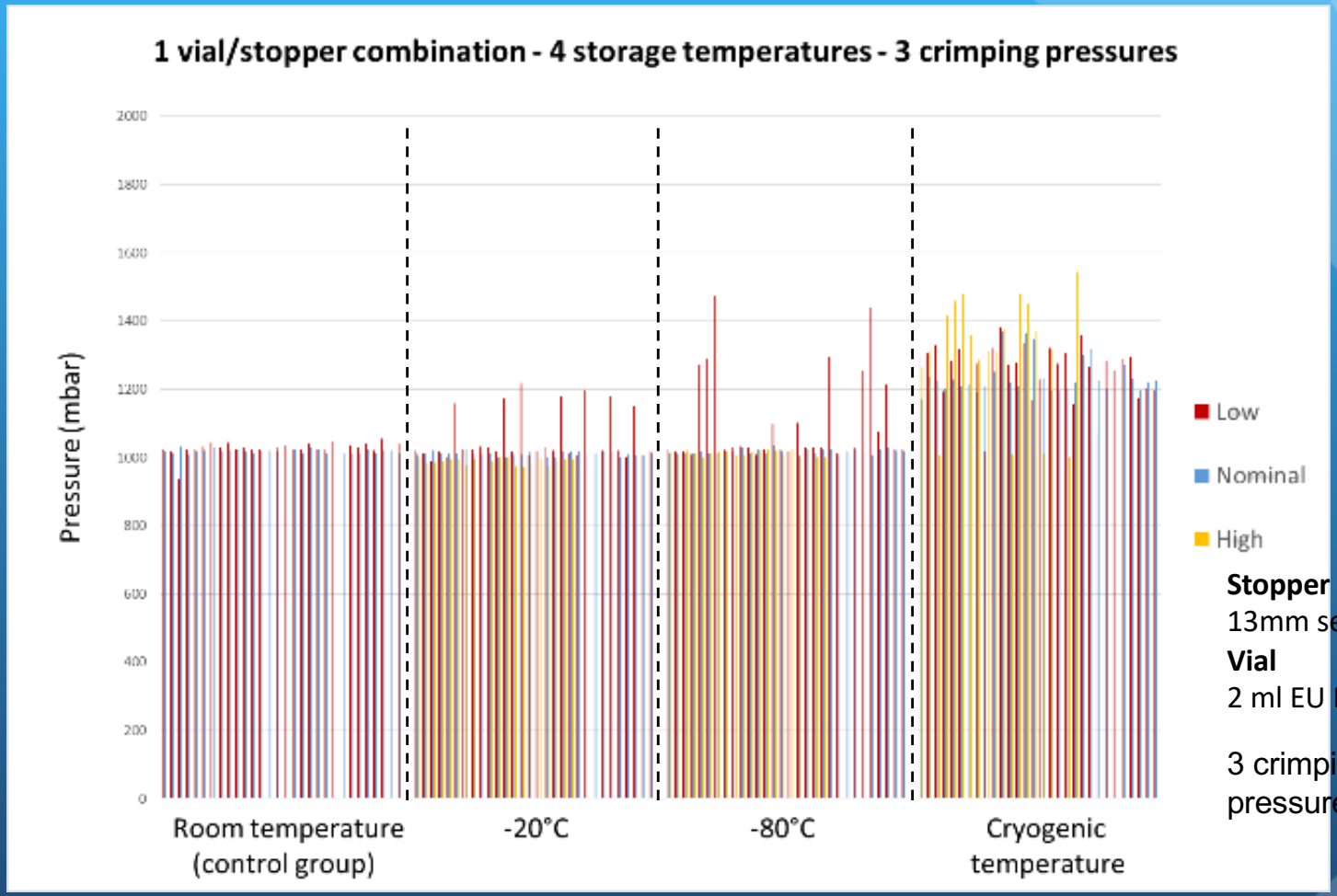


FEA Results – Nominal Dimensions

Finite Element Analysis (FEA)

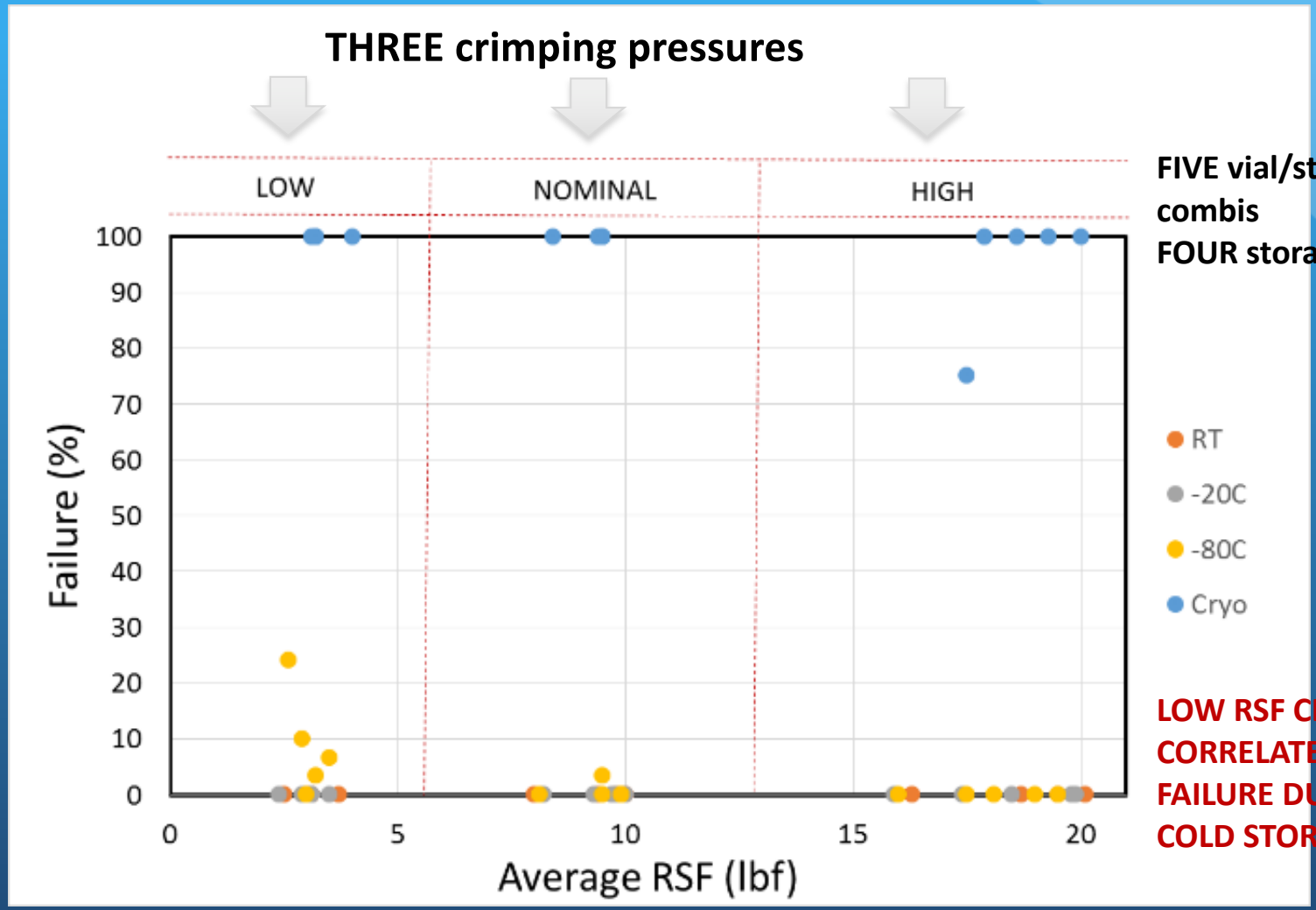


Results: Overpressure vs Temp



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)

