APOTEX
Canadian-Based
Global Health Company

Plunger Movement Assessment for Prefilled Syringes: Ensuring Sterility Assurance and Container Closure Integrity

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FDA RRAs Approval Readiness

Agenda

- ❑Sterility Assurance & Container Closure Integrity Overview
- ❑Transportation Challenges for PFS
- ❑Impact of Altitude on Plunger Stopper Movement
- ❑ISO 11040-8:2026 Updates and guidance Expectations
- ❑Sterile barrier zone and theoretical assessment
- ❑Challenge Studies: Microbial and Dye Ingress
- ❑Development consideration for Plunger movement studies

Sterility assurance is a continuous lifecycle framework

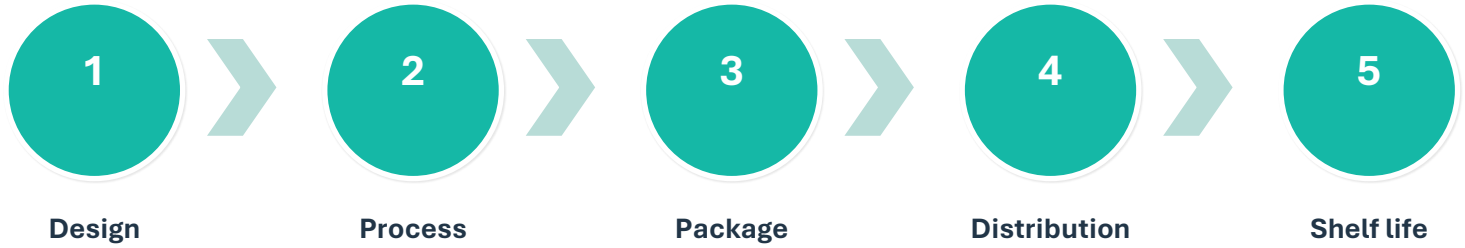
End-product testing provides evidence. It does not create sterility.

STERILITY IS BUILT INTO THE PROCESS, NOT TESTED INTO THE PRODUCT

Assurance comes from an integrated control strategy spanning design, manufacture, packaging, storage and transportation.

Scientific + engineering + microbiological + process controls

Controls must remain effective across the full product lifecycle



TRADITIONAL / PROBABILISTIC

- ❑Destructive
- ❑AQL based testing
- ❑Poor sensitivity, false negative

Dye ingress, microbial challenge etc.

MODERN / DETERMINISTIC

- ❑ Often non-destructive
- ❑ 100% batch assurance
- ❑Highly sensitive

Vacuum/pressure decay, helium leak, mass extraction, HLVD etc.

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Overview of Deterministic CCI Methodologies (USP <1207>)

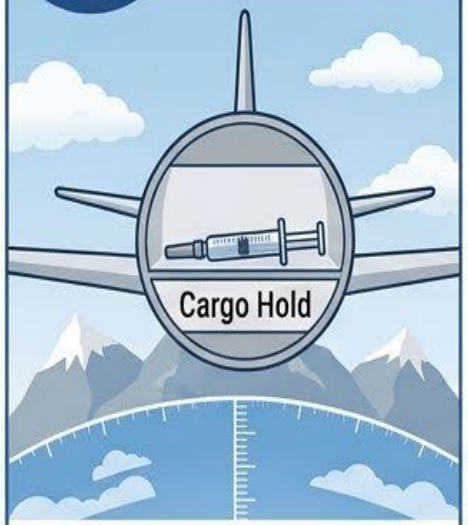
USP <1207> Method	Core Physics & Mechanism	Leak detection*	Primary Constraints
High Voltage Leak Detection (HVLD)	Measures changes in electrical current and conductivity across a non-conductive package when a conductive liquid product bridges a leak path.	~2–5 µm (USP Row 3)	Requires electrically conductive liquid product; not suitable for non-conductive formulations (e.g., oils); package material must be electrically resistive.
Vacuum Decay	Measures pressure rise in an evacuated test chamber caused by gas escaping from a leaking container.	~5–10 µm (USP Row 3)	Sensitivity may be affected by product blocking the leak path; requires stable temperature and appropriate chamber design.
Headspace Gas Analysis (HSA/TDLAS)	Uses Tunable Diode Laser Absorption Spectroscopy to monitor oxygen, moisture, CO_2, or pressure changes within package headspace.	~1–2 µm (USP Row 1)	Requires gas headspace; package must be transparent or semi-transparent to laser wavelength; less suitable for completely filled systems.
Helium Leak Detection (Tracer Gas)	Uses mass spectrometry to quantify helium escaping from a pressurized container through a leak path.	~0.1–1 µm (USP Row 1)	Requires helium filling or charging; specialized instrumentation; typically used during development rather than routine production testing.
Mass Extraction	Measures gas or vapor mass flow extracted from a container under deep vacuum conditions.	~2–5 µm (USP Row 3)	Product characteristics may affect performance; flexible packages often require support fixtures; method setup can be complex.
Pressure Decay	Measures loss of pressure from a pressurized package over time.	~10–20 µm (USP Row 3)	Less sensitive than vacuum decay; requires access to gas space; temperature fluctuations can impact results.

