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# Stopper Movement and Headspace (Air Bubble Size) Limitations for 2.25 mL Prefilled Syringe

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**Abstract:**

The Sterile Barrier is one of the most important aspects of the Container Closure Integrity (CCI) for a prefilled syringe (PFS or syringe). This crucial barrier enables the protection of the syringe contents from contamination. The plunger stopper (stopper) is naturally in a stationary position that is controlled by the static friction between the plunger stopper and the syringe barrel wall. When an applied force is greater than the static friction which is commonly known as the Break Loose force, the plunger stopper will move. In such conditions, the stopper movement can further be increased if an air bubble is introduced between the liquid fill in the syringe and the stopper during the stoppering process. This additional movement can occur when the pressure differential between the gaseous headspace inside the syringe and the external atmosphere is large enough that the force exerted on the stopper exceeds the Break Loose force of the syringe. This can occur during altitude or temperature changes incurred during aerial or mountainous transport.

This paper, therefore, discusses the relationship between stopper movement and initial headspace (air bubble size/ABS/AB) in a 2.25mL Type I glass syringe using theoretical and empirical approaches. The results showed the maximum initial headspace needed to enable CCI at specified altitudes and plunger stopper movements for the syringe-plunger stopper combination used in the study. Empirical data also indicated that CCI can be maintained for this syringe-plunger stopper combination with up to 9.0mm initial headspace at altitudes up to 17,000 feet.

**Keywords:**

2.25ML PFS; CCI; Container Closure Integrity; PFS; Prefilled Syringe; Sterile Barrier

## 1 INTRODUCTION:

Prefillable syringes (PFS) are a common packaging system for parenteral pharmaceutical products [1]. A PFS system typically consists of a glass syringe barrel with a staked stainless steel cannula, adhesive to fix the cannula in place, an elastomeric plunger stopper, a needle shield, silicone oil lubricant to ensure syringe functionality, and a plunger rod [2]. The needle shield and plunger stopper comprise the non-rigid components which establish the sterile barrier between the syringe contents and the external environment [2]. Figure 1 illustrates the components and terminologies of a typical Prefilled Syringe.

The plunger stopper is designed to move relatively freely in order to minimize the forces required to expel the syringe contents [3]. Often the syringe contents include a liquid solution and a gaseous headspace [3]. The interior of the syringe barrel between the plunger stopper and needle shield is sterile while the interior of the syringe barrel above the plunger stopper is not sterile [4].

The plunger stopper ribs are designed to act as the sterile barrier [4]. Depending on the plunger stopper design, the height of the sterile barrier could vary; ranging from the distance between the furthermost ribs to the overall length of the plunger stopper itself [5]. If the plunger stopper were to travel outward along the syringe barrel a distance greater than the sterile barrier height, a non-sterile portion of the barrel wall would become exposed to the sterile side of the plunger stopper; potentially contaminating the syringe contents [4].

The plunger stopper is normally held in a stationary position by the static friction between the plunger stopper and the syringe barrel wall [6]. A plunger stopper movement results when an applied force is greater than this static friction; otherwise referred to as the Break-Loose force [2]. This plunger stopper movement is normally caused by the user depressing the plunger rod, but it can be unintentionally induced if the pressure differential between the gaseous headspace inside

the syringe and the external atmosphere is sufficiently large such that the force exerted on the plunger stopper exceeds the Break-Loose force of the PFS [7]. Such a differential in gas pressure can occur during altitude and/or temperature changes incurred during aerial or mountainous transport. Plunger stoppers may also move during manufacturing when they are moved from room temperature during filling/stoppering to refrigerated storage.

Today, as biologics become increasingly more complex, the need for technologies to enable their efficient delivery is as essential as ever [5]. These deliveries usually require these large molecules to be injected which implies an increase in injection volume and/or an increase in the drug concentration [5]. As a result, high volume and high viscosity considerations represent two of the principal challenges that must be overcome with new delivery strategies [5]. These require syringes or devices larger than the traditional 1.0mL size. The 2.25mL syringe is one of such potential options.

This paper discusses the associated theoretical principles for plunger stopper movement during simulated altitude excursions for 2.25mL syringes.

## 2 THEORY:

The enclosed headspace within the syringe barrel can be thought of as a balloon, or more precisely, as a pneumatic cylinder. As the external pressure changes, the headspace inside the syringe will attempt to expand or contract accordingly [8]. If the pressure differential between the external environment and the headspace is large enough to overcome the static friction between the syringe barrel wall and the plunger stopper, the plunger stopper will move in order to re-establish the pressure equilibrium between the interior and exterior of the syringe [2]. Since atmospheric pressure is a function of altitude, transport of syringes involving large changes in altitude can induce plunger stopper movements which can pose a sterility risk in situations where

the movements are greater than the height of the sterile barrier afforded by the plunger stopper [7].