Results: Failure rate vs. RSF



FIVE vial/stopper combis
FOUR storage temps

LOW RSF CLEARLY CORRELATES TO HIGH CCI FAILURE DURING DEEP COLD STORAGE

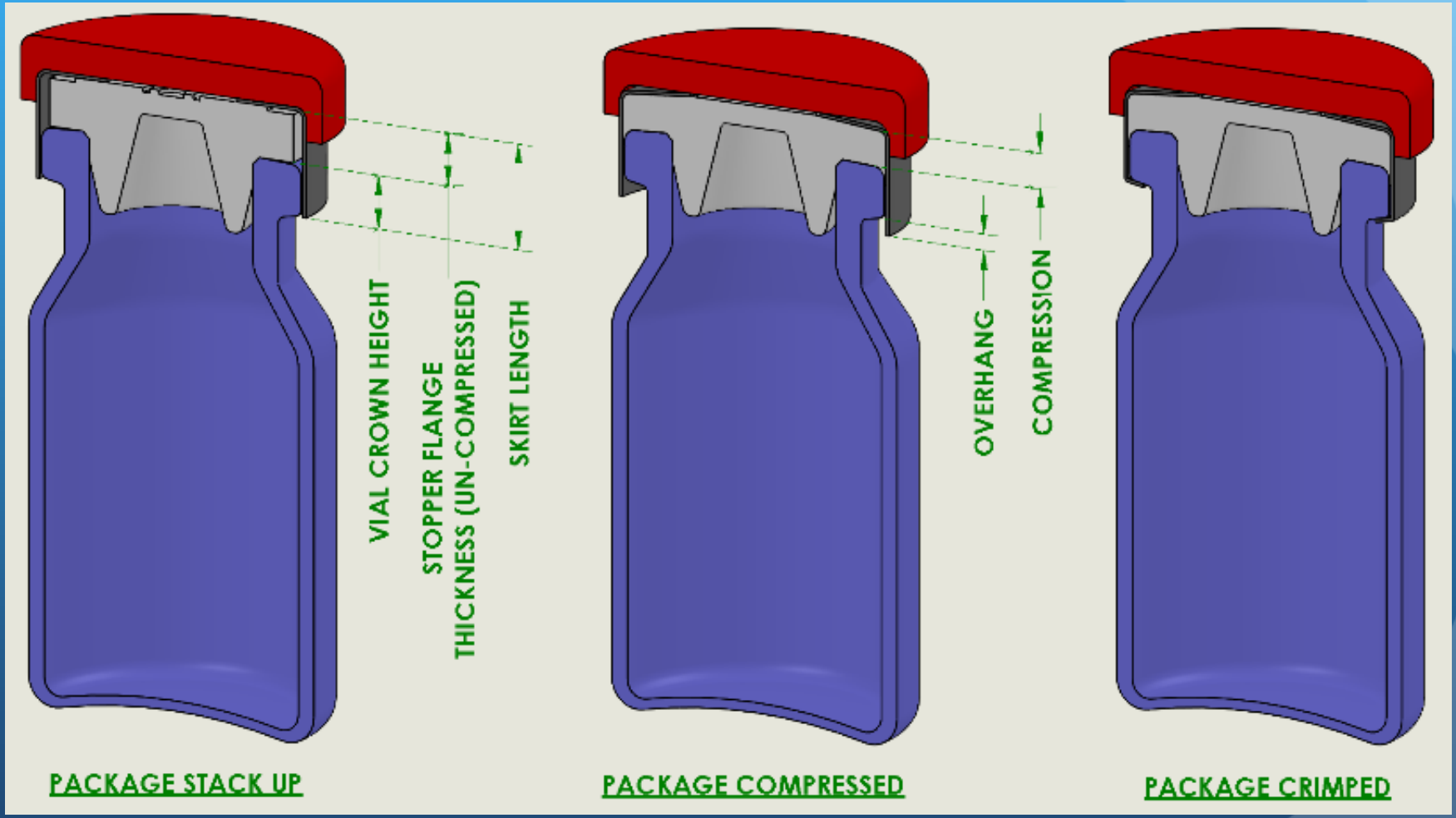
Duncan, D.; Asselta, R. "Correlating Vial Seal Tightness to Container Closure Integrity at Various Storage Temperatures" proceedings of *PDA Parenteral Packaging Conference,* Frankfurt, Germany; (2015)

Conclusions

- There is **risk for CCI failure** at storage temperatures **below the T_g** of the rubber stopper formulation.
- CCI failures can be mitigated by **ensuring appropriate vial / stopper** combination and **capping & crimping** parameters
- **RSF measurements** can be a useful tool in quantifying seal tightness and predictive of CCI failure at low temps
- **Laser Headspace Analysis** is a suitable non-destructive method to detect (temporary) leaks in cold storage

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)

Component Stack-Up



Tolerance Stack-Up

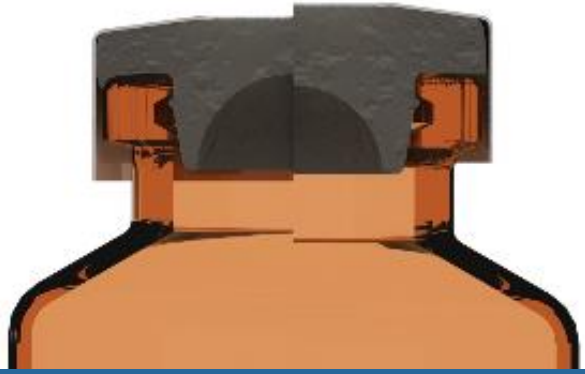
- In any sealing application, the tolerances of ALL the packaging system components in contact with the rubber must be considered in order to create an effective seal. The combination of these tolerances is the tolerance stack-up.
- Additionally the amount of stopper compression should be considered in the component review and stack-up analysis.

Component Tolerance Stack-Up Variation

Example 20mm Serum Finish

Stacked Components
With No Compression

Compressed Components at
Crimping

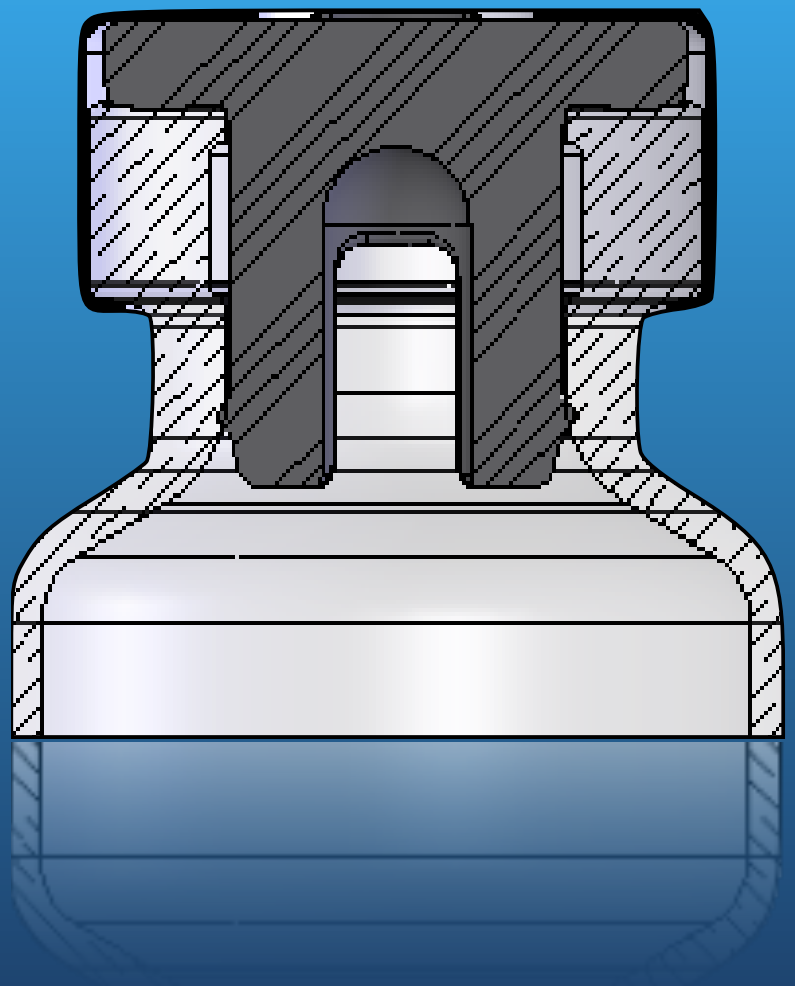


Min	Vial Flange Thickness	Max
Min	Stopper Flange	Max
Max	Seal Skirt Length	Min
Max	Vial Neck Diameter	Min

25% (High) Compression of Stopper Flange

15% (Low) Compression of Stopper Flange

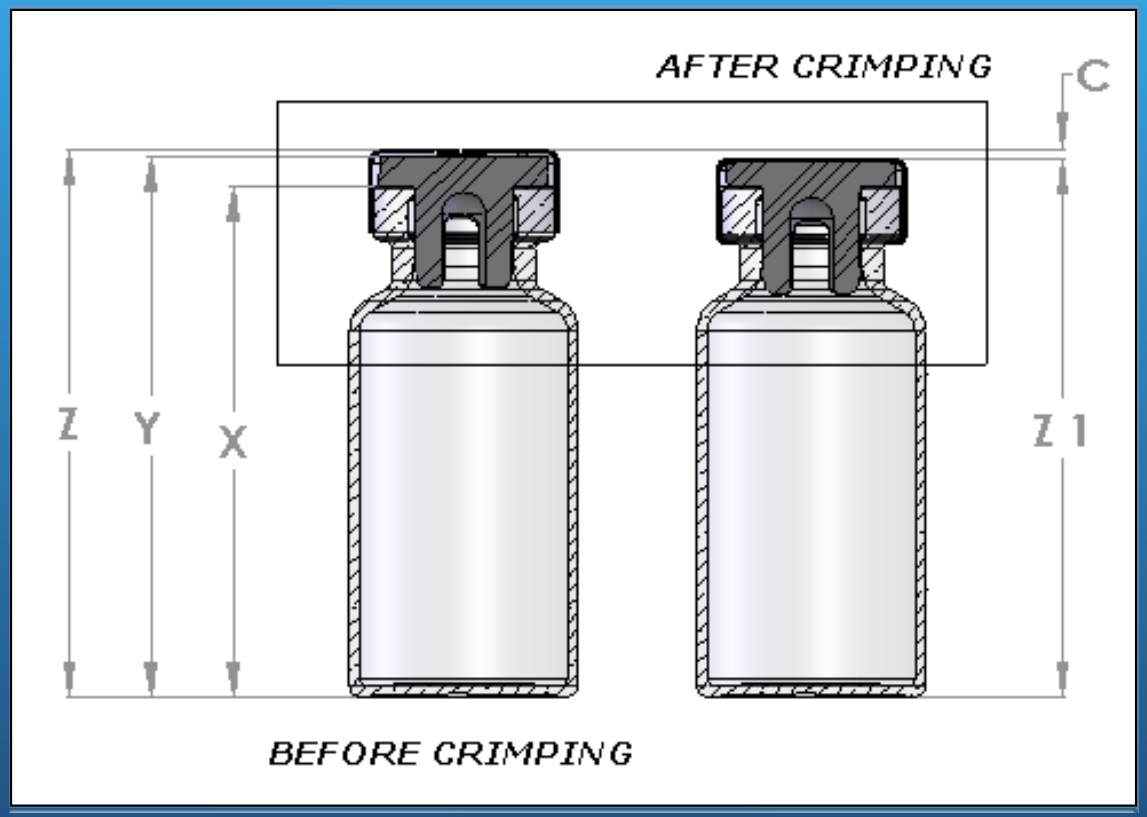
Component Variables



- Vial Flange Thickness
- Stopper Flange Thickness
- Aluminum Seal Skirt Length
- Elastomer Durometer
- Vial Inside Neck Diameter
- Stopper Plug Diameter
- Vial Inside Neck Geometry
- Stopper Plug Geometry
- Stopper Lubricity
- Vial Neck Diameter
- Sealing Surface Crown
- Vial Flange Underside Angle/Radius
- Vial Overall Height

