Importance of Residual seal force (RSF) for establishing Vial capping parameter

Establishing capping parameter is one of the difficult task in injectable process. However based on the OEM provided parameter firms are performed the qualification and established the limit for routine process. Most of the firm are performing the container closer integrity (CCIT) the qualitative method or probabilistic method, from which it very difficult to identify the actual leak rate. Now a day's number of quantitative detection methods are available to detect the actual leak rate after container getting sealed. Vacuum Decay, Pressure Decay, High Voltage Leak Detection, Oxygen Headspace, Helium Leak Detection are renowned method which consider as quantitative method or deterministic methods (*click here for details*).

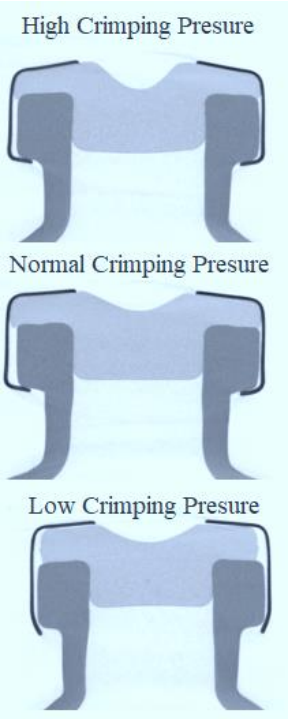


Figure 2: X-Ray imaging with different crimping pressure

In this article we will try to provide clarity about the correlation between of RSF and CCIT. Currently number of OEM are available who are providing the RSF tester. But RSF and CCIT both the concept are not correctly understood till now. Number of market complaint or recall are identified now a days which are related to container closer integrity. But we are spending most of the time in investigation and identified as lowlight area is packing materials. Because glass container, rubber stopper and seal these three variables are available for every product and change in any of the items will have impact on the integrity. That means if we consider 20 mm rubber stopper for stoppering, we should remember that different material of construction (MOC) having different elastomeric properties, which will impact on the compression force to be applied during capping.

Figure 1: Container, stopper and seal

Even design of vials (Blowback or non-blow back), type of formulation (liquid or lyophilized), atmospheric condition of storage (Room temperature or 2-8°C) all those variability can impact the qualification of capping process. Regulators expectation is *"Closures for parenteral preparation containers should be equipped with a firm seal to prevent entry of microorganisms and other contaminants while permitting the withdrawal of a part or the whole of the contents without removal of the closure. They should not be made of components that react with the contents, nor should they allow foreign substances to diffuse into the preparation. Plastic materials or elastomers of which the closure is composed should be sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles. Closures for multidose containers should be sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened".*

Figure 3: Different type of rubber stopper used as per the process requirement

Residual seal force (RSF) is considered the only quantifiable attribute for measuring seal "goodness" and potentially enables nonsubjective, consistent setting of cappers across manufacturing sites. However, the consistency and reliability of RSF measurement and data have been scarcely reported, and the relationship between RSF and container closure integrity (CCI) remains poorly understood. Residual seal force is not a leak test, but is an indirect measure of the compressive force applied by the stopper on the vial's land surface. A slow, constant rate of strain is applied to the top of a capped vial and the resistance to compression is monitored and reported. An appropriate amount of compressive force is required to ensure a quality seal.

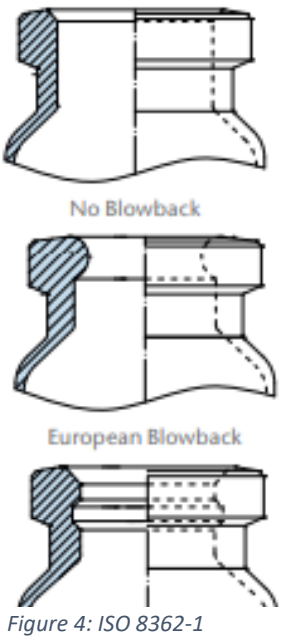


Figure 4: ISO 8362-1 Blowback Variation

Vials capped at an insufficient force may leak from the sealing surface. On the other hand, vials capped at an excessive force may experience cracking and bulging, also risking the integrity of the closure system.