The Ideal Gas Law describes the relation between the pressure (p), temperature (T) and volume (V) of the gas [9]. This is given below:

$$pV = nRT \tag{1}$$

$$where\ n = is\ number\ of\ moles, R = is\ the\ Universal\ Gas\ Constant$$

Since the amount of gas is kept constant, the function becomes a constant:

$$\frac{\boldsymbol{P_1 V_1}}{\boldsymbol{T_1}} = \frac{\boldsymbol{P_2 V_2}}{\boldsymbol{T_2}} \tag{2}$$

where: 1 and 2 denote the initial and final states of the system respectively.

$$\frac{\boldsymbol{P_1(A * h_1)}}{\boldsymbol{T_1}} = \frac{\boldsymbol{P_2(A * h_2)}}{\boldsymbol{T_2}} \tag{2.1}$$

For a PFS filled at sea-level altitude, the pressure in the headspace of the syringe would be approximately 1.0 atmosphere or ~14.7psia [10]. As altitude increases, atmospheric pressure decreases [11]. This is likely to occur during shipment on an airplane or land transport across mountains, resulting in a differential pressure across the plunger stopper.

Boyle's Law−which states that the pressure of a gas varies directly with the volume at constant temperature−would describe the expansion of the enclosed headspace in the PFS as the plunger stopper moves in order to equilibrate the internal and external pressures [11], and derives from the Ideal Gas Law at constant temperature and amount of substance. In a real-world PFS, where friction is present, plunger stopper movement occurs only when the Break-Loose force (differential pressure between the syringe interior and exterior) is exceeded and Glide force, or

the sustaining force, is the force required to maintain the plunger stopper movement once static friction has been overcome [2].

Since the volumetric expansion inside the PFS barrel is limited to one axis (along the barrel length), Equation (2.1) becomes:

$$\frac{P_1 h_1}{T_1} = \frac{P_2 h_2}{T_2} \tag{3}$$

*where h=height of the enclosed gaseous headspace, A=barrel interior cross-sectional area, P=pressure, and T=temperature*

## 2.1 Sterile Barrier of the Plunger Stopper:

The plunger stoppering process usually introduces a headspace between the liquid fill in the syringe and the plunger stopper [10]. The volume of this bubble proportionally increases the risk of the plunger stopper moving in the syringe into a non-sterile area during shipping due to pressure variations [10].

The redundant rib design of plunger stoppers allows the plunger stopper to move a maximum distance between the first and last rib [12]. In the case of the plunger stoppers used in these studies for example, the minimum distance is approximately 2.2mm from rib 1 to rib 3 (Figure 2). This minimum tolerance is a worst case as it does not consider:

1. the plunger stopper compression in the barrel which increases the plunger stopper height;
2. the rib thickness when compressed within the syringe barrel;
3. that the sterile barrier can be larger than the ribs.

In the absence of any defect or contamination that might otherwise impact the plunger stopper's integrity, the multiple ribs individually represent a minimum sterile barrier protecting the subsequent rib [4].

In the least conservative scenario for CCI to be maintained, the plunger stopper movement should not be more than the plunger stopper length in its unstressed or relaxed state ($l_s$) in the syringe [4]. In other words, any point between a or b (shown in Figure 3) on the plunger stopper should not be displaced more than the plunger stopper length.

Mathematically,

$$\boldsymbol{h_2 - h_1 \leq l_s} \tag{4}$$

In the conservative limits, $l_s$ should be minimized. Solving Equation (3) for $h_2$ and substituting into Equation (4),

$$\boldsymbol{h_1 \leq \left(\frac{P_2 T_1}{P_1 T_2 - P_2 T_1}\right) l_{s,min}} \tag{5}$$

Thus, for the case of this plunger stopper used in this study, $l_{s,\,min}$ is the length of the stopper (7.3mm) for the least conservative, while the most conservative $l_{s,\,min}$ is the distance between ribs 1 and 3 (2.2mm).