Characterizing a “Well Sealed” Vial

Measuring Compression



$(Z-Z_1)/(Y-X)$

Residual Seal Force (RSF)

- 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).
- 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

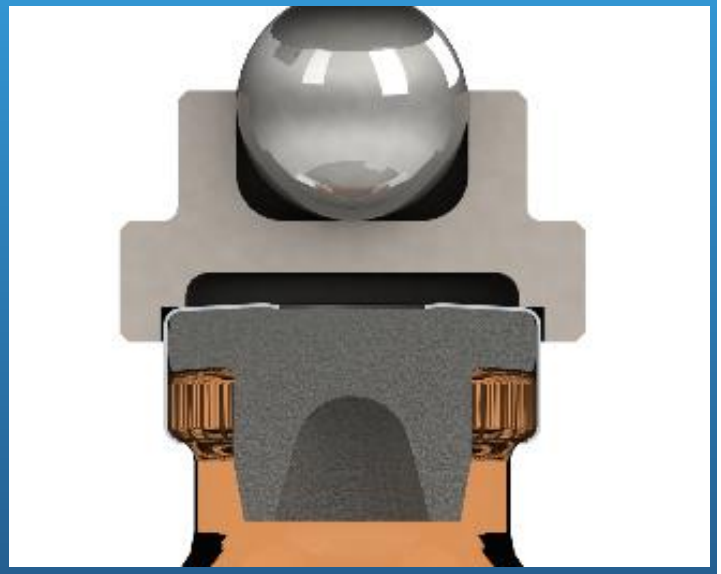
RSF Testers

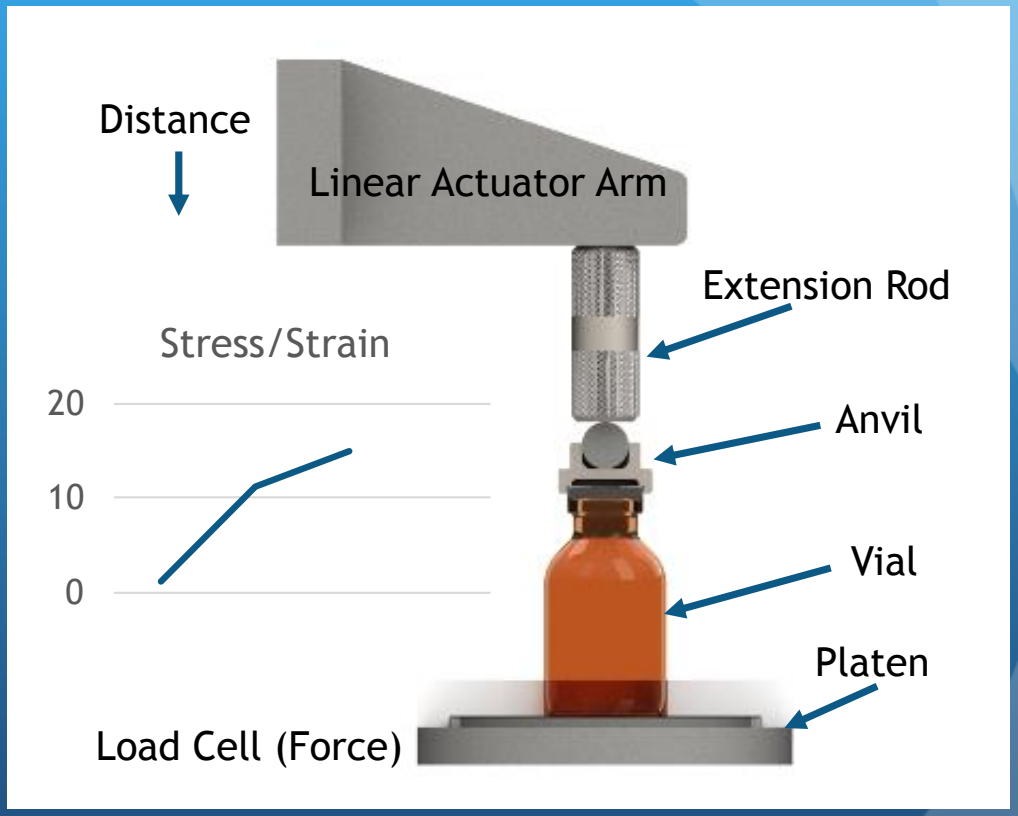
Genesis Model AWG

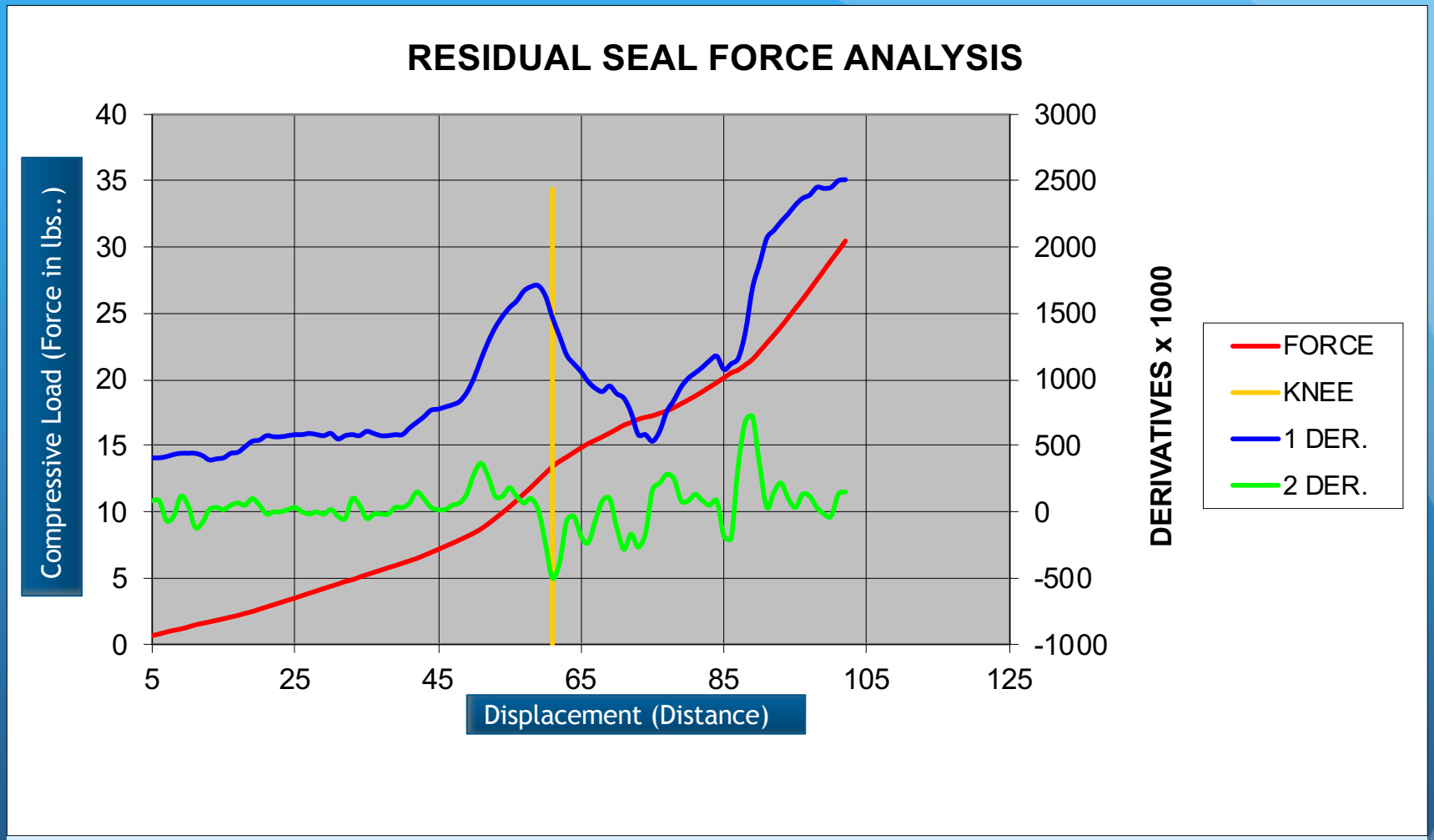
Fixtures for Instron®

Fixtures for Zwick®

RSF Tester







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.