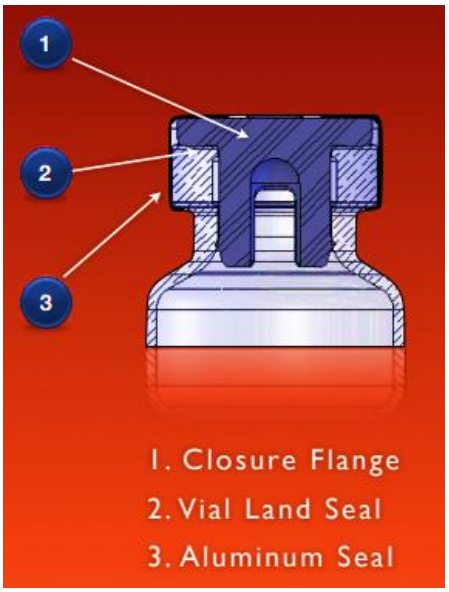


Figure 5: Parenteral Vial seal

What is Residual Seal Force?

A parenteral vial system consists of a vial, a stopper and an overseal. Container/closure integrity of this parenteral vial system is achieved primarily by the proper deformation of the rubber stopper. Deformation is achieved by compressing the stopper against the sealing surface of the vial finish. Once compressed, the stopper is held in place by crimping an aluminum ferrule or seal around the components.

In deforming the rubber stopper, the viscous flow of the elastomer fills and seals the voids between the sealing surfaces of the vial finish and the stopper flange. The elastomeric property of the rubber, which is the tendency of the elastomer to revert to its original shape while being held it in the deformed state, creates a force (strain) that effectively maintains the created seal. Although the compression of the stopper plug created by the interference fit between the plug and the inside diameter of the neck of the vial may also create a seal, it is the vertical force from the compression of the stopper flange against the top of the vial finish that creates the primary and more reliable seal.

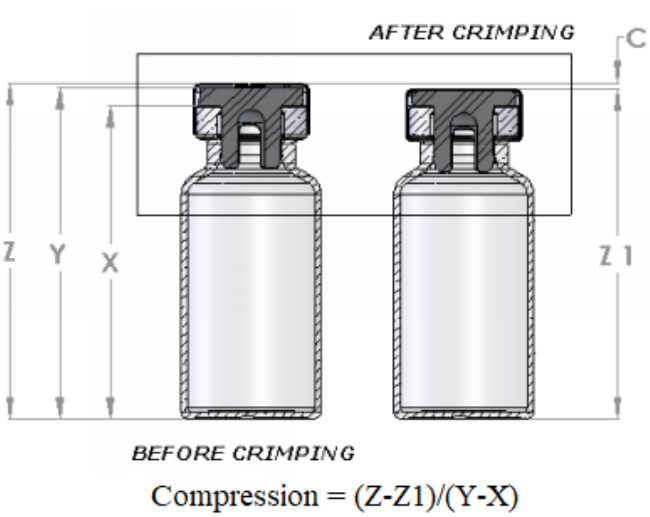


Figure 6: Compression force

The force applied to deform the stopper creates a reciprocal force in the stopper. Once the applied force is released from the crimped stopper the reciprocal force created by the deformed elastomer becomes the Residual Seal Force (RSF) of the package. Residual Seal Force, then, is the stress an elastomeric closure will continue to exert against the glass vial finish and the overseal after the capping operation is complete.

It is important to understand that Residual Seal Force is not a constant value. Changes in RSF are the result of stress relaxation and the compression set of the elastomer. Over time, as indicated by the curve, the elastomeric stress continues to very slowly decline due to the rheological characteristics of the rubber until a relative plateau is reached.