If there is no temperature excursion such that the syringe is stored at the same temperature at initial storage and at altitude, Equation (5) becomes:

$$\boldsymbol{h_1 \leq \frac{P_2 l_{s,min}}{P_1 - P_2}} \tag{6}$$

This equation can be used to generate the relationship between the initial headspace and the minimum plunger stopper measurement to maintain CCI. For example, using the Barometric formula, at an altitude of 12,000 feet and an estimated environmental pressure of 14.7 psia [13, 14], Equation (6) becomes:

$$\boldsymbol{h_1 \leq 1.734 \cdot l_{s,min}} \tag{7}$$

The prediction from Equation (7) assumes zero friction after Break Loose force is exceeded and plunger stopper movement begins. Actual Glide force will reduce the distance the plunger stopper travels as the force on the plunger stopper is proportional to the pressure differential minus the Glide force.

# 3 EXPERIMENTAL METHODOLOGY

The preceding analyses summarize the theoretical limits of the correlation between initial headspace and allowable plunger stopper movement in a typical glass prefilled syringe. The following will discuss the experimental work that supports the described theoretical exercise. This includes the dimensional measurements as shown in Figure 4.

## 3.1 Measurement System:

Measurement systems such as indicator powder, mechanical depth gauges, and/or image analysis systems can be combined with a vacuum chamber to determine the plunger stopper level in syringes at various altitudes. An unpublished internal assessment has explored these various methodologies. Subsequently a high-resolution image analysis system with various necessary hardware, i.e. a Lab Vision System (LVS), was developed and used in conjunction with powder indicators to measure plunger stopper locations/syringe dimensions. The LVS permits manual adjustment of the atmospheric pressure applied to the PFS system with high precision and has very precise measurements. When used without an indicator powder, the LVS system does not disturb the silicone oil layer of the syringe nor does the fill volume affect the measurement. An internal gauge R&R was also completed for this system.

### *3.1.1* Equipment:

#### *3.1.1.1* Lab Vision System With Associated Equipment:

- Pressure transducer−Omega model PXT41T0-015AI

- Yokogawa Digital Data Recorder−Model DX1006-1-4-2
- Glass Photolithograph Pattern−Checker board pattern, 2.20mm squares accurate to ± 2.4µm. Sourced from Opto-Engineering, distributed by Texas Industrial Optics Inc., 11261 Richmond Ave, Houston Tx 77082; catalog number PT064-096
- 30 psia air provided by in-house facilities or by a Gast diaphragm pump, model DOA-P14-AA
- Vacuum source provided by in-house facilities or by a Gast diaphragm pump

#### *3.1.1.2* Optical Comparator:

- Optical Comparator, Nikon, 1300065

### 3.2 Materials:

Components used in this study are shown in Table 1.

### 3.3 Methods:

Two different studies were conducted to assess the contributions of various factors on the sterile barrier of a syringe. The first study was to determine the inter-rib distances along the plunger stopper length. The length of the compressed plunger stopper (plunger stopper inside of the syringe barrel) was measured using the optical comparator. Figure 2 shows the schematic example of the plunger stopper ribs. Two lots of 2.25mL syringes were vent tube plunger stoppered with two lots of the 1-3mL plunger stopper according to Table 2. This study determined the compressed length of the plunger stopper, post-insertion into a syringe, and the effects of lot-to-lot variabilities.

In the second study, we explored the relation between initial headspace and plunger stopper movement over time. This provides an understanding of the time effects on Break-Loose and Glide forces which is relevant for potential device integration and CCI. Two syringe and two plunger stopper lots were used with a fill volume of 1.0mL of sterile water. Three different targeted headspace sizes (2.0mm-low, 3.5mm-medium, 5.0mm-high) were created using the vent tube plunger stoppering mechanism. Samples were divided into groups based on planned time-

point and storage conditions as shown in the Table 3. Samples were tested at temperature 2-8℃ by using the LVS inside a cold chamber. The simulated altitude was controlled by using the digital data recorder and vacuum equipment.

# 4 RESULTS AND DISCUSSION:

## 4.1 Plunger Stopper Length Results:

The results for the compressed plunger stopper length (in syringes) are shown in Figure 5. As expected, the plunger stoppers are elongated under radial compression in the syringe barrel. The average elongation is 8.4% compared to the nominal, uncompressed length. The results also indicate lot-to-lot variation between plunger stopper batches with measured elongations of 7.2% (for plunger stopper Lot 1) vs 9.5% (for plunger stopper Lot 2).

Furthermore, it was observed (as depicted in Figure 5) that plunger stopper lot was a primary factor for plunger stopper elongated lengths under compression. Syringe lot differences were shown to be of lesser influence.

## 4.2 Air Bubble and Plunger Stopper Movement Results:

### *4.2.1 Plunger Stopper Movement Characterization in Syringes induced by Simulated Altitude Excursions*

The plot of final headspace against the initial headspace for the 2.25mL syringes are presented in Figures 6-8.