* **Note:** Leak-size values are industry-accepted approximate sensitivities and can vary significantly depending on package design, defect geometry, product properties, and method validation. USP <1207> officially classifies technologies using relative sensitivity categories (Row 1–Row 4) rather than assigning fixed defect sizes.

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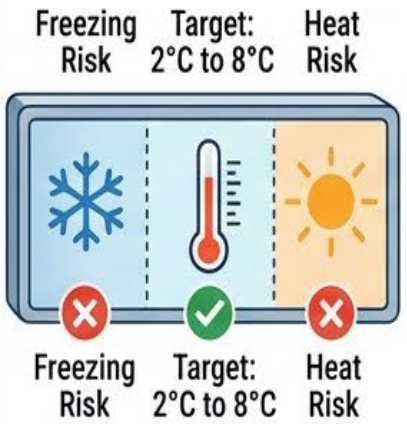
Challenges in Transportation

High-Altitude



Reduced ambient pressure

Temp. Excursions



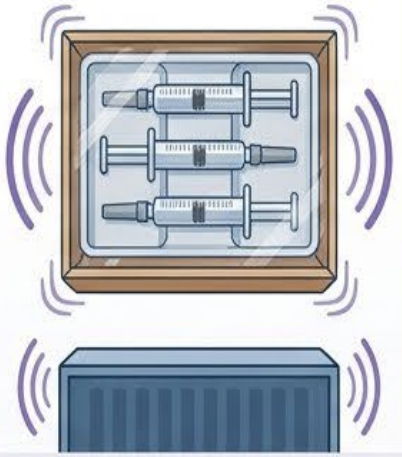
Cold and heat exposure

Shock & Impact



Drops and handling impacts

Vibration & Resonance



Repeated motion during transit

Intermodal Handling



Air, road, and sea transfers

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Prefilled Syringes (PFS): In-Transit Vulnerabilities

⚠ **CRITICAL RISK:** Low High-Altitude Pressure Causes Air Bubble Expansion, Potential Plunger Movement, and Sterility Risks.



ASCENT





STEP 1: AT GROUND LEVEL
(Normal Pressure - ~101 kPa)

The air bubble is compressed at normal atmospheric pressure. Plunger and stopper are in original positions.

STEP 2: HIGH ALTITUDE CONDITIONS
(Reduced Pressure)

A large enough air bubble can expand at high altitude due to low pressure, causing the plunger to move outwards, leading to potential risks.

STEP 3: POTENTIAL PLUNGER MOVEMENT
(Dislodged Stopper Risk)

The significant air bubble expansion drives the plunger/stopper outward. Risk of dislodged stopper, leakage, or loss of sterility.