A specific RSF value is meaningless unless its location on the curve is known since the changes in stress are not linear. This degeneration and its effects on RSF need to be understood for each elastomeric formulation and stopper design. The physical and mechanical properties of the closure are determined by the rubber formulation and the stopper dimensions. These properties include durometer (relative hardness), compression set and modulus of elongation. Thus the stress relaxation curve and residual seal force may vary with each different rubber formulation. Processing and storage parameters, particularly temperature, may also influence this curve. By correlating RSF values with the compression of the rubber stopper and the corresponding leak rates, the measurement of RSF can be used to effectively evaluate proper and continued sealing of the vial system.

FDA in its Guidance for Industry Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products recognizes the usefulness of properly validated seal force testing. Most importantly, RSF is useful in the establishment, validation and control of capping machine settings.

What is the function of RSF tester?

The function of the Residual Seal Force Tester is to evaluate seal tightness by measuring the Residual Seal Force in the stopper/seal combination created as a result of the sealing process.

Method	Application
Dimensional Analysis	Critical review of component technical specifications Dimensions and tolerances, variabilty (Cp, CpK) Stacking, interference, worst case probability
Visualization of Component Design and Fit	Component fit analysis for pre-capping integrity Lessens risk of headspace loss Lessens risk of misassembly
Raised Stopper Test	Monitors stopper position just prior to capping Lessens risk of headspace loss Lessens risk of misassembly
Finite Element Anaylysis	Break down components into elements Apply laws of physics at the element level Solve for physical state elements (e.g.: temperature, stress, strain, pressure, etc.)
X-Ray Tomography	Evaluates, component fit, elastomer deformation
Residual Seal Force (RSF)	Verifies compressive force of crimped closure on vial land seal surface Indirect measure of elastomer compression (deformation) Ensures seal force Consistency
Experimental Design	Identify and evaluate factors that affect seal integrity and capping forces. Design optimization and critical parameter settings