The syringes were created with targeted headspaces of 2.0mm, 3.5mm, and 5mm. This resulted in a continuum of headspaces between 2.0mm and 5.0mm, (with ~±2.0mm tolerances).

The regression lines obtained from the graphs yielded a correlation greater than 99% with increasing slopes at increasing altitudes. This is because the atmospheric pressure reduces at higher altitudes thereby causing larger plunger stopper movement evidenced by the increasing

slopes. As stated before when the pressure differential between the external environment and the headspace is large enough to overcome the static friction between the plunger stopper and syringe barrel wall, the plunger stopper will move in order to regain pressure equilibrium.

In order to facilitate comparison of results, the regression line parameters are tabulated in Table 5. The regression lines obtained from the experiments are observed to be of lower slope than the theoretical line. This is expected because the theoretical line is an estimate of the plunger stopper movement in a frictionless system. In practice however, actual movements involve friction which increases the Glide force leading to lower observed plunger stopper movements. Moreover, it is possible to obtain deviations in these scenarios; especially if syringes are filled at a different temperature or atmospheric pressure from the conditions in which the simulated altitude experiments were performed. These temperature effects were observed throughout the internal assessments.

### *4.2.2 Time Effects:*

It is expected that the friction between the inner walls of the syringe barrel and the plunger stopper (and hence the Glide force) will increase over time because of fluid squeeze-out from the asperity contact regions. The Break Loose friction force will increase continuously with the time of stationary contact. This resulted in reduced plunger stopper movements compared to the initial time-point. [6] The slope of the plunger stopper movement versus initial headspace plot should also be expected to decrease over time and is reflected by the values of the Break-Loose and especially, the Glide forces. The plots of Figures 9-11 depict average Break-Loose and Gliding forces at varying temperatures, viscosities and time-points.

For development purposes, the plunger stopper movement at the initial time point, can be employed as the worst-case condition since the largest movements are expected at those early times.

## 5 IMPLICATIONS:

The implications of the preceding analysis are quite significant. First, they provide a fundamental theory on plunger stopper movements and corresponding headspace. Also, they show excellent correlation between the theoretical principles and empirical data. The following analysis describes the data of subsequent verification studies and resulting proposed headspace limits.

### 5.1 Plunger Stopper Movement Challenge Studies: Microbial Challenge & Dye Ingress at 12,000 feet:

Microbial Ingress and Dye Ingress studies were conducted to challenge the headspace initial size limit and by extension, the plunger stopper movement. 12,000 feet typically represents the maximum altitude where people are known to cohabit (LaPaz, Bolivia).

#### *5.1.1 Microbial Ingress Study:*

In this study, syringe samples were created with initial target headspace ranging from 7mm to 9mm and filled with approximately 1.5 mL of growth media under sterile conditions [14, 15]. The actual samples created have tolerances of up to ±2.0mm with measured initial headspace values distributed between 5.3mm and 8.8mm. The samples were incubated at $30 - 35℃$ for 7 days to ensure no bacterial growth and to confirm sterility prior to testing.

Next, 100µL of bacteria culture, *Brevundimonas diminuta,* was placed at the back of the plunger stopper as shown in Figure 12. This suspension contained $10^6 - 10^8\, CFU/mL$. Subsequently, the samples were subjected to a simulated altitude excursion of approximately 12,000 feet in

order to effect plunger stopper movement, and then returned to the laboratory atmospheric pressure, followed by incubation at $30 - 35℃$ for 7 days.

The syringes exhibited no bacterial growth, demonstrating that the sterile barrier was not compromised by the plunger stopper movement induced by the pressure excursion. This suggests that CCI can be maintained in syringes with up to 8.8mm initial headspace which correlates to a plunger stopper movement of 4.1mm using data from Table 5.

### *5.1.2 Dye Ingress Study:*

Using the same components, sample size and combination as in Table 6, a separate set of syringes were filled with 1.5mL of sterile water without placing the microbial inoculum at the back of the plunger stopper [12]. In this case, the actual samples created had measured initial headspace values distributed between 6.3mm and 9.6mm [12]. These were then exposed to a simulated 12,000 feet of altitude and subsequently subjected to a Dye Ingress test. The samples were compared against control (positive and negative) samples. All samples passed with no dye observed in the ridges of the plunger stopper between the ribs. Similar to the microbial ingress study, this also suggests that CCI can be maintained in syringes with up to 9.6mm initial headspace which correlates to a plunger stopper movement of 4.5mm using Equation (7) and data from Table 5.