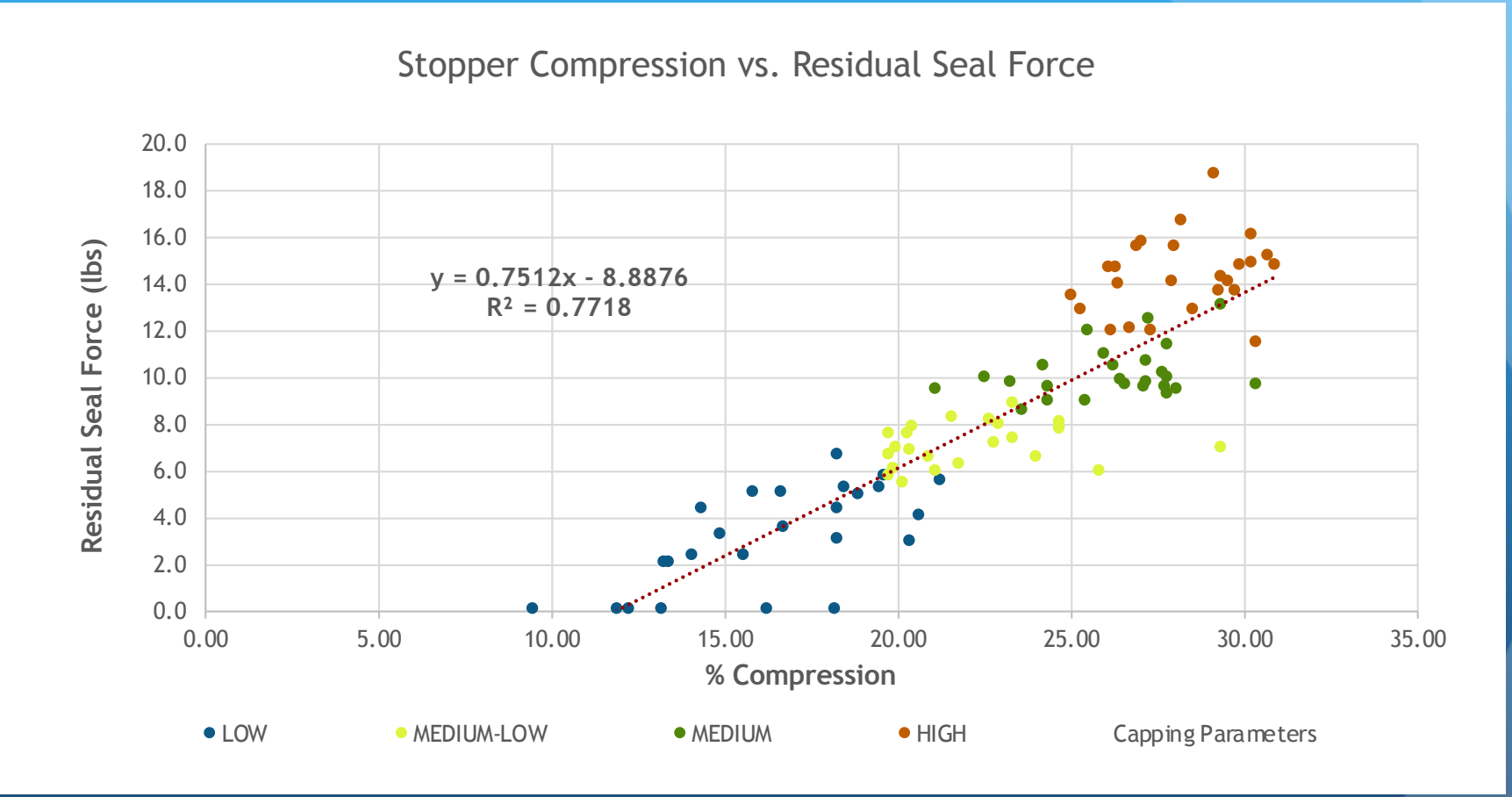
Ludwig J, Nolan P, Davis C, Automated method for determining Instron residual seal force of glass vial/rubber stopper closure systems, *PDA J Pharm Sci & Technol* 47, (1993) 211 – 218

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

RSF Testing, Its so easy…

Correlation of RSF to Compression

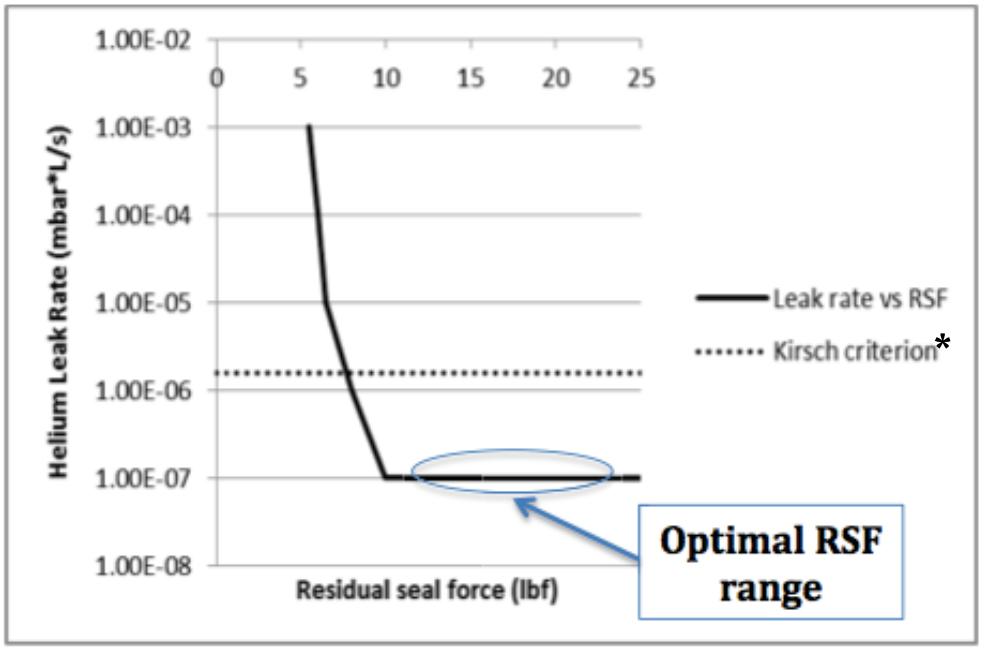


Example: 20mm Serum Soft Stopper

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

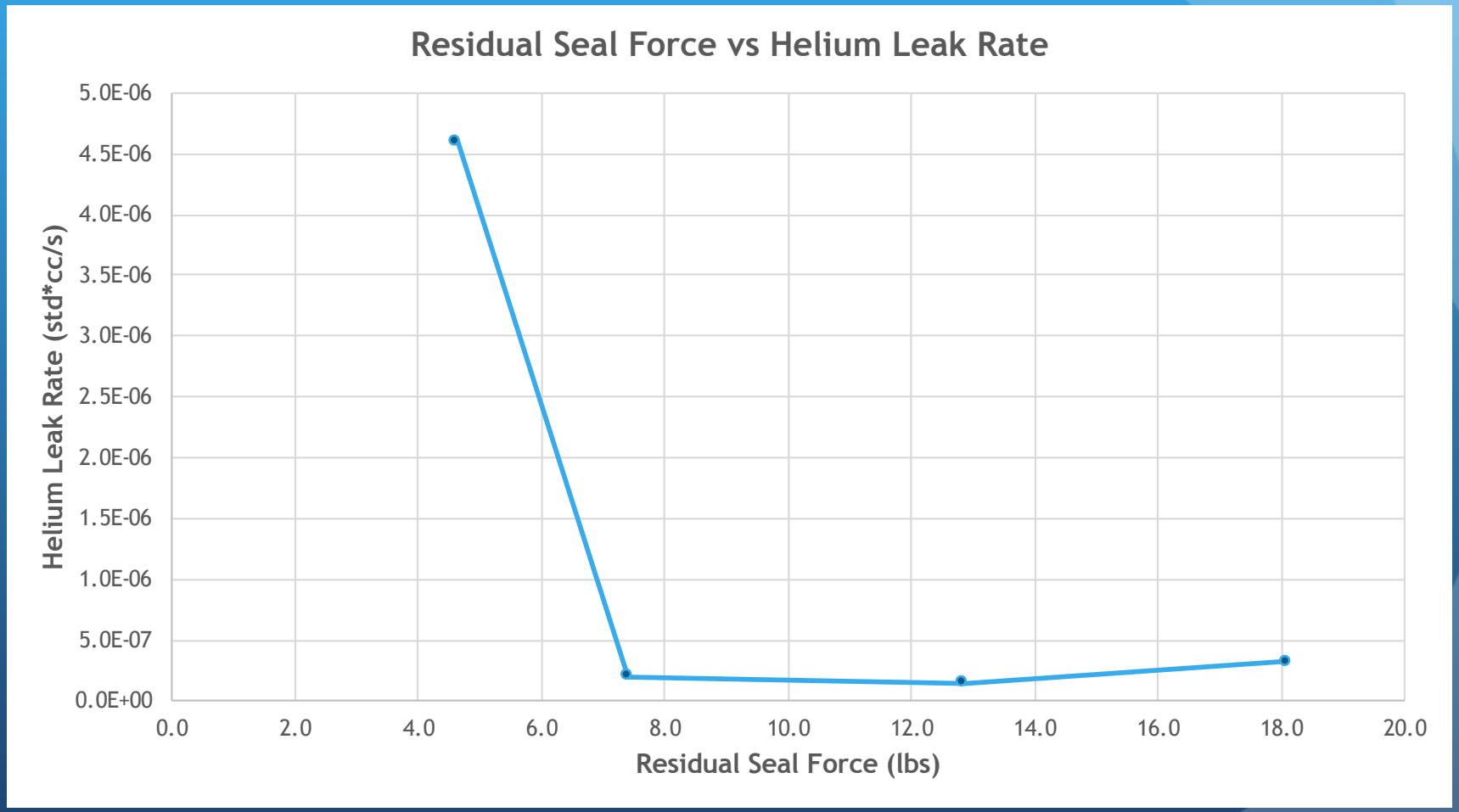


Ref. L Kirsch, L Nguyen, C Moeckly, R Gerth, *Pharmaceutical container/closure integrity II: The relationship between microbial ingress and helium leak rates in rubber-stoppered glass vials,* PDA J Pharm Sci & Tech 51, 1997, 195 – 202