POTENTIAL MOVEMENT

POTENTIAL MOVEMENT

Transit Exposure Scenarios	SCENARIO A	SCENARIO B	SCENARIO C
	A: CARGO JETS ~8,000 ft (2,438 m) @ 20-23°C (68-74°F)	**B: GROUND ALTITUDE (MAX PASS)** ~12,000 ft (3,658 m)	**C: NON-PRESSURIZED FEEDER AIRCRAFT** 13,000 ft to 16,000 ft (3,962 m to 4,877 m)





ISO 11040-8 updates: Key Revisions from 2016 to 2026

Previous 2016 guidance

- ❑ Container closure integrity should be maintained during transportation (considering differential external air pressure) to ensure content sterility and to prevent leakage.

Updated 2026 guidance

New Requirement

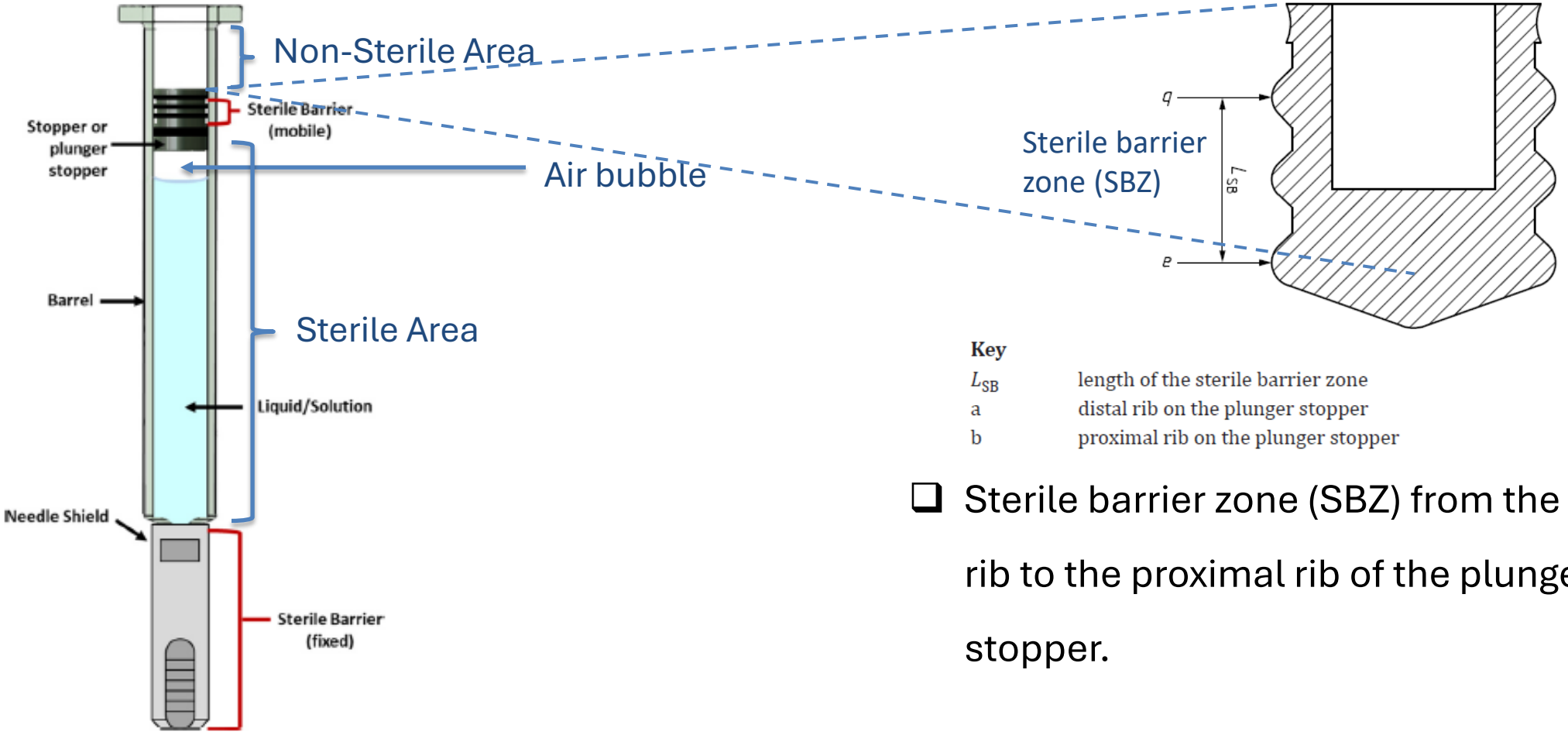
- ❑ Evaluation of unintended plunger stopper movement (PSM) in finished PFS:

1. **Measurement of maximum plunger stopper displacement**
2. **High-altitude simulation** per ASTM D6653/D6653M
3. **Verification** that movement remains within the sterile barrier region
4. **Follow-up confirmation** of applicable CQAs (like CCI, sterility, and other product quality attributes)

1. ISO 11040-8:2016. *Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes*. International Organization for Standardization (ISO), Geneva, Switzerland, 2016.
2. ISO 11040-8:2026. *Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes*. International Organization for Standardization (ISO), Geneva, Switzerland, 2026.

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Sterile barrier zone (SBZ)



Key

L_{SB}	length of the sterile barrier zone
a	distal rib on the plunger stopper
b	proximal rib on the plunger stopper

- Sterile barrier zone (SBZ) from the distal rib to the proximal rib of the plunger stopper.

1. ASTM International D6653/D6653M-13, Standard Test Methods for Determining the Effects of High Altitude on Packaging Systems by Vacuum Method.
2. Evans, C. M., Oni, Y., Paniagua, D., Franck, J., Dahlheim, C., & Kulshrestha, A. (2023). Stopper movement and headspace (air bubble size) limitations for 2.25mL prefilled syringe. PDA Journal of Pharmaceutical Science and Technology, 77(6), 472–484.

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Theoretical Assessment : Boyle's Law

- Equation to determine change plunger stopper height:

$$h_2 = \frac{P_1 h_1 T_2}{p_2 T_1}$$

h_2= gaseous headspace at higher altitude

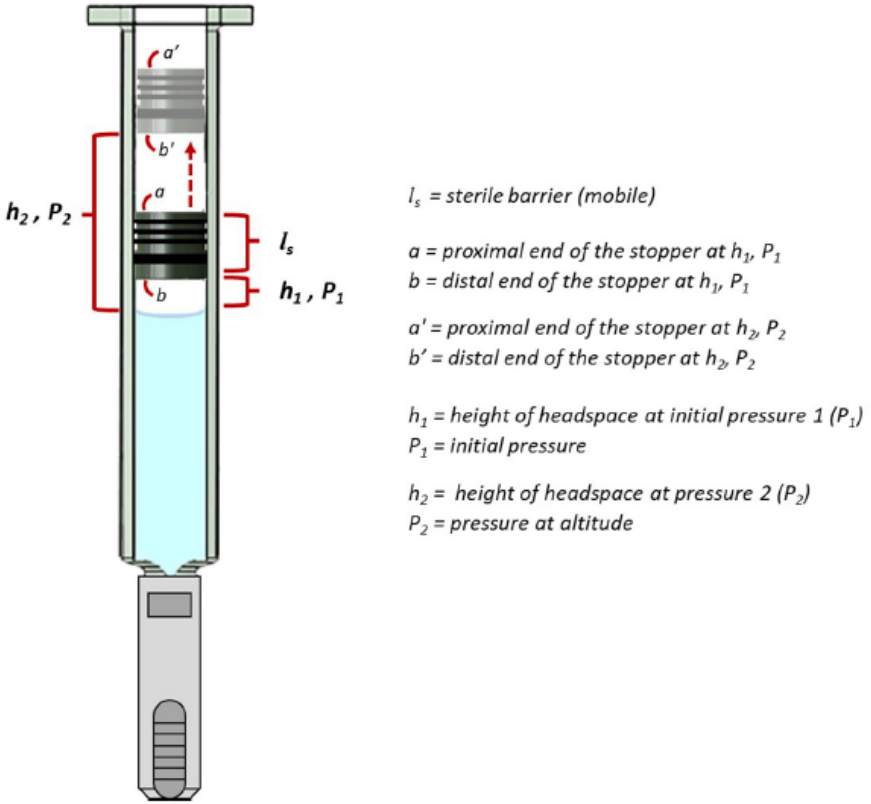
P_1= atmospheric pressure (1 atm or 14.7 psi)

h_1= gaseous headspace at atmospheric pressure

T_2= temperature at higher altitude

P_2=pressure at higher altitude (0.743 atm/10.92 PSI to 0.542/7.96 PSI)

