Helium Mass Spectrometry for CCIT

Brian Mulhall, CEO
Leak Detection Associates

2020 PDA Container Closure Integrity Workshop

CONNECTING PEOPLE SCIENCE AND REGULATION®

Overview

- Introduction to Helium Leak Testing
  - Why helium?
  - Principles of operation
- Helium Leak Testing Methods
  - Sniffer Mode
    - Approach
  - Vacuum Mode
    - Approach
    - Case Studies

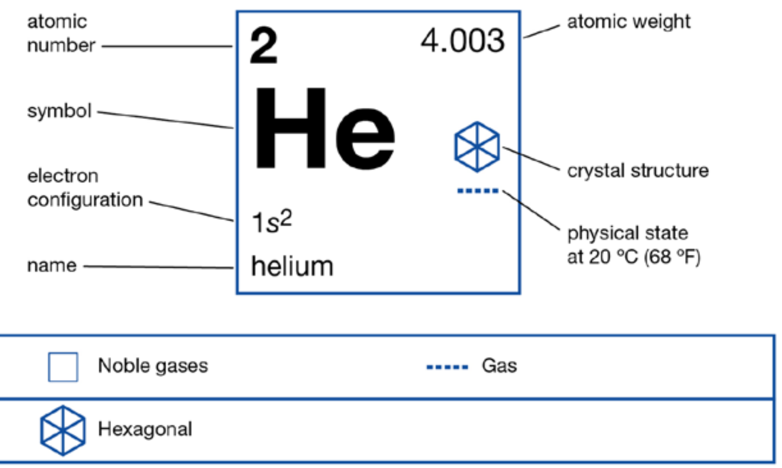
Introduction

Principles of operation and test methods

Why Helium?

- Extremely small molecule
- Noble gas
  - Non-toxic
  - Chemically inert
  - Non-flammable
- Atmospherically rare
  - ~5ppm
  - Selectable

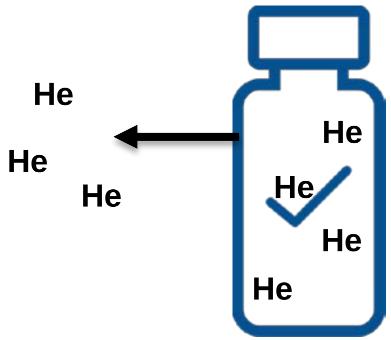
Helium



© Encyclopædia Britannica, Inc.

To Convert to Leakage Rate of:	Multiply Helium Leakage Rate by:	
	Laminar Flow	Molecular Flow
Argon	0.88	0.316
Air	1.08	0.374
Nitrogen	1.12	0.374
Water vapor	2.09	0.469
Hydrogen	2.23	1.410

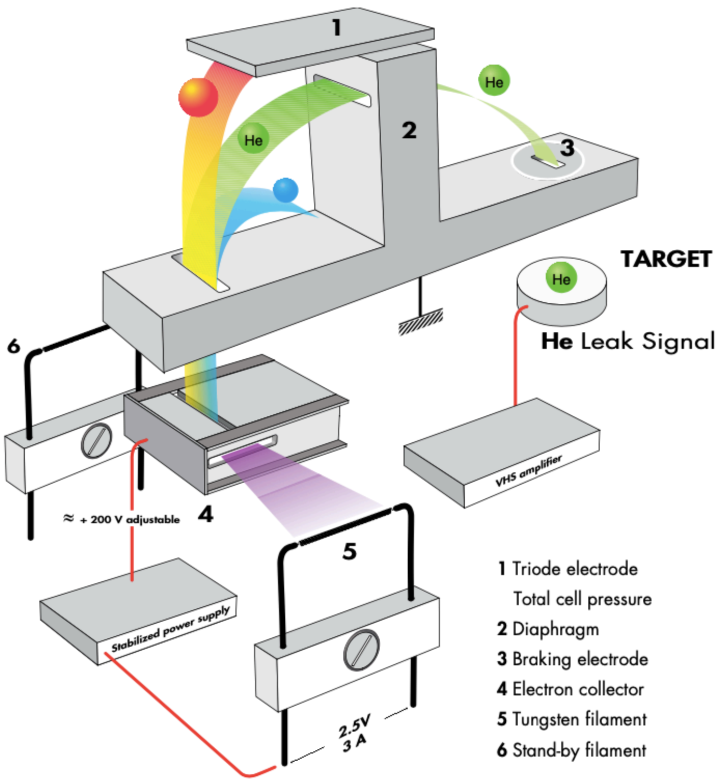
Helium Leak Detection
Principle of Operation