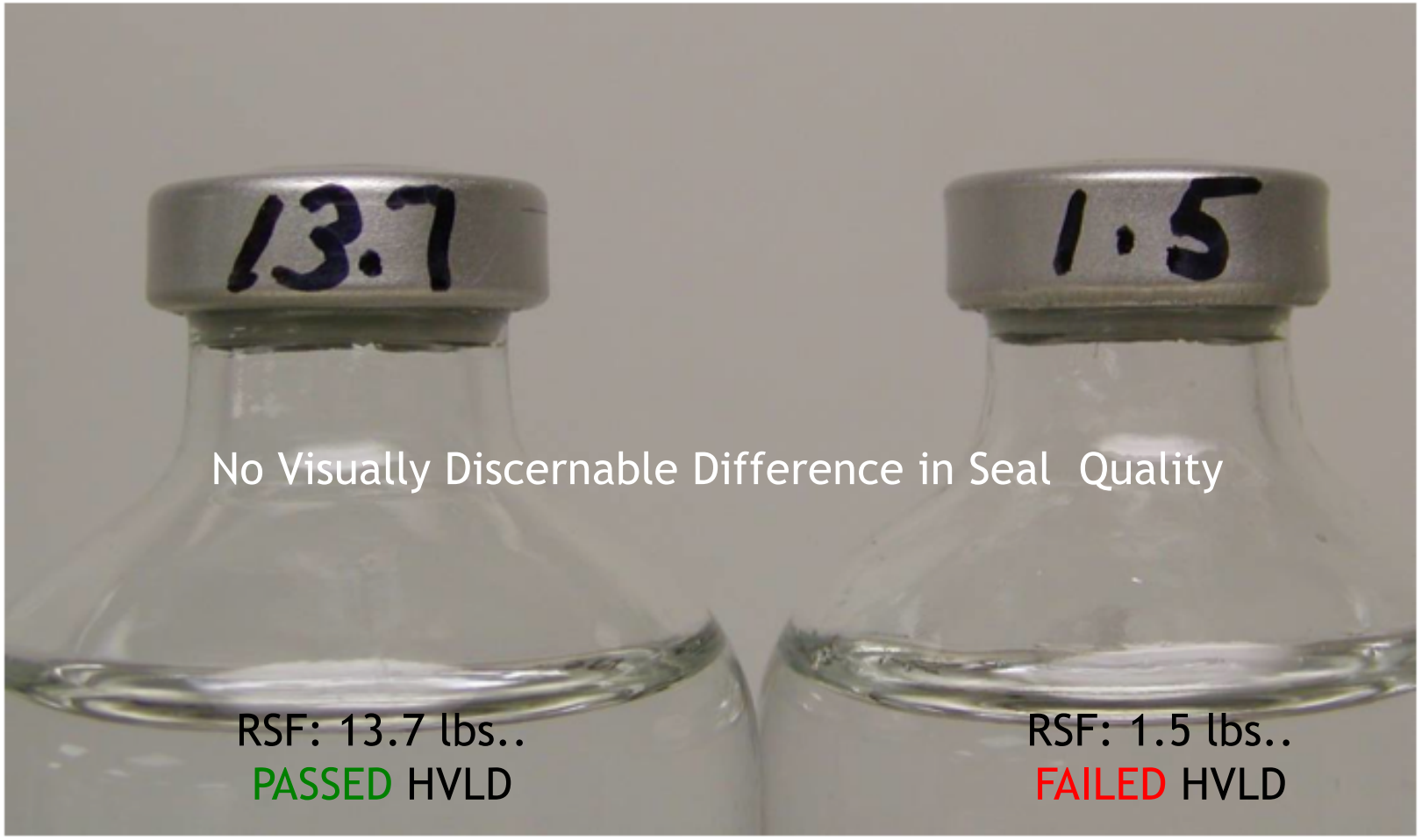
*Microbial ingress is a probability function. Critical leakage rate of log 5.8 or about 0.2-0.3µ

Illustrative purpose only. Courtesy of Dana Guazzo, PhD RxPax

Residual Seal Force vs Helium Leak Rate

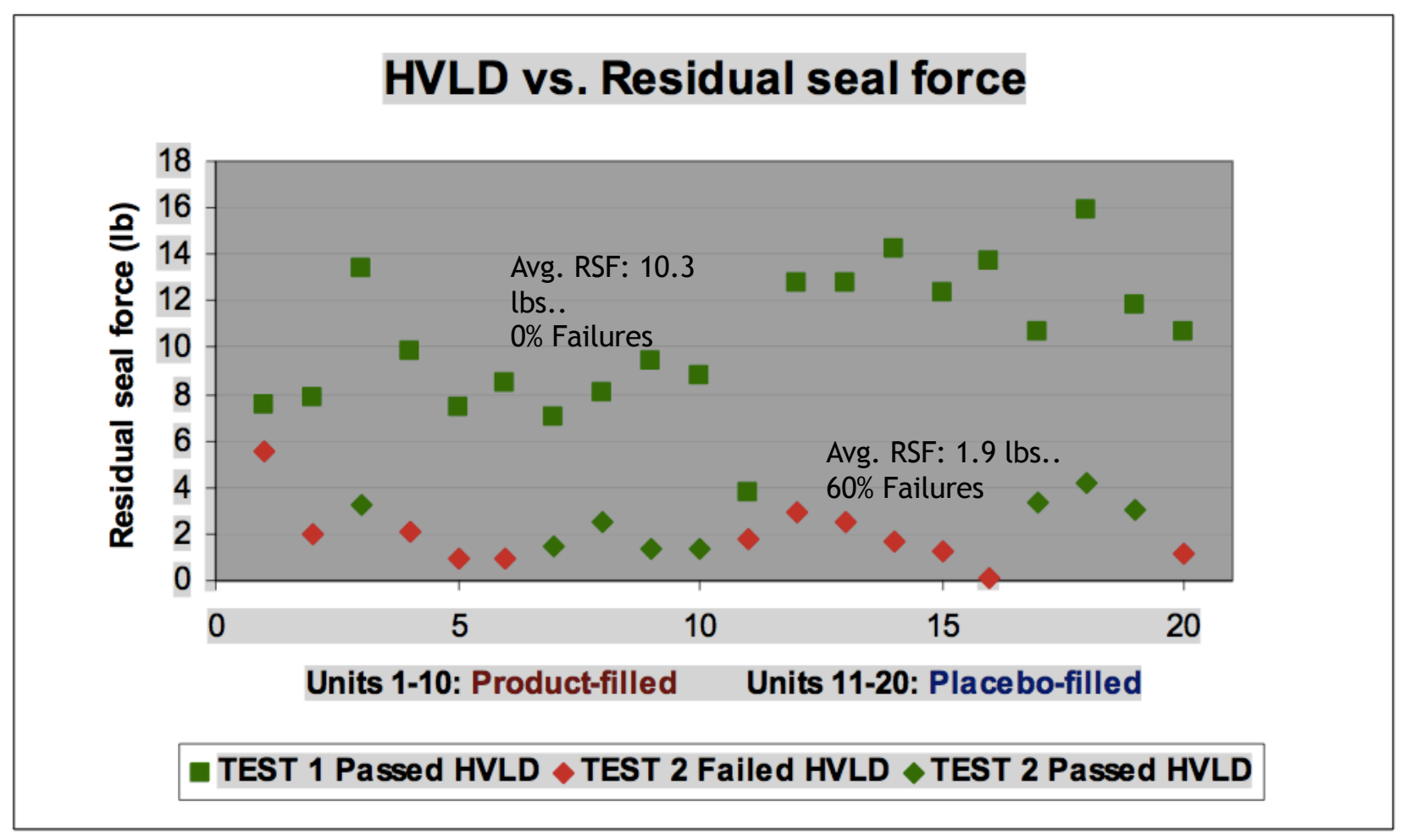


HV Leak Detection / RSF



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

Leakage Failures, High vs. Low RSF



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

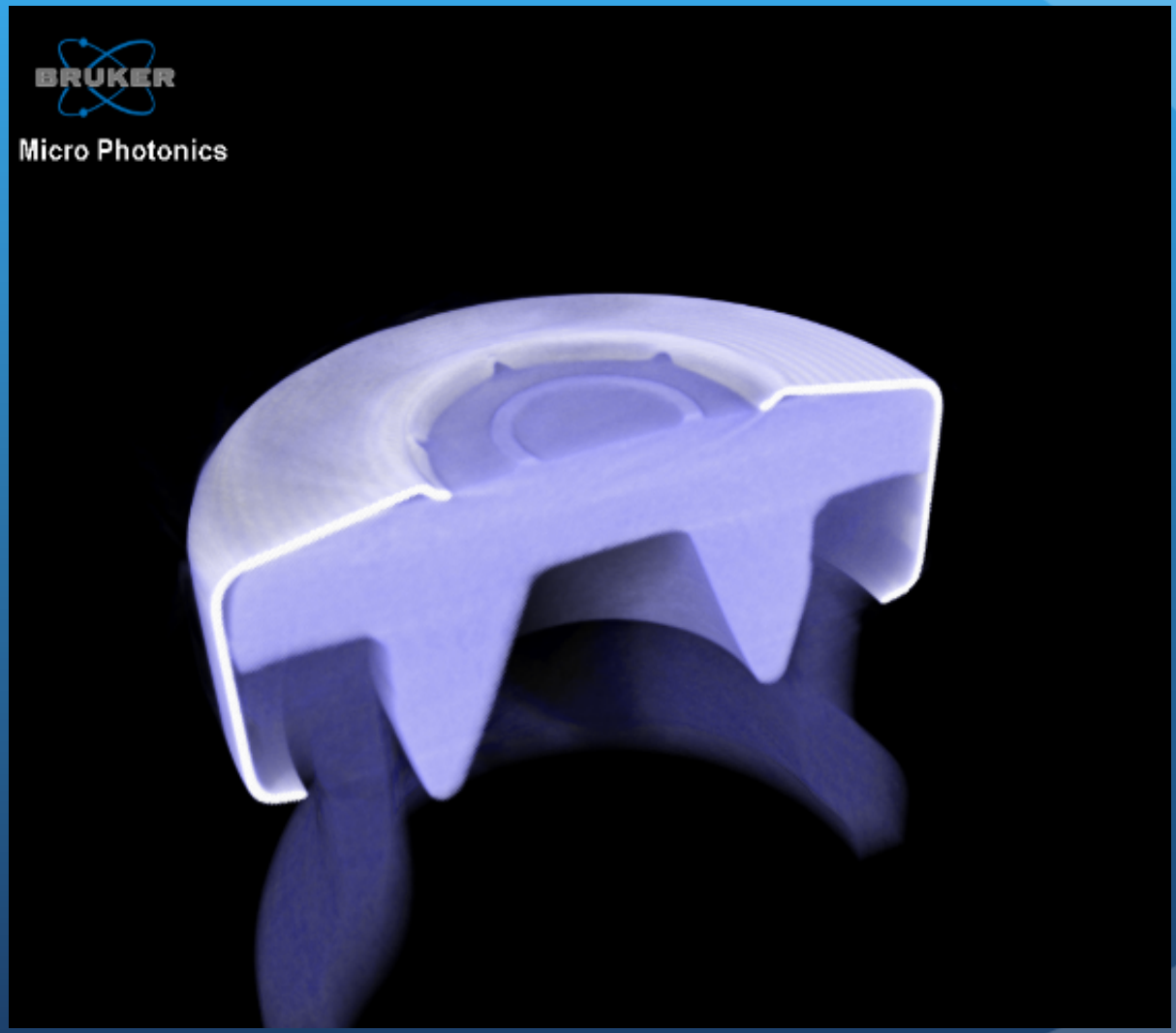
”RSF values may be used in effectively setting up vial cappers and for monitoring the crimping process. With an understanding of compression and leak rate cut-off, RSF can be further used as a predictor of leakage risk.”