Figure 7: Advance version of seal quality evaluation methodologies

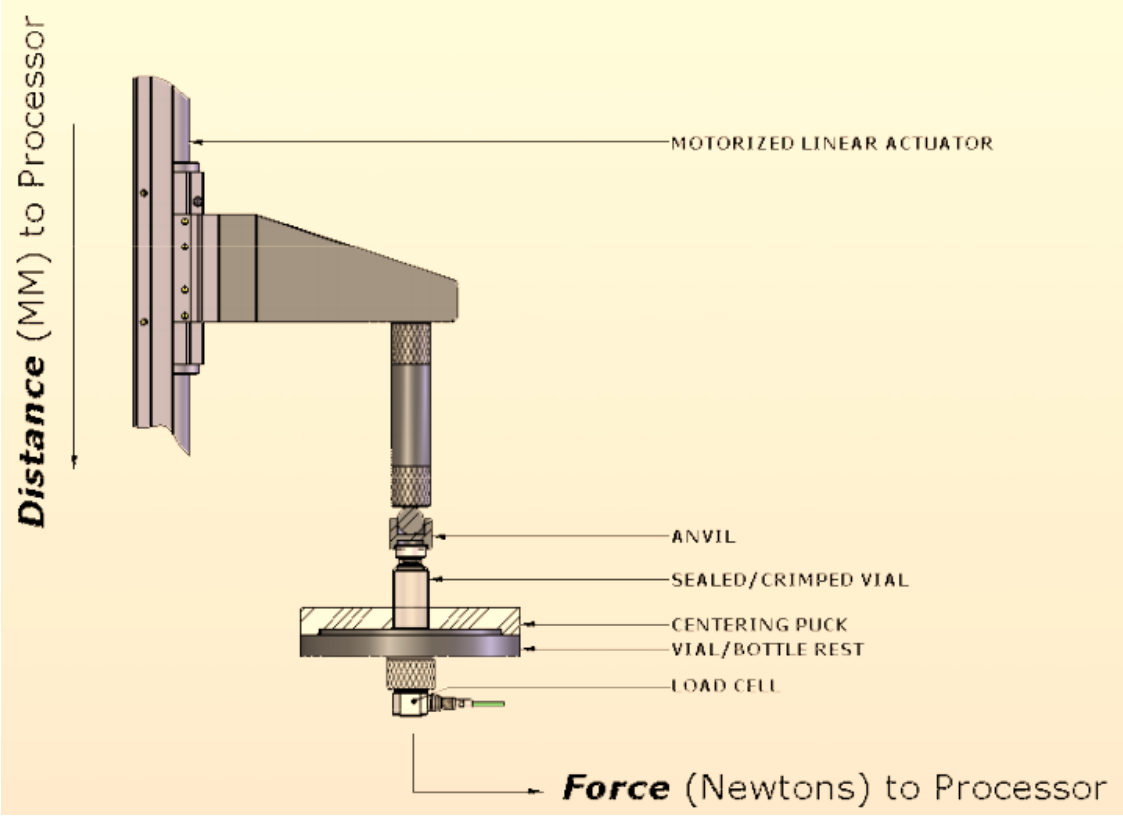
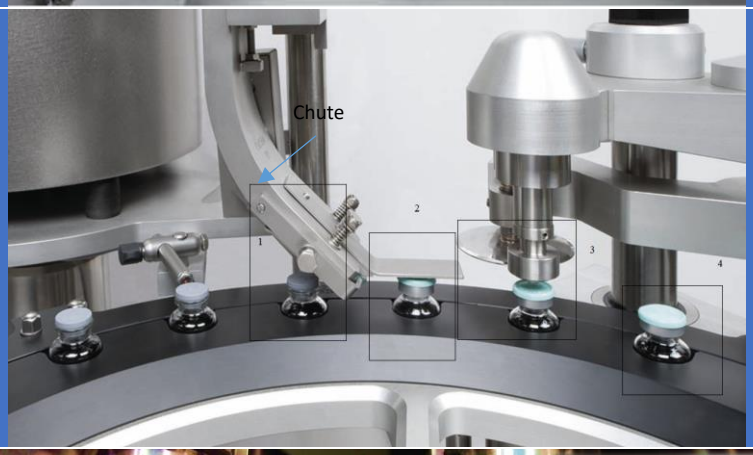
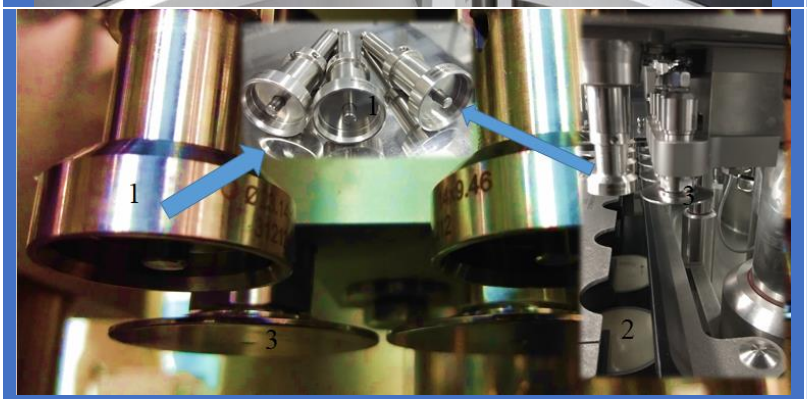


Figure 8: Automated RSF Tester

Table 1: Presentation of general sealing sequence in capping machine

Pictorial	Description
	After filling container moving to stoppering star wheel, 1. Vial entering to stoppering station 2. Stopper head 3. After full stoppering vial moving through stopper check sensor
	Top view of capping section, 1. Vial travelling from stoppering section to sealing section 2. Seal hopper, vibrator and chute assembly 3. Single head sealer
	Closer view of capper station, 1. Seal getting dispensed from chute 2. Seal level adjustment 3. Sealing head 4. Sealed container
	Closer view of capping head assembly, 1. Adjustable head to grip the container head with cap 2. Platform to hold pressure during compression 3. Moving arm to perform uniform seal

