

# RESIDUAL SEAL FORCE

## AN INTRODUCTION

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# OVERVIEW

Since the early part of the last century crimped, stoppered vials have been a primary packaging system for parenteral medicines. The system has proved effective and reliable in containing and protecting the quality, safety and efficacy of many injectable drug products. Still widely used today the storage requirements of some vaccines, biopharmaceuticals and gene and cell therapies such as deep cold storage present new challenges to the robustness of the traditional vial systems. Traditionally, drug products may have been stored and transported at or near room temperature (20°), chilled (4 to 8°) or frozen (down to -20°). Today, some vaccines and biopharmaceuticals require temperatures down to -80° and some cell therapies need cryopreservation (-150 to -195°).

For a vial system to be suitable for its intended use of containing and protecting the quality, safety and efficacy of the parenteral drug product it must be “well sealed” and maintain integrity through administration to the patient. This life-cycle approach mandates a thorough understanding of Container-Closure Integrity (CCI), Maximum Allowable Leakage Limits (MALL), and Inherent Package Integrity (IPI).

Container-Closure integrity is defined in USP <1207> as “the ability of a package to prevent product loss, to block micro-organism ingress, and to limit entry of detrimental gases or other substances, thus ensuring that the product meets all necessary safety and quality standards”.

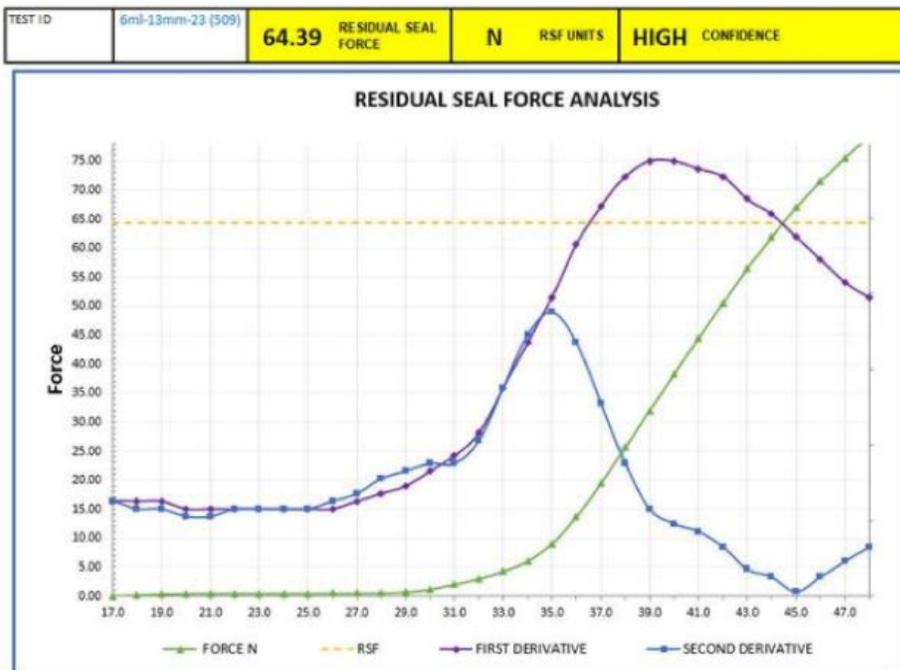
USP <1207> introduces two important concepts in considering parenteral packaging integrity. First, the Maximum Allowable Leakage Limit (MALL) which is the greatest leakage rate (or leak size) tolerable for a given product-package that poses no risk to product safety and no or inconsequential impact on product quality. The second concept is Inherent Package Integrity (IPI), defined as the leakage rate of a well-assembled (sealed) container/closure system (CCS) using defect-free components. Defect free does not mean perfect or even nominal, but that they conform to specification. Packaging component and system variation must be well understood to determine IPI.

MALL establishes the requirements for CCI that are necessary to protect the critical quality characteristics of the drug product. Inherent Package Integrity is the ability of the container closure system to meet those needs. Understanding a drug product's MALL and the intended container's IPI should be integrated into the risk assessment process and part of a holistic approach in life cycle management.

An important seal quality test to assess how well a vial is sealed is the measurement of the Residual Seal Force (RSF) of the compressed rubber stopper (USP<1207.3>). Correlating RSF to a Container Closure Integrity Test (CCIT) method and evaluating changes over time and conditions will determine the system's Inherent Package Integrity.