- Helium is present inside a closed system (container)
  - Numerous approaches to sample prep
- Helium escapes
- Collected by vacuum source
  - Sniffer probe or instrument inlet port
- Gases passed through spectrometer analyzer cell and quantified

Helium Mass Spectrometry
Analyzer Cell Basics

- Gas molecules flow into an ionization chamber
- Tungsten filament electron beam ionizes molecules
- Ions travel according to an electrical field, and magnetic field causes deflection relative to mass/charge
- The analyzer cell is tuned for the mass/charge of helium
- Stream of ions hitting the target is reported as leak rate



Helium Leak Detection Methods

- Numerous options
  - Sniffer mode
  - Vacuum mode
    - Fill pre-sealing
    - Fill post-sealing
    - Continuous Flush
- In our industry, typically run according to ASTM F2391 (05)

Helium Leak Detection in the Sniffer Mode

Procedure, advantages, limitations.

Helium Leak Detection
Procedure A - Sniffer

- Sample Prep
  - Fill prior to sealing
  - Puncture to fill
- Sniffer probe, connected to HeLD, vacuum pulled on the tip
- Place tip near area of interest
- Scan area of interest at ~1/8in (3mm) per second
- Results recorded real-time
- Increase in observed HeLR indicative of leakage

Helium Leak Detection
Procedure A - Sniffer

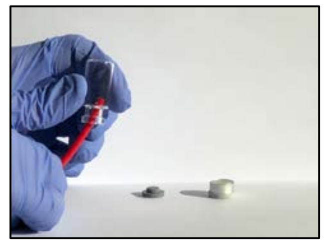
- Advantages
  - Location-specific leak testing
  - Test packages not conducive to fixturing / chambering
- Limitations
  - Considered probabilistic
  - Semi-quantitative
    - Leakage reported, but typically qualitatively interpreted

Helium Leak Detection in the Vacuum Mode

Procedure, advantages, limitations, and case studies.

Helium Leak Detection
Procedure B – Vacuum Mode

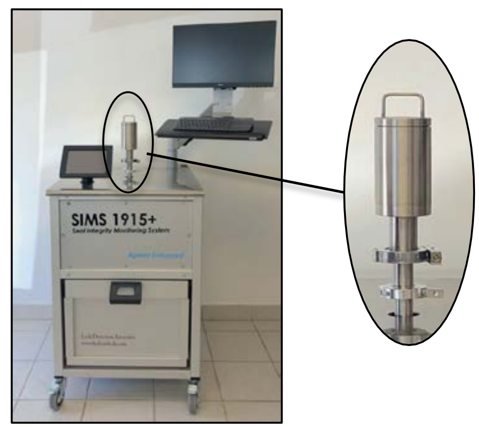
- Sample Prep
  - **Fill prior to sealing**
  - Fill post-sealing
  - Continuous Fill
- Test Sequence:
  - Filled sample placed in chamber
  - Vacuum pulled, leak rate obtained
  - Helium concentration measured, result corrected