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

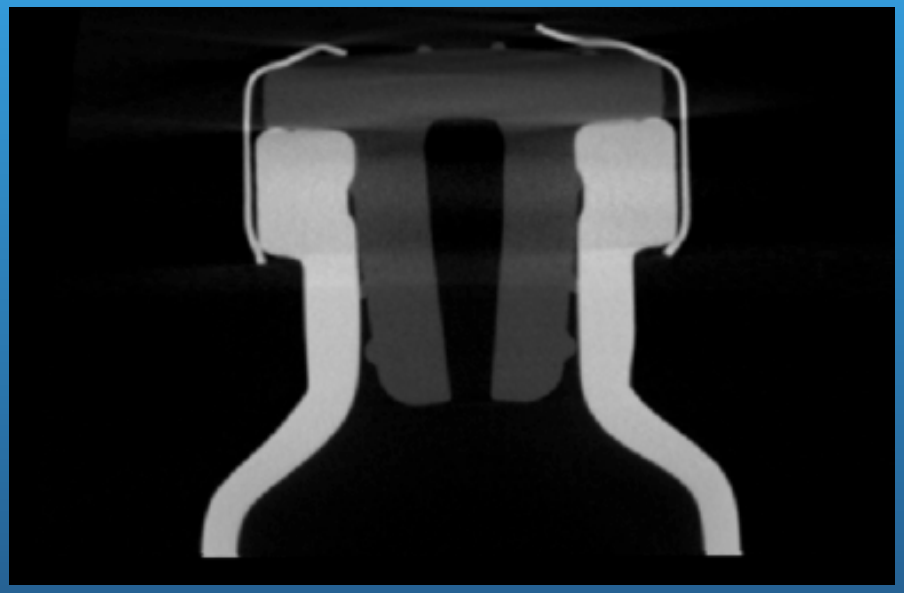
"The RSF tester can be used to characterize the resulting residual seal force of a capped vial independent of the capping equipment used, which can facilitate the comparison of seal quality of DP units manufactured in different facilities. In addition, a suitable RSF range that would still show full 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

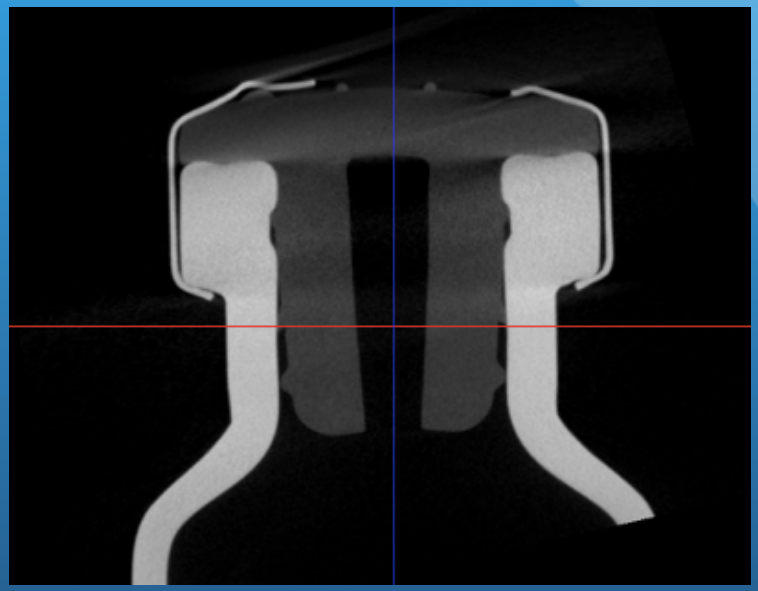
X-ray Computer Aided Tomography



Compression/RSF/X-Ray Tomography



Calculated Compression (%): 16.0
RSF Value (lbs..): 3.8
Measured Compression (%): 14.1

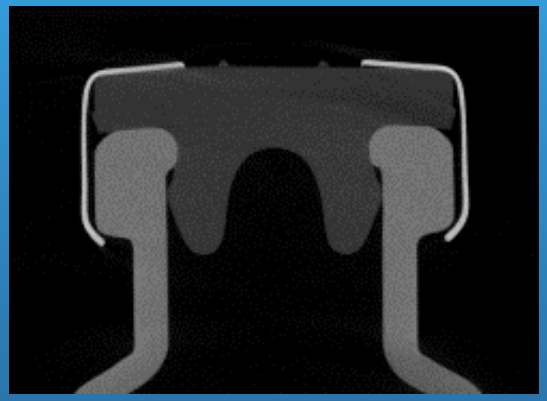


Calculated Compression (%): 32.2
RSF Value (lbs..): 13.9
Measured Compression (%): 36.7

SkyScan Image Courtesy of Micro Photonics, Inc.

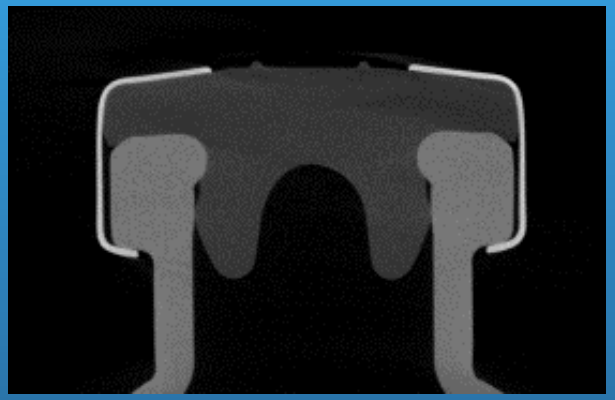
X-Ray Tomography

Various Capping Forces



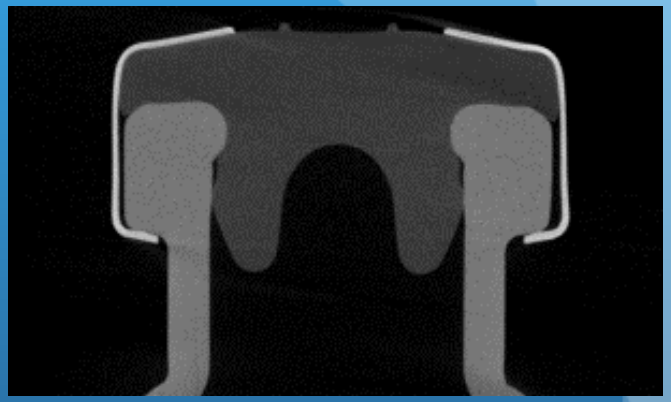
Low crimping pressure

10.3% Compression avg.
3.1 lbs. RSF avg.



Nominal crimping pressure

22.7% Compression avg.
9.6 lbs. RSF avg.



High crimping pressure

27.4% Compression avg.
16.5 lbs. RSF avg.

Images by Micro Photonics Inc. Allentown, PA USA using Bruker Micro CT SkyScan 1173

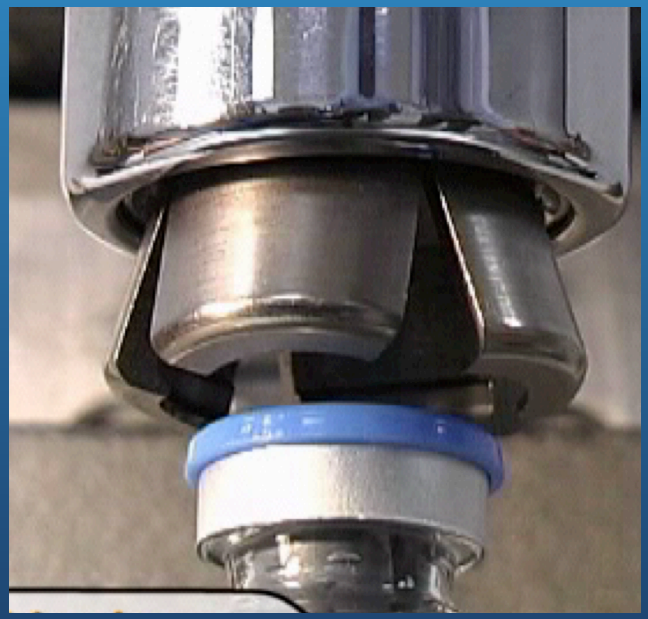
Vial Sealing

- Compression of Stopper Flange by an Applied Force
  - The force required to achieve proper seal is the result of three main factors:
    1. The cross section of the component(s)
    2. The durometer (hardness) of the rubber
    3. The per cent of compression required to achieve leak rate cut-off
- Crimping of Metal Skirt to Maintain Compression
- Can Be Accomplished By:
  - Jaw Type Crimping
  - Spinning Rollers
  - Rail Sealing

Jaw Crimping

Stainless steel jaws draw up the vial finish and crimp the aluminum seal skirt as compression of the rubber occurs within the crimper head.