T_1= atmospheric temperature



Parameters (With constant temperature)	At atmospheric pressure	8000 ft	12000ft	16000 ft
Atmospheric pressure	14.7 PSI (P_1)	10.92 PSI (P_2)	9.34 PSI (P_2)	7.96 PSI (P_2)
Gaseous headspace	4 mm (h_1)	5.38 mm (h_2)	6.29 mm (h_2)	7.38 mm (h_2)
Increase in height	-	1.38 mm	2.29 mm	3.38 mm
Sterile barrier zone	-	3.0 mm		

Evans, C. M., Oni, Y., Paniagua, D., Franck, J., Dahlheim, C., & Kulshrestha, A. (2023). Stopper movement and headspace (air bubble size) limitations for 2.25mL prefilled syringe. PDA Journal of Pharmaceutical Science and Technology, 77(6), 472–484.

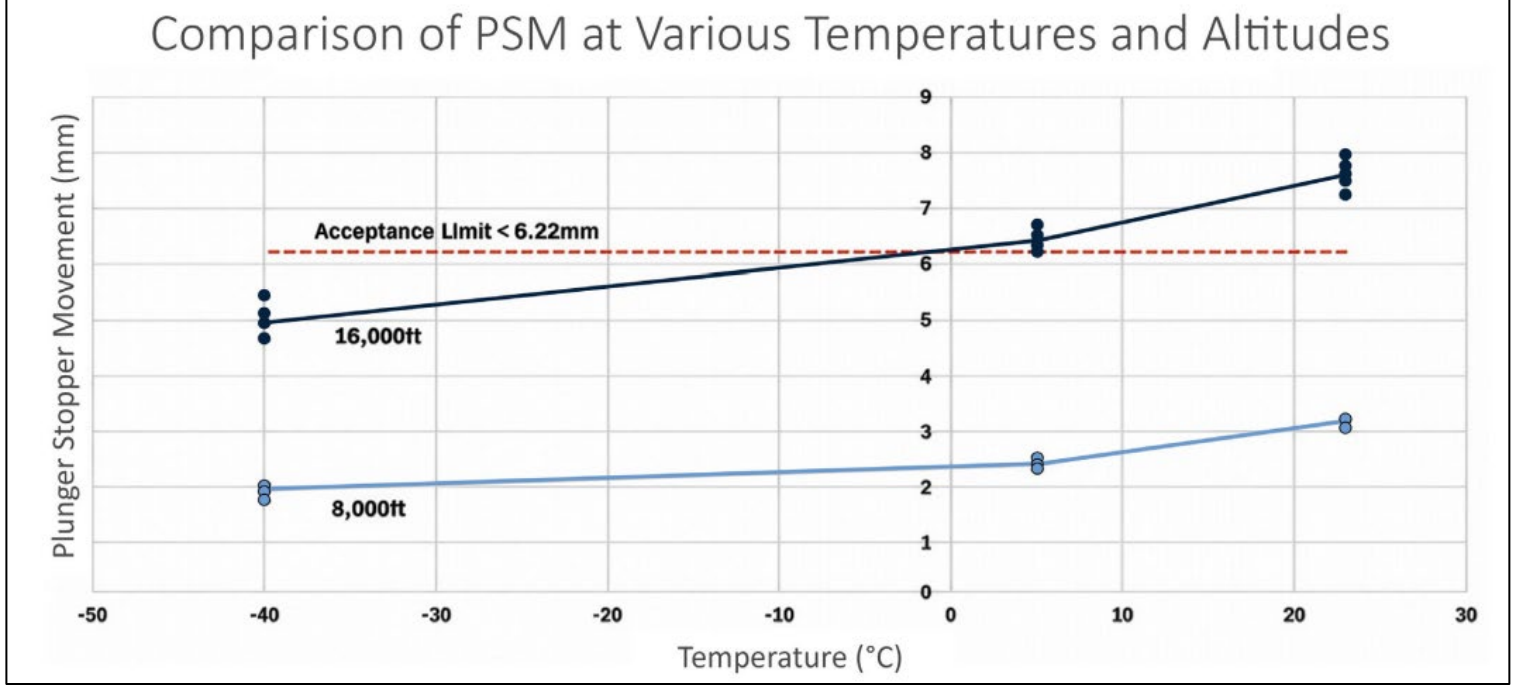
Impact of temperature and altitudes on plunger movement