## 5.2 Limits For Headspace:

The minimum headspace specification of **$\geq$ 0.0mm** prevents the plunger stopper from contacting the meniscus of the drug product inside the syringe which can result in migration of the syringe contents up the barrel wall during plunger stopper insertion. The theoretical maximum specification is derived from gas laws previously described.

Using the plots from Figures 6-8, the correlation between the plunger stopper movement and the initial headspace can be obtained. Hence, for a conservative maximum allowable plunger stopper movement of 2.2mm (inter-rib distance), the maximum initial headspace to maintain CCI is calculated as 5.0mm at 12,000 feet. Similar analyses can be performed for other altitudes.

As a final exercise, the maximum possible headspace at an altitude of above 17,000 feet to maintain CCI. This altitude was the maximum reported during typical airplane transport [15]. Hence, dye ingress studies were conducted for syringes filled with 1cP and 20cP viscosity solutions with target headspace of 9.0mm. These samples were subjected to a pressure of about 7.49psia, which correlates to ≥17,000 feet above sea level during the vacuum/pressure cycles. All samples passed with no dye observed in any of the solutions. These results support the premise that the container closure integrity of 2.25 mL syringes and associated plunger stopper component is maintained with up to 9.0mm headspace and an atmospheric pressure equivalent to that found at more than 17,000 feet.

The outcome of this CCI study demonstrate that even when the plunger stopper moves in excess of the inter-rib distance, CCI, and therefore, sterility may be assured. This expectation of no CCI or sterility loss past the inter-rib plunger stopper movement is based on the rationale that the unassembled plunger stopper outer diameter is larger than the syringe barrel inner diameter so that when assembled, the interference between the two results in the plunger stopper exerting pressure on the syringe barrel wall which prohibits any microbial ingress or loss of CCI despite plunger stopper movement. This is often referred to as the “windshield wiper effect”.

## 6 CONCLUSION:

This paper describes the relationship between plunger stopper movement and initial headspace in a 2.25 mL syringe using theoretical and empirical approaches. The results showed that for the

syringes used in the studies, a conservative plunger stopper movement of 2.2mm (inter-rib distance) requires a maximum initial headspace of 5.8mm at 12,000 feet; in order to maintain CCI.

Furthermore, empirical data indicated that CCI can be maintained for this syringe/plunger stopper combination with up to 9mm initial headspace and at up to 17,000 feet. Although the data presented was for one brand of syringe from a manufacturer, these analyses are still relevant for syringes from other vendors, or from alternate manufacturing sites. Appropriate assessments may be performed for each combination of syringe and/or plunger stopper or integration within a device.

Finally, once an initial headspace limit has been determined, the limits for target fill volume and plunger stopper (including tolerances) can be calculated. Theoretical modeling such as Monte Carlo Analysis can then be used to predict the confidence level regarding maintenance of an effective sterile barrier when parameters are kept within the various tolerance limits.

**Conflict of Interest Declaration**

The authors declare that they have no competing interests.