Hand Crimper

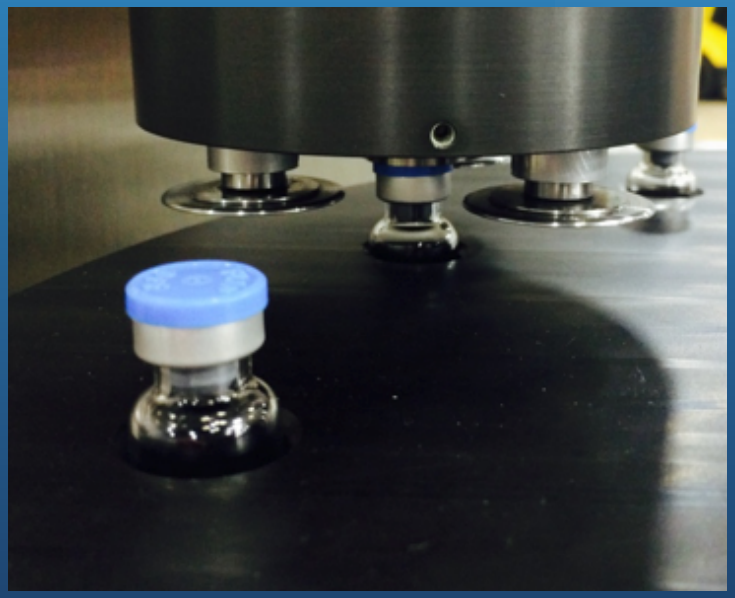



Kebby Benchmark


Semi-automatic

Spinning Rollers

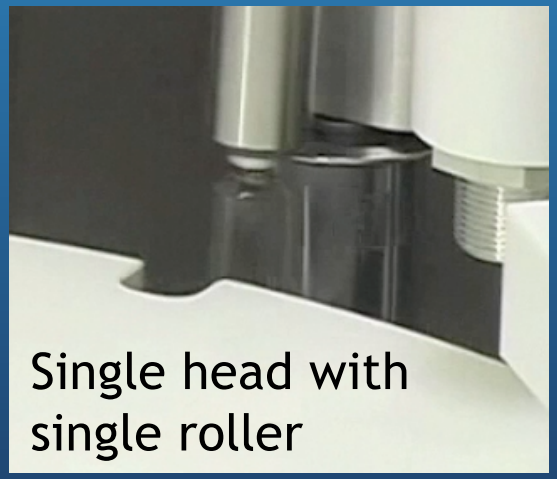
The vial is raised, or the head is lowered causing the rubber to be compressed against a sealing pressure block (or plunger). The rollers constrict to tuck the metal of the cap skirt beneath the vial flange.



Genesis Integra Capper

Single head with multiple rollers

Spinning Roller

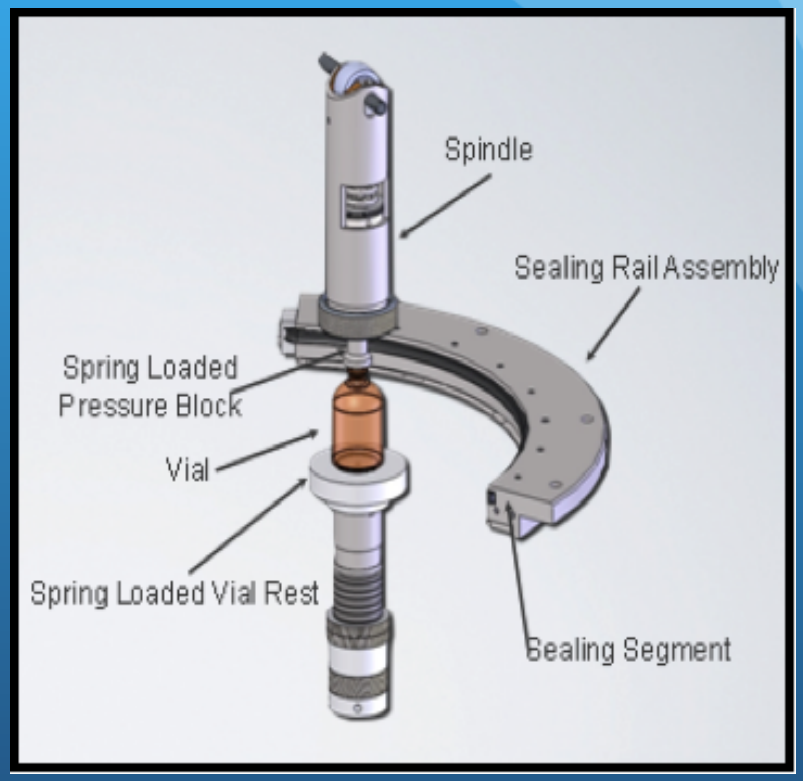


Single head with single roller

Multiple heads with single roller

Sealing Rail

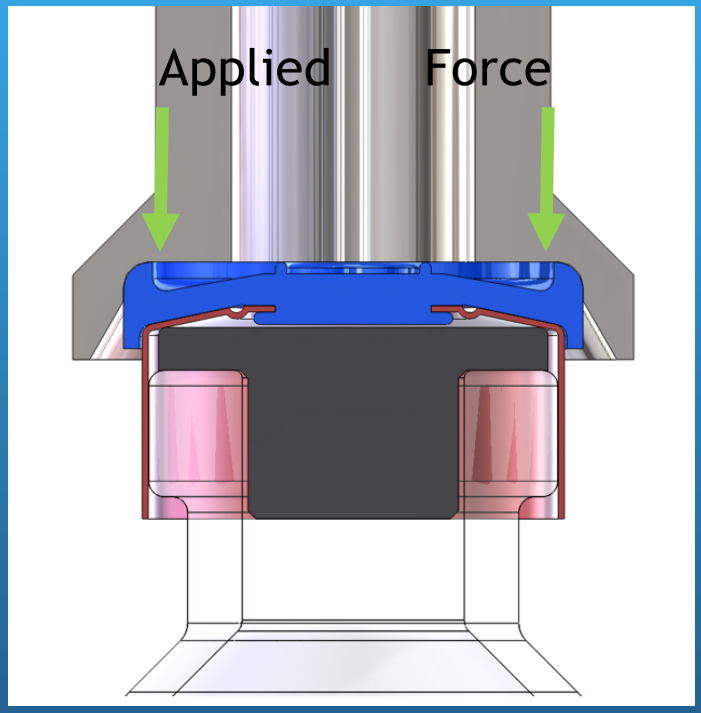
A semi-circular hardened stainless steel section (sealing rail assembly) with a gradually decreasing angle (typically 45° to 15°) performs the crimping action as the vial is compressed between spring loaded platens (pressure block and vial rest). The vial rotates and revolves around a turret with the cap skirt against the crimping rail.

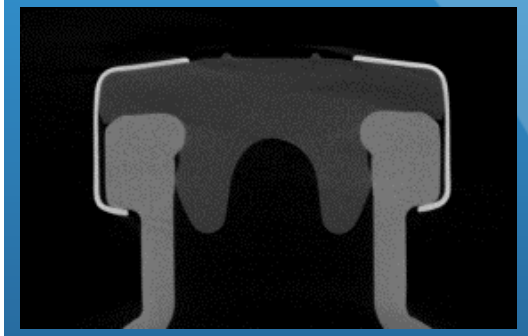


Aluminum Ferrule Designs

Aluminum Ferrule Varieties

Sealing Pressure Block/Cap Fit



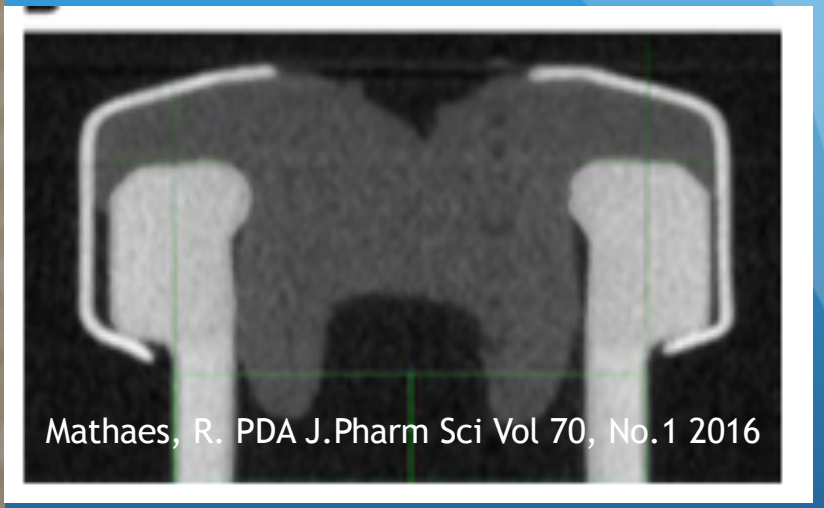


Applied Force Must Be Balanced

- Too Much Force
  - Glass Breakage
  - Dimpling or Bulging of Stopper
  - Pop-off of Plastic Button
  - Formation of Folds in Coatings Potentially Causing Capillary Leaks
  - Poor Seal Aesthetics
- Too Little Force
  - Too Little Compression
    - Failure to Seal
  - Loose Cap
  - Eventual Loss of Integrity