Study Overview

Samples were exposed to simulated altitudes of 8,000 ft (typical pressurised cargo aircraft conditions) and 16,000 ft (non-pressurised aircraft conditions)

Temperature conditions:
- Ambient (23 ±5 °C)
- Cool (5 ±3 °C)
- Cold (-40 °C)

Each sample was exposed to vacuum conditions for 1 hour, and plunger stopper movement was measured before and after exposure.



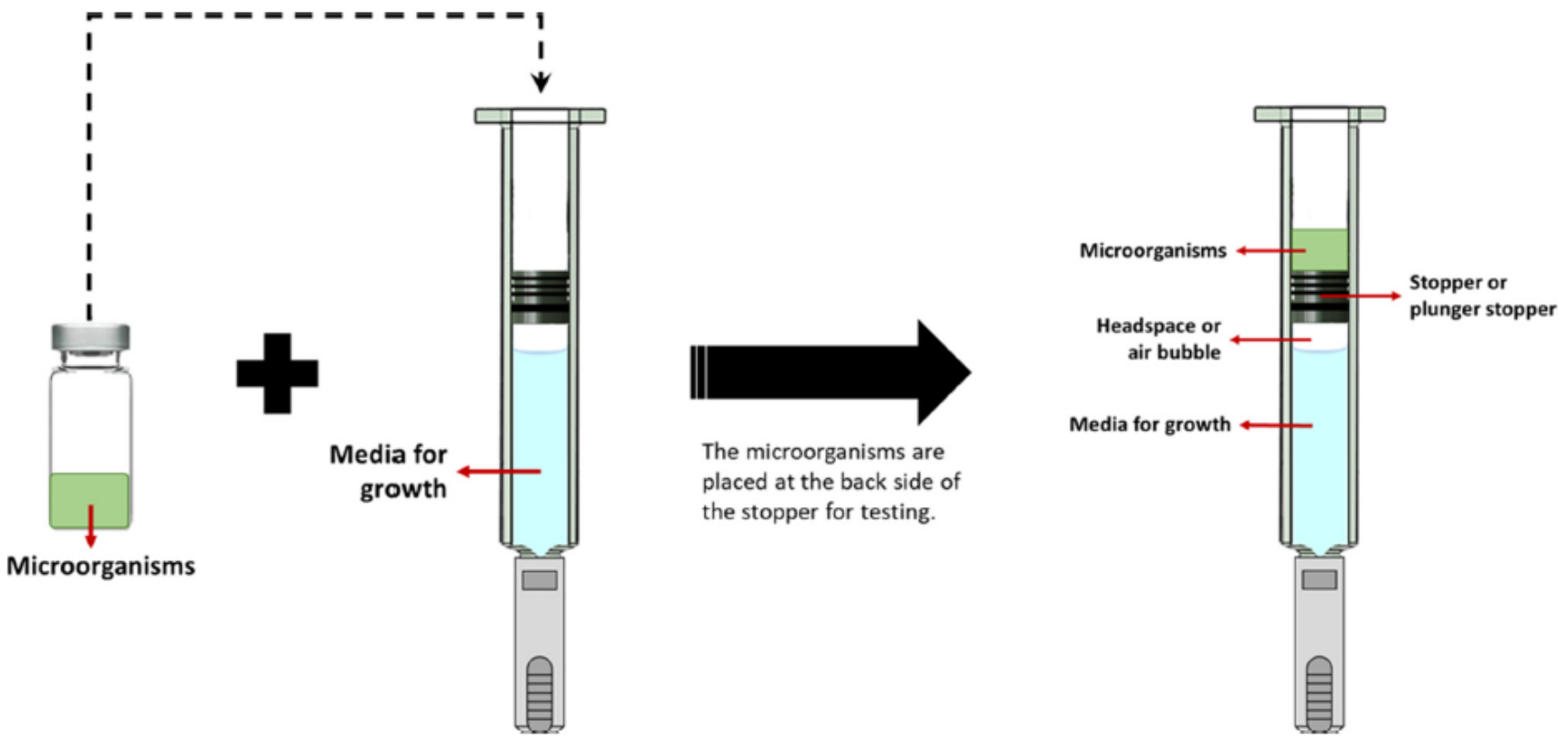
Key findings:

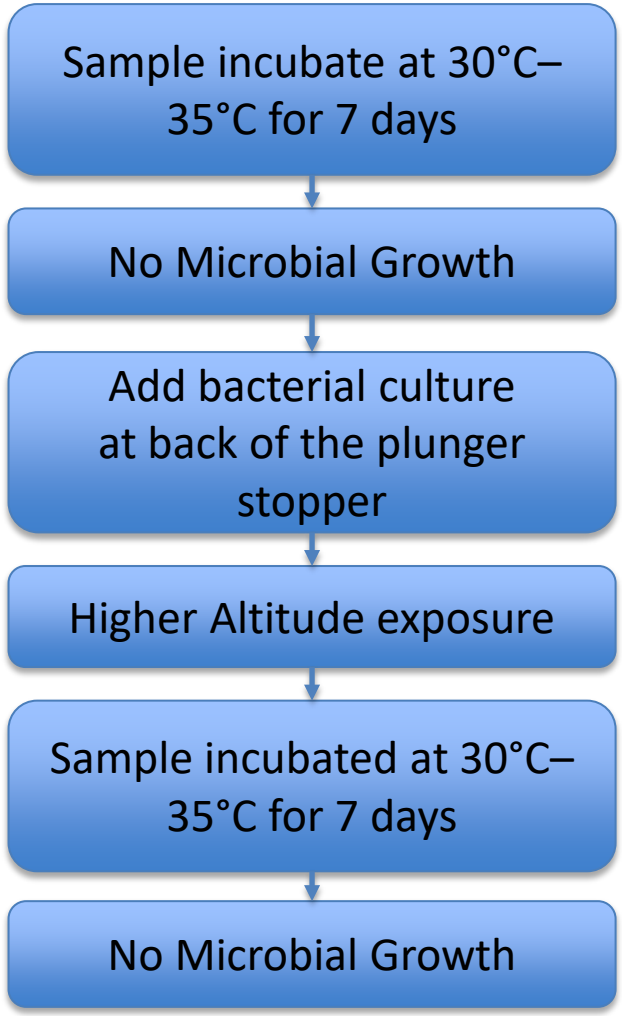
- ❑ Plunger movement increased substantially at higher simulated altitudes.
- ❑ Lower temperatures reduce plunger movement
- ❑ Temperature does not fully offset pressure effects.

Smithers. *Variable Temperature Plunger Stopper Movement Testing for Prefilled Syringes*. Smithers White Paper, April 2026.
Reference link: https://www.smithers.com/resources/2026/april/variable-temperature-plunger-stopper-movement-test

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Challenge study-Microbial or Dye Ingress





- ❑ Same methodology can be applied for Dye Ingress Testing

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Alternative Strategies to restrict plunger movement

1 Vacuum Stoppering
Minimize or eliminate air headspace



Fill under vacuum to remove or reduce headspace volume.

2 Blister Pack and Terminal Surface Sterilize using VHP
Restrict travel and maintain sterility



Physical pocket limits plunger travel; packaging surfaces are decontaminated using VHP.

3 Backstop in PFS
Provide a mechanical stop



Hard mechanical block prevents plunger displacement, even under pressure changes.

Pressure Control (Vacuum Stoppering) + **Travel Restriction** (VHP Sterilized Blister) + **Mechanical Restraint** (Backstop)

Sterility Assurance Maintained
Protects product quality and patient safety

Development Pathway