Fill

Stopper

Crimp

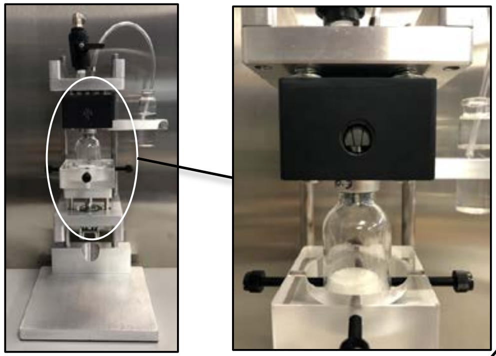


LDA SIMS 1915+ Vial

LDA Headspace Analyzing Module (HSAM)

Helium Leak Detection
Procedure B – Vacuum Mode

- Sample Prep
  - Fill prior to sealing
  - **Fill post-sealing**
  - Continuous Fill
- Test Sequence:
  - Filled sample placed in chamber
  - Vacuum pulled, leak rate obtained
  - Helium concentration measured, result corrected



LDA Vial Filler

LDA SIMS 1915+

Vial Chamber

Helium Leak Detection
Procedure B – Vacuum Mode

- Sample Prep
  - Fill prior to sealing
  - Fill post-sealing
  - **Continuous Fill**
- Test Sequence:
  - Sample fixtured in place
  - Vacuum pulled
  - Baseline taken, 100% helium introduced
  - Helium leak rate recorded without adjustment

Sample

100% Helium Fill

Case #1 – Vial Capping Optimization

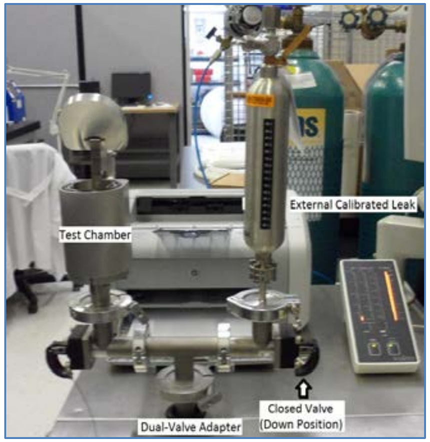
In support of package development & package integrity profile.

Capping Optimization

- Lifecycle approach to CCI
  - Contributes to package integrity profile
- Package / Process Development
  - Aid in component selection
  - Establish dimensional specifications
  - Establish manufacturing requirements
  - Demonstrate inherent integrity to MALL
  - Inform in-process seal quality tests

Vial Capping

RSF



HeLD

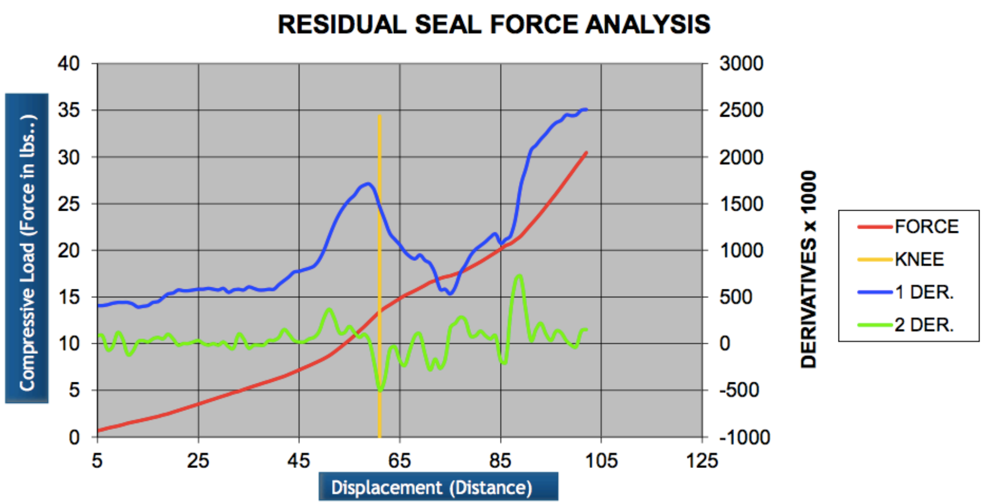
Capping Optimization

- Incorporates
  - Dimensional Variation
  - Capping Settings
  - Compression Analysis
  - Residual Seal Force (RSF)
  - Leak Detection (HeLD)
- Yields:
  - Quantitative data
  - Correlation between capping, compression, RSF, and leakage
  - Provides feedback or confirmation of the assembly process