**References:**


1) Zhao J, Lavalley V, Mangiagalli P, Wright JM, Bankston TE. Glass delamination: a comparison of the inner surface performance of vials and pre-filled syringes. *AAPS PharmSciTech.* 2014; 15(6):1398-1409. doi:10.1208/s12249-014-0167-y.
2) Sacha, G.A., Rogers, J., & Miller, R.L. (2015). Pre-filled syringes: a review of the history, manufacturing and challenges. *Pharmaceutical Development and Technology, 20*, 1 - 11.
3) Zeiss, B. (2015, September). SYRINGE STUDY – Gerresheimer – Scrutinizing 20,000 Syringes, a Long-Term Study (2011-2015). Retrieved from https://drug-dev.com/syringe-study-gerresheimer-scrutinizing-20000-syringes-a-long-term-study-2011-2015/.
4) Stauffer, O., & Wolf, H. (2014, March 17). Defining the Sterile Barrier of Complex Drug Delivery Systems. Retrieved from https://www.biopharminternational.com/view/defining-sterile-barrier-complex-drug-delivery-systems-0.
5) Stauffer, O., & Wolf, H. (2014, April 2). Evaluating the Sterile Barrier of Complex Drug Delivery Systems. Retrieved from https://www.pharmtech.com/view/j-j-vaccine-approved-for-emergency-use.
6) Lorenz, B., Krick, B. A., Rodriguez, N., Sawyer, W. G., Mangiagalli, P., & Persson, B. N. (2013, October 16). Static or breakloose friction for lubricated contacts: The role of surface roughness and dewetting.
7) Berry, C., & Salzstein, R. (n.d.). Plunger Stopper Movement Under Low Pressure. Retrieved from https://www.smithers.com/resources/2021/jan/plunger-stopper-movement-under-low-pressure.
8) Chan, E., Maa, Y., & Overcashier, D. (2012, May 8). Manufacturing Consideration in Developing a Prefilled Syringe – Investigating the Effect of Headspace Pressure.
9) Welch B, "Critical Considerations in Choosing High Viscosity/High Volume Drug Delivery Devices". ONdrugDelivery Magazine, Issue 83 (Feb 2018), pp 50-53.
10) Wagner, A. (2008, March 1). Advances in Prefilled Syringe Technology.
11) Kent, M. (n.d.). *The Oxford Dictionary of Sports Science & Medicine* (3rd ed.). Oxford University Press.
12) ELN A23F5-027 Stopper Rib Measurements.
13) Blancher, M., Repellin, M., Maignan, M. *et al.* Accuracy of low-weight versus standard syringe infusion pump devices depending on altitude. *Scand J Trauma Resusc Emerg Med* 27**,** 65 (2019). https://doi.org/10.1186/s13049-019-0643-1.
14) R Nave. (n.d.). The Barometric formula. http://hyperphysics.phy-astr.gsu.edu/hbase/Kinetic/barfor.html.
15) Singh, S.P., Singh, J., Stallings, J., Burgess G., and Saha, K., Measurement and Analysis of Temperature and Pressure in High Altitude Air Shipments, Packaging Technology and Science, 23:35–46, 2010

## Figure Captions

**Figure 1.** Syringe terminology

**Figure 2.** Example schematic of a typical plunger stopper showing the ribs

**Figure 3.** Schematic of a prefilled syringe before and during plunger stopper movement

**Figure 4.** Terminology for dimensional measurements of the syringe

**Figure 5.** Compressed plunger stopper length

**Figure 6.** Headspace measurements at altitude (8,000 ft), 25°C

**Figure 7.** Headspace measurements at altitude (12,000 ft), 25°C

**Figure 8.** Headspace measurements at altitude (14,000 ft), 25°C

**Figure 9.** Average break-loose and gliding forces for syringes 40°C

**Figure 10.** Average break-loose and gliding forces for syringes 25°C

**Figure 11.** Average break-loose and gliding forces for syringes at 5°C

**Figure 12.** Schematic of the microbial study

**Table 1. Components Used in the Study**

| Component | Material Description |
|---|---|
| 2.25mL 27G Syringe | 2.25mL glass syringe with a 27G 1/2" staked needle and rigid needle shield. |
| 1-3mL Plunger Stopper | 1-3mL plunger stopper, in either nested packaging or transfer-port packaging or bagged packaging. |

**Table 2. Sampling Plan of Component Lots Used in Plunger Stopper Length Study**

| | STOPPER/SYRINGE LOT COMBINATIONS | | | |
|---|---|---|---|---|
| | **Stopper Lot 1/ Syringe Lot 1** | **Stopper Lot 1/ Syringe Lot 2** | **Stopper Lot 2/ Syringe Lot 1** | **Stopper Lot 2/ Syringe Lot 2** |
| **Sample Count** | 30 Samples | 30 Samples | 30 Samples | 30 Samples |

**Table 3. Sampling Plan for the Headspace and Plunger Stopper Movement Study**

| Bubble Size (mm, approx.) | Altitude: 8000 ft | Altitude: 12000 ft | Altitude: 14000 ft |
|---|---|---|---|
| 2.0 (Low) | 10 samples per time-point* | 10 samples per time-point* | 10 samples per time-point* |
| 3.5 (Medium) | 10 samples per time-point* | 10 samples per time-point* | 10 samples per time-point* |
| 5.0 (High) | 10 samples per time-point* | 10 samples per time-point* | 10 samples per time-point* |

**Time-points: Day 1, Day 14, Month 1, Month 3, Month 6, Month 12, Month 24*

**Table 4. Pressure and Altitude Correlation Settings**

| Altitude | | Pressure | |
|---|---|---|---|
| **(ft)** | **(m)** | **(Pa)** | **(psia)** |
| 12,000 | 3659 | 64433 | 9.34 |