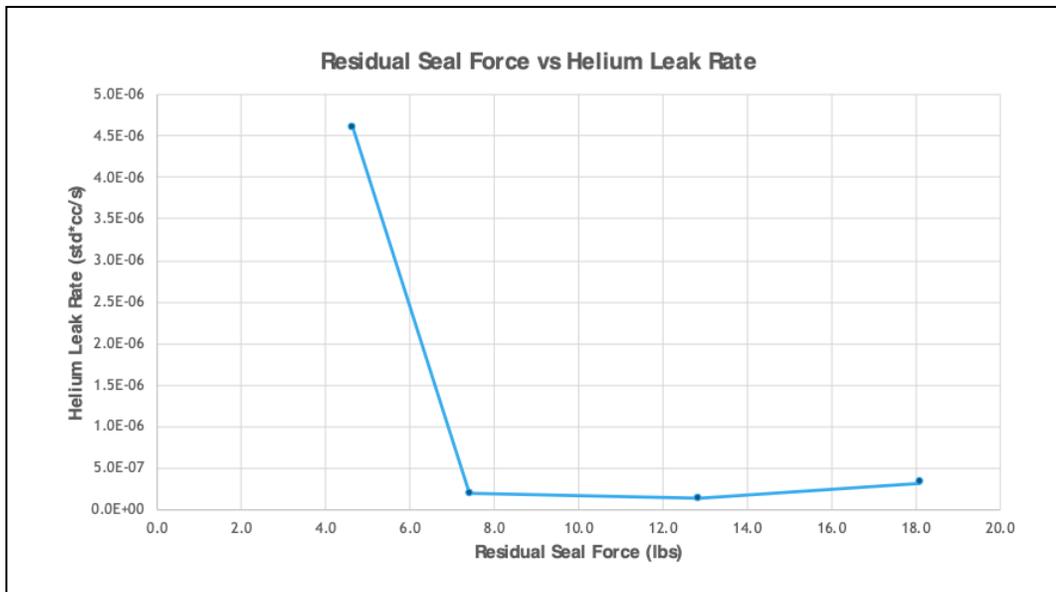
Since the 1970's and long before its inclusion as a seal quality test in USP <1207.3>, RSF has been used in assessing parenteral vial sealing. To seal a stoppered vial, an applied stress (sealing force) deforms or compresses the elastomeric stopper against the container sealing surface and induces a corresponding strain in the stopper, creating a contact stress at the vial/stopper interface. The strain is "locked-in" by applying and crimping an aluminum ferrule over the stopper. This locked-in compression or stored internal energy is the Residual Seal Force (RSF). RSF is the stress a compressed rubber stopper flange continues to exert on the vial's sealing surface after crimping the aluminum seal. RSF is a measure of vial seal tightness.

RSF is determined by identifying the point at which an applied force to the sealed vial further deforms the elastomeric stopper. Initially this was performed visually using a stereoscope, to observe when the bottom of the crimp first moves down as the force is applied. Techniques using universal testers were developed to evaluate the further deflection of the deformed rubber and plotting a stress/strain (distance v. force) curve. 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. The bend or "knee" in that curve indicates the point of further deflection and is identified as the Residual Seal Force.



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

In 1993 John Ludwig and colleagues applied sophisticated algorithms to evaluating the stress/strain curve providing more objective analysis. Meanwhile Dana Morton (Guazzo) demonstrated the correlation of RSF to stopper compression and leak rate cut-off, showing the higher the compression of the stopper flange, the higher the RSF value, the lower the leak rate.



These early works led to the application of RSF testing in the package development and validation of parenteral vials systems including; the choice of materials and components, understanding the effects of material and component variation; confirmation of seal tightness; characterizing a well-sealed vial; during assembly and the crimping process; establish optimum crimping process parameters and control; and aid in appropriate crimping process validation.

In 2010, Orosz and Guazzo demonstrated a correlation RSF to leaking marketed vials and were able differentiate between well sealed vials and those presenting a "sterility" risk. "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". In 2012, Zuleger established qualitatively an "appropriately tight capping and crimping process" is important for storage at -80°. Duncan and Asselta (2015) demonstrated the suitability of RSF as a suitable qualitative test method to evaluate seal tightness in deep cold applications: "RSF measurements can be a useful tool in quantifying seal tightness and predictive of CCI failure at low temperatures".

Mathaes and his colleagues showed how: "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 drug product units manufactured in different facilities". Additionally, they demonstrated that 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. Ovadia et al

(2019) did extensive work evaluating the applicability of RSF testing in evaluating capping processes and understanding variation, writing: "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". As critical as CCI is to a parenteral product, aesthetic quality or "pharmaceutical elegance" should be considered. Oni et al (2019) demonstrated how RSF can be used to balance CCI with aesthetic quality and can influence the selection of components.

Combining RSF with CCI test methods and other tools such as x-ray tomography and predictive modeling form provide a robust and holistic approach to assuring a parenteral vial system's container closure integrity through its life cycle.



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**W**e provide advanced vial sealing equipment for the packaging of critical injectable pharmaceutical products. Genesis designs, develops and builds vial cappers with innovative technologies that meet the technical challenges of parenteral pharmaceutical packaging, assuring seal integrity and in compliance with advancing regulatory requirements for aseptic processing and container closure integrity. Offering our customers the tools and knowledge to consistently achieve container closure integrity remains our priority. To that end, Genesis also manufactures a specialized instrument to test a key attribute of the sealed parenteral vial: Residual Seal Force. Not only do we provide the equipment to generate residual seal force data but Genesis provides the knowledge on just how to use that data to help create process parameters that consistently deliver integral seals.

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