Example 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

RSF



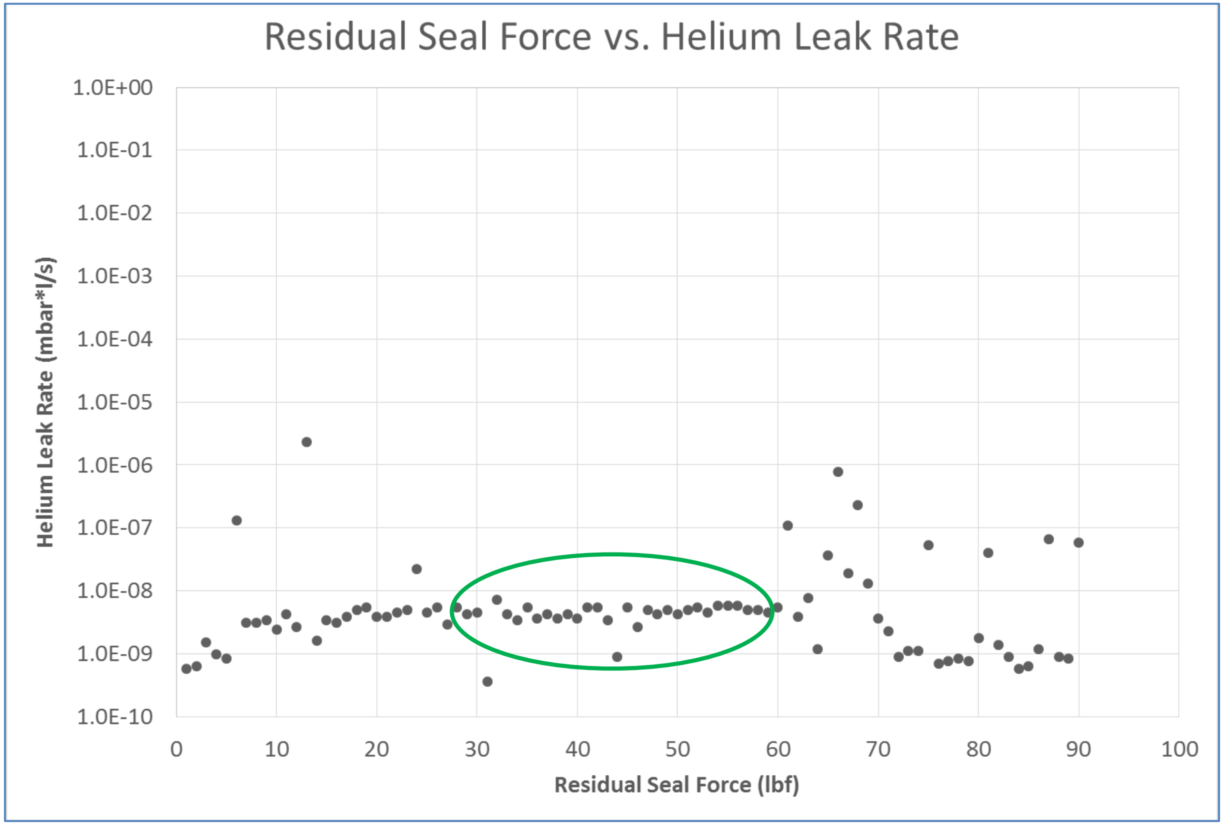
The compression curve (red) is a combination of the viscous and elastic responses to the stress from tester load. "The knee"(yellow) is where additional deformation occurs. An algorithm is applied, using the 1st (blue) and 2nd (green) derivatives to accurately identify that knee.