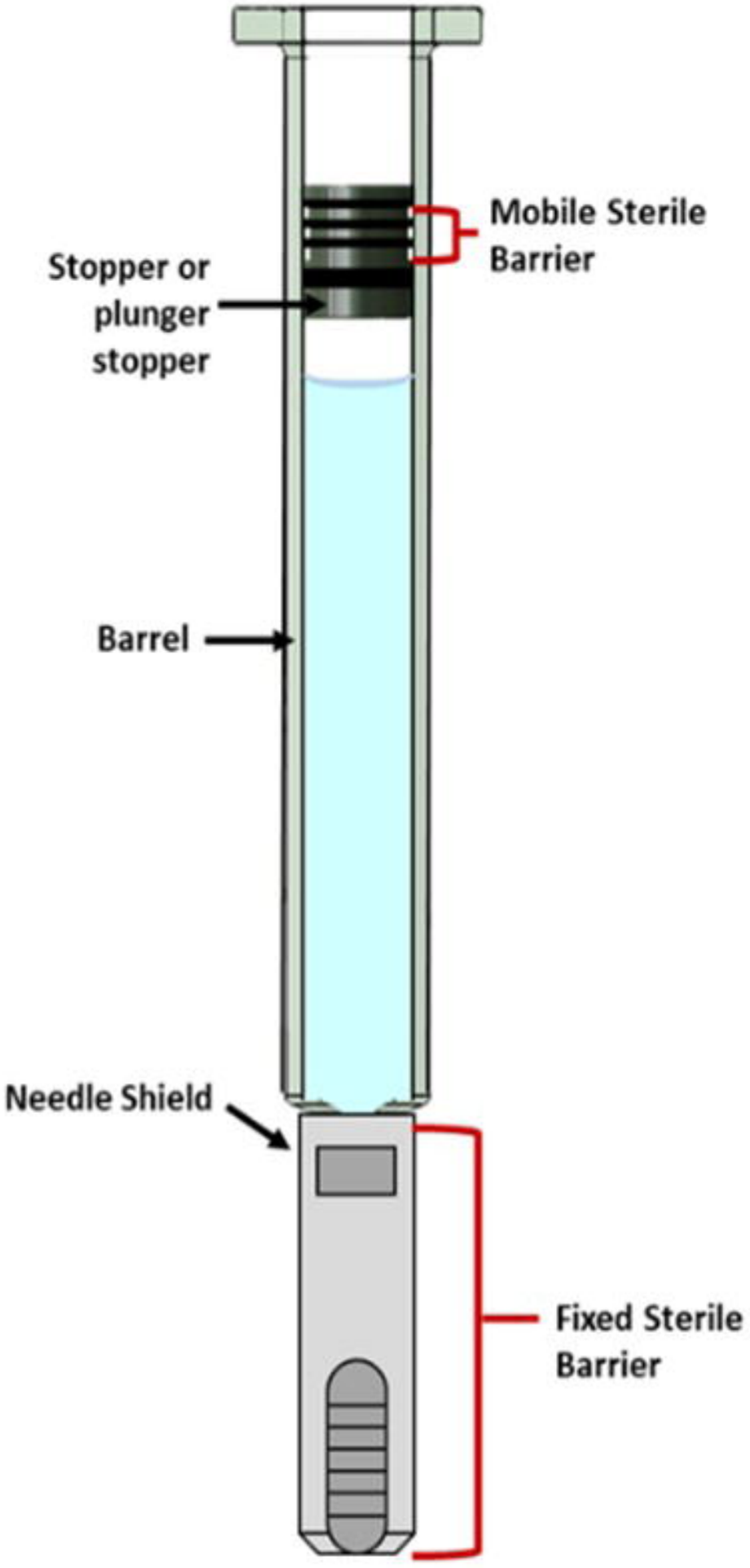
**Table 5. Equations for Air Bubble Size at Various Elevations**