Reference:

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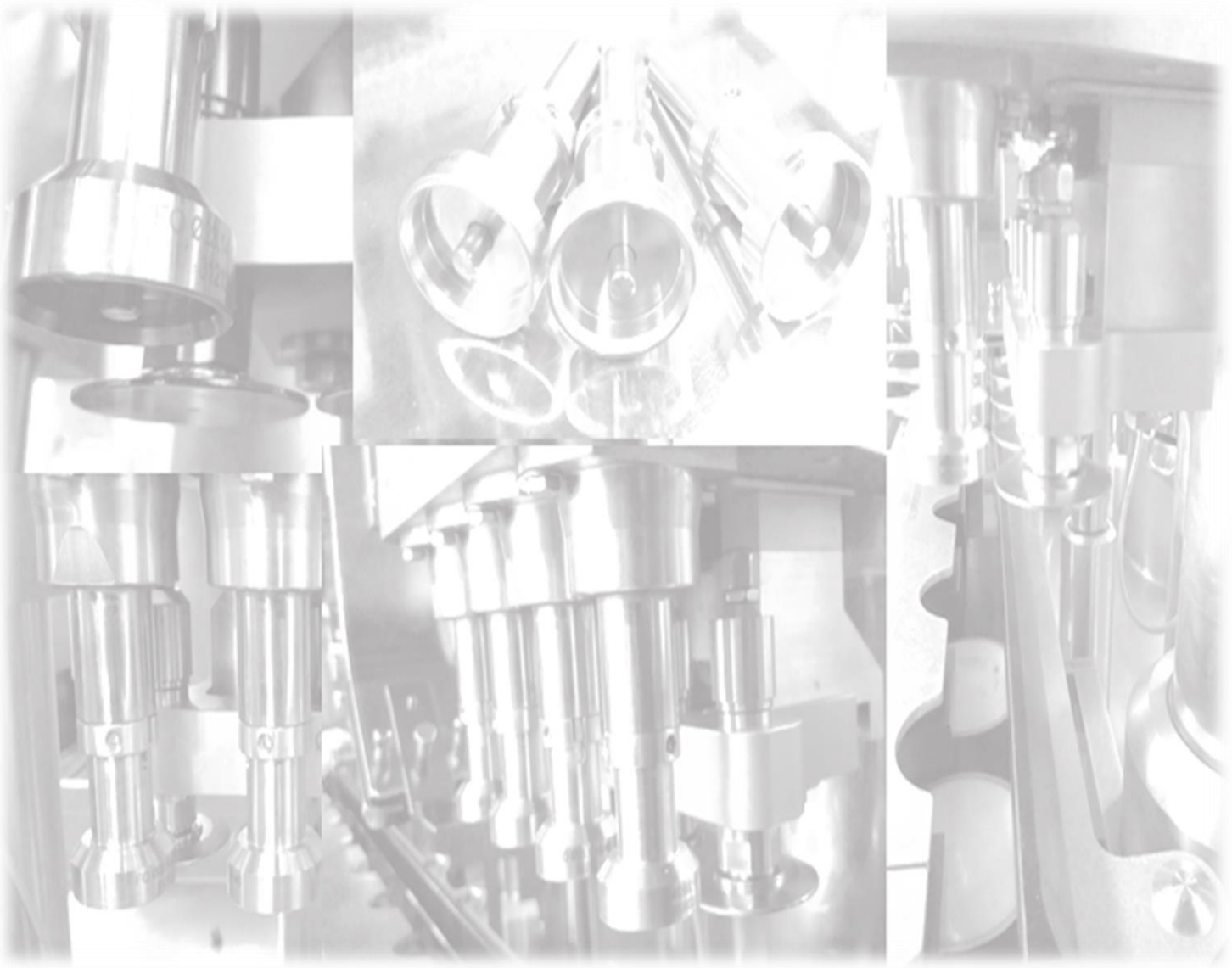

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