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



RSF can now be checked during manufacturing

Case #2 – Cartridge Package Development

Component selection, dimensional specifications, and processing.

Introduction: Background

- In 2015, collaboration began on a new plunger for a parenteral cartridge package system with respect to CCIT
  - Goal: Improve technical properties and leachable profile of plunger thus expanding usability in future parenteral formulations/applications
- After selecting dimensions and elastomer formulation, one variable remained:
  - Smooth plunger surface vs roughened plunger surface

4

Connecting People, Science and Regulation®

M. Rasmussen, B. Zurawlow. The Effect of a Plunger Surface Roughening Treatment on CCI, PDA Europe Parenteral Packaging Conference, Barcelona, Spain, 15 March 2017

Introduction: Smooth vs Rough Plunger Surface

- Benefits offered by a roughened plunger surface:
  1. Increased aesthetic appeal vs smooth plunger
     - Perceived "softness" of the design
  2. Reduced plunger-to-plunger "stickiness"
     - Reduces instances of plungers stuck in hoppers
     - Decreases line shutdowns, increases production rate

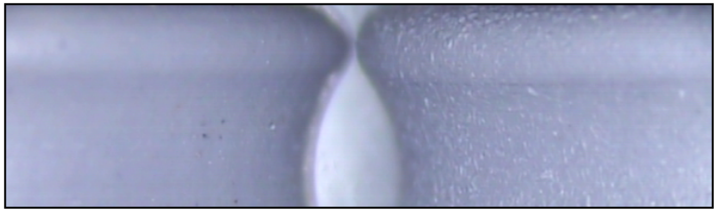


Figure 1. Smooth (left) vs. Rough (right) Plunger Surface

Note: Photo taken under video microscope, 23x

5

Connecting People, Science and Regulation®

M. Rasmussen, B. Zurawlow. The Effect of a Plunger Surface Roughening Treatment on CCI, PDA Europe Parenteral Packaging Conference, Barcelona, Spain, 15 March 2017