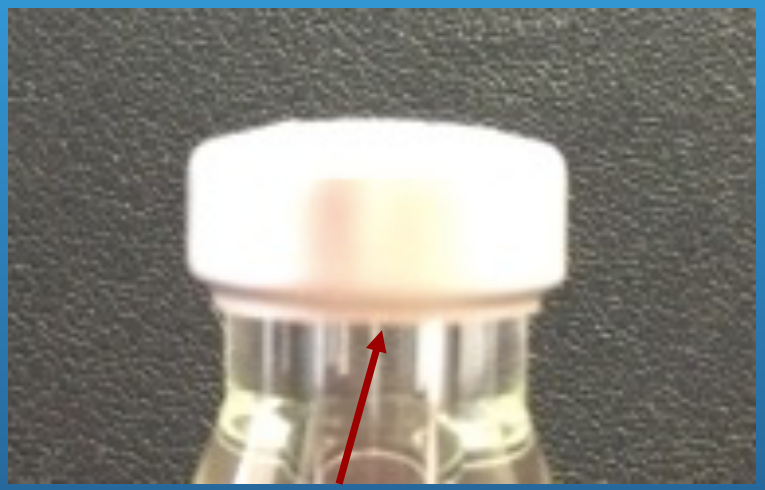
Example of Breakage from Too Much Force

Example of Dimpling from Too Much Force



Mathaes, R. PDA J.Pharm Sci Vol 70, No.1 2016

Poor Seal Aesthetics



Metal running down neck of vial

Wrinkling of crimp

Optimizing the Sealing *Process*

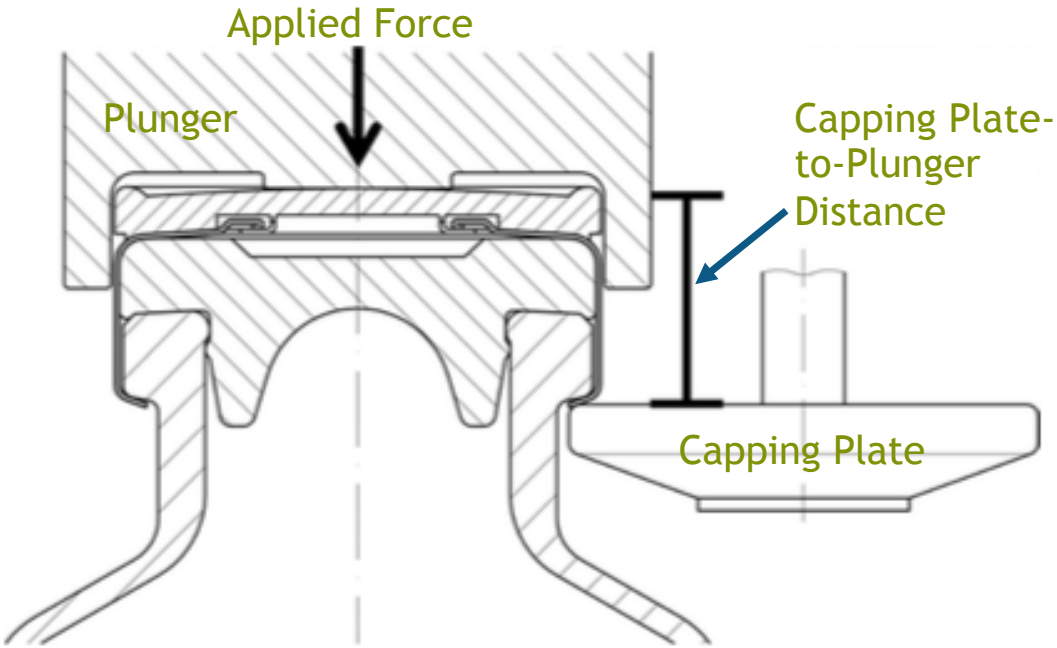
Capping Optimization

Genesis RW 600 Westcapper®

Capper Optimization

- To identify those capping parameters that influence achieving appropriate seal integrity and aesthetic quality.
- Establish set-up and operational ranges for those parameters.
- The development of these capper settings is based upon achieving sufficient stopper compression using RSF correlations and confirmed with specific CCI testing.
- On site using actual line, with specific packaging system
- (Machinability of Components)

Capping Plate-to-Plunger Distance (Sealing Gap or Compression Zone)



Impact of Vial Capping on Residual Seal Force and Container Closure Integrity

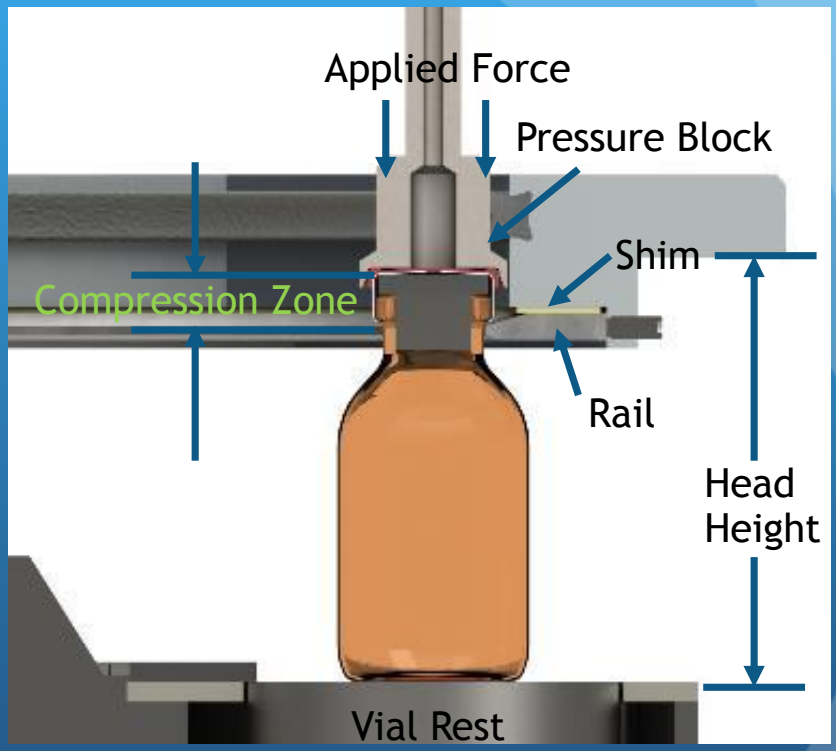
Roman Mathaes, Hanns-Christian Mahler, Yves Roggo, et al.

PDA J Pharm Sci and Tech **2016**, *70* 12-29

"The vial capping process is a complex interplay of several process parameters and the CCS configuration. …The capping plate-to-plunger distance has a major influence on the resulting RSF."

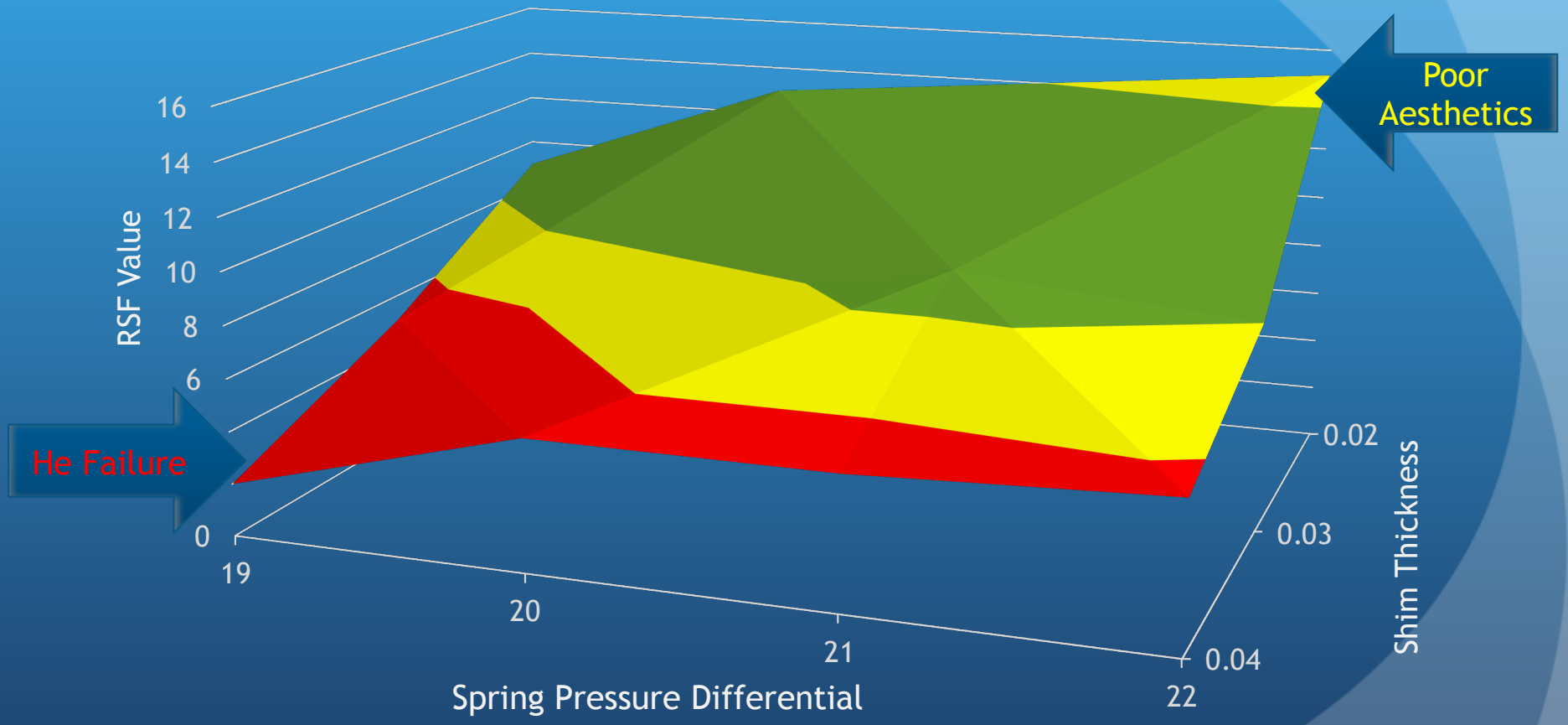
RW Capper Parameter Variables

- Head Height (Sealing Head Relative to Vial Rest)
- Pressure Block (Top Spring Pressure)
- Vial Rest Position (Bottom Spring Pressure)
- Pre-Compression Force (Spring Pressure Differential)
- Applied Force at Crimping (Force Exerted on Closure/Vial Flange between Pressure Block and rail)
- Sealing Rail Vertical Position (Shim)
- Sealing Rail Lateral Position (Set Screw)
- Sealing Rail Angles and Angle Gradation or Contour



Compression Zone (the distance from the top inside surface of the pressure block to the top contact point of the rail at the moment of crimping).

Surface Plot: Interaction of Shim and Spring Pressures on RSF



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Pharmaceutical Quality for the 21st Century: A Risk-Based Approach
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm128080.htm

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- Phillipe Lam, Genenentech

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