Method: Modified Approach

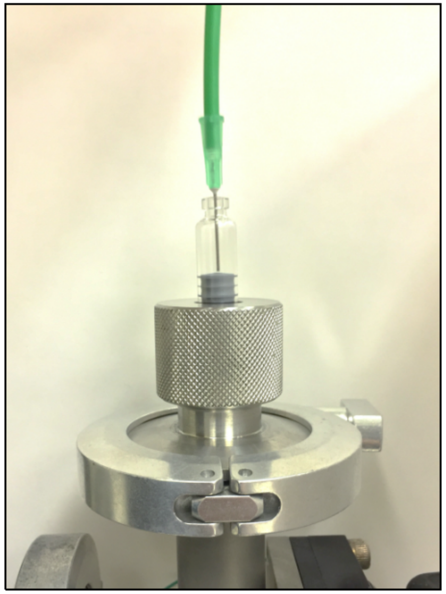


Figure 3. Example of Test Setup

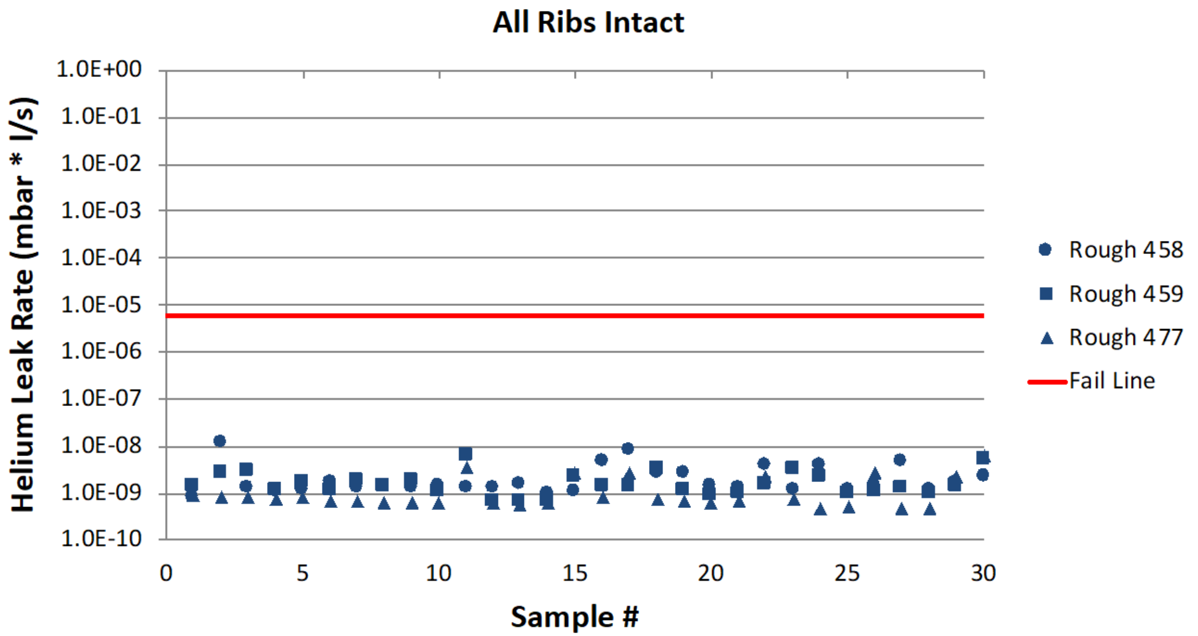
- For each sample, the following procedure was followed:
  1. Pull vacuum (1 atm differential)
  2. Take baseline reading
  3. Flood cartridge with 100% Helium
  4. Take final Helium Leak Rate (HeLR) 30 seconds post-introduction

9

Connecting People, Science and Regulation®

M. Rasmussen, B. Zurawlow. The Effect of a Plunger Surface Roughening Treatment on CCI, PDA Europe Parenteral Packaging Conference, Barcelona, Spain, 15 March 2017

Results: Post-Treatment Sample Sets



What about a closer look? 11

Connecting People, Science and Regulation®

M. Rasmussen, B. Zurawlow. The Effect of a Plunger Surface Roughening Treatment on CCI, PDA Europe Parenteral Packaging Conference, Barcelona, Spain, 15 March 2017

Method: Sample Sets

Ribs to Be Tested
Fully Intact (All Ribs)
Top Rib Only
Top and Middle Rib
Middle Rib Only
Middle and Bottom Rib
Bottom Rib Only

Figure 4. Sample Configurations

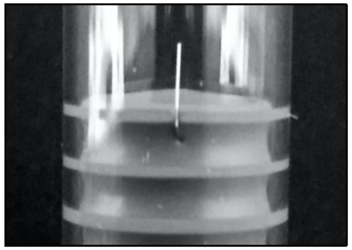


Figure 5. Example of Middle and Bottom Rib Test Sample

- Desire to assess rib by rib
  - Adjacent configurations were evaluated
  - 120µm acupuncture needles were used to isolate ribs
  - Limited smooth samples available
- Relevance:
  - Define sterile barrier
  - Risk of liquid between ribs
  - Risk of plunger movement

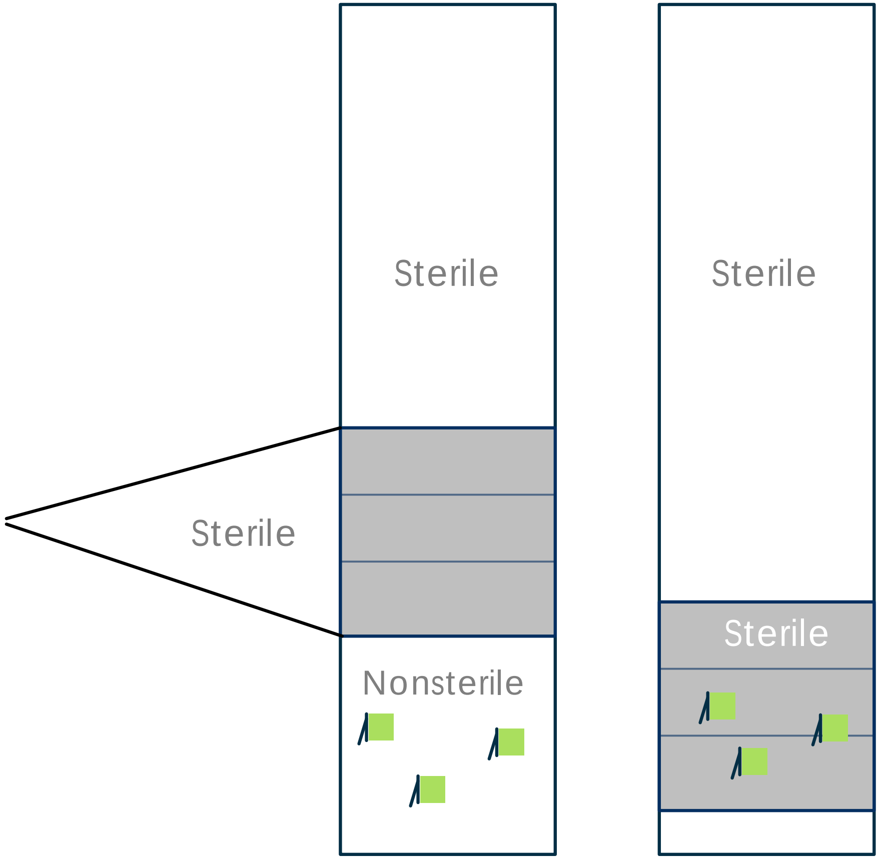
12

Connecting People, Science and Regulation®

M. Rasmussen, B. Zurawlow. The Effect of a Plunger Surface Roughening Treatment on CCI, PDA Europe Parenteral Packaging Conference, Barcelona, Spain, 15 March 2017

Plunger Movement

The integrity of these two seals create a "sterile window".



Thus, plunger movement within this "window" is at low risk for microbial contamination.

Results: Summary

Rib Configuration	Surface Type	Average HeLR (mbar*l/s)	Minimum HeLR (mbar*l/s)	Maximum HeLR (mbar*l/s)
All	Rough	1.9×10^{-9}	4.8×10^{-10}	1.2×10^{-8}
Top	Smooth	2.2×10^{-9}	3.6×10^{-10}	3.6×10^{-9}
	Rough	8.1×10^{-9}	2.7×10^{-10}	2.0×10^{-7}
Top and Middle	Smooth	5.6×10^{-10}	3.6×10^{-10}	1.3×10^{-9}
	Rough	2.3×10^{-6}	1.5×10^{-10}	1.9×10^{-4}
Middle	Smooth	1.2×10^{-8}	3.3×10^{-10}	1.9×10^{-8}
	Rough	8.4×10^{-5}	2.7×10^{-10}	2.0×10^{-3}
Middle and Bottom	Smooth	8.4×10^{-10}	3.6×10^{-10}	1.9×10^{-9}
	Rough	2.5×10^{-9}	1.7×10^{-10}	8.3×10^{-8}
Bottom	Rough	1.3×10^{-9}	3.3×10^{-10}	1.0×10^{-8}

18

Connecting People, Science and Regulation®

M. Rasmussen, B. Zurawlow. The Effect of a Plunger Surface Roughening Treatment on CCI, PDA Europe Parenteral Packaging Conference, Barcelona, Spain, 15 March 2017

Conclusions

Helium Leak Detection Conclusions

- Helium is a reliable, sensitive test
  - Capable of analyzing to MALL of most all products
- Application is extremely flexible based on:
  - Sample prep approach
  - Fixturing / chambering approach
- Powerful tool for package development, inherent integrity, and development of package integrity profile
  - Sensitivity allows for comparison of slight changes, such as component design
  - Flexibility allows for targeting of specific seal areas