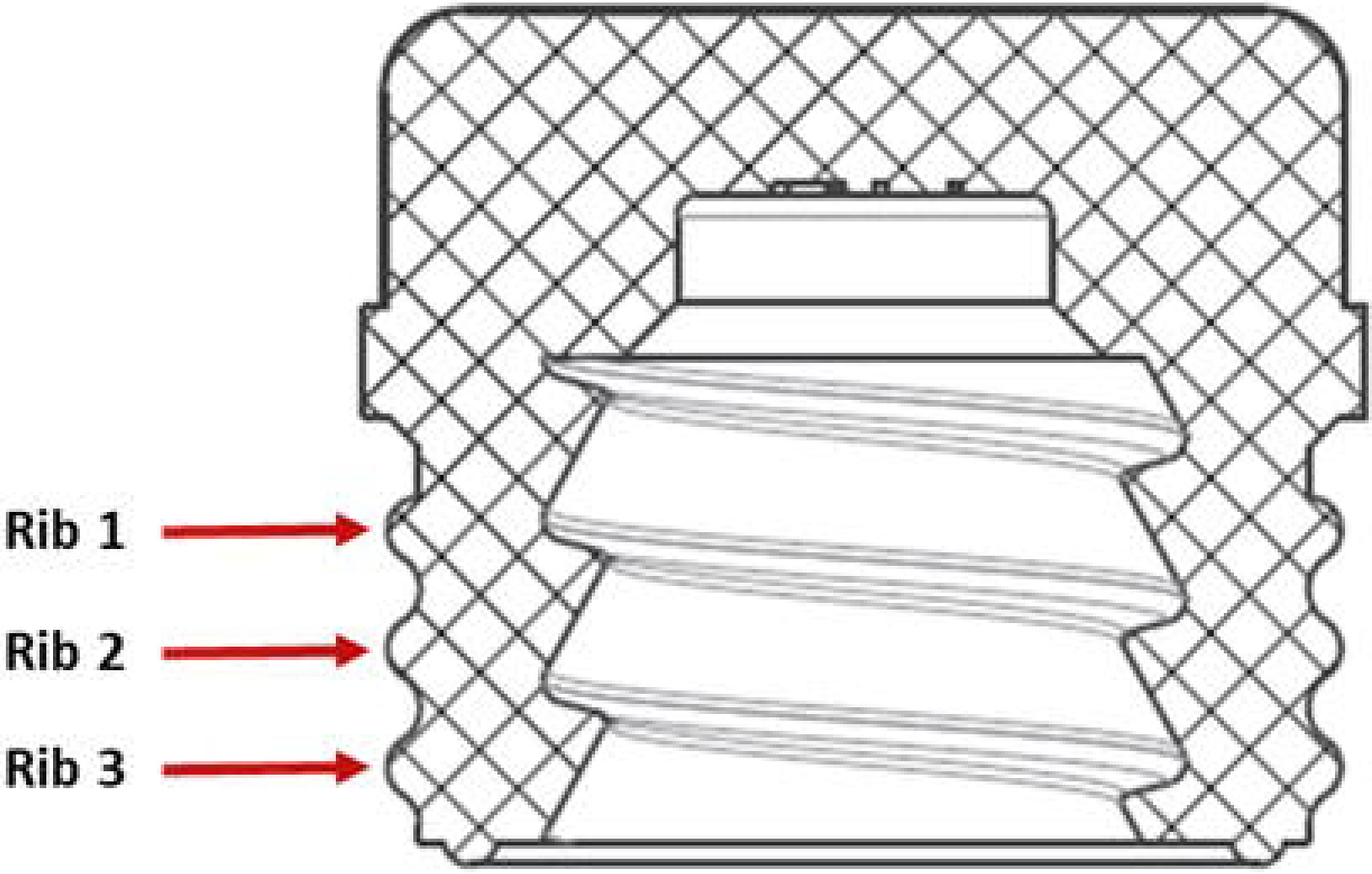
| | | | |
|---|---|---|---|
| | **Slope** | **y-intercept** [a] | **Fitted Plot Line Equation** |
| **8,000 ft** | 1.237 | -0.04728 | Final ABS = 1.237 x Initial ABS - 0.04728 |
| **12,000 ft** | 1.458 | -0.08428 | Final ABS = 1.458 x Initial ABS - 0.08428 |
| **14,000 ft** | 1.576 | -0.1193 | Final ABS = 1.576 x Initial ABS - 0.1193 |

[a] The reductions in y-intercepts for the experimental results in comparison to the theoretical value are indicative of the frictional effects in the PFS.

**Table 6. Syringes and Plunger Stoppers Combination Used in the Study**

| **Air Bubble Size** | **Syringe Lot 1/ Stopper Lot 1** | **Syringe Lot 1/ Stopper Lot 2** | **Syringe Lot 2/ Stopper Lot 1** | **Syringe Lot 2/ Stopper Lot 2** |
|---|---|---|---|---|
| 7.0mm | 12 Samples | 13 Samples | 12 Samples | 13 Samples |
| 8.0mm | 13 Samples | 12 Samples | 13 Samples | 12 Samples |
| 9.0mm | 12 Samples | 13 Samples | 12 Samples | 13 Samples |


Mobile Sterile Barrier
Stopper or plunger stopper
Barrel
Needle Shield
Fixed Sterile Barrier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Rib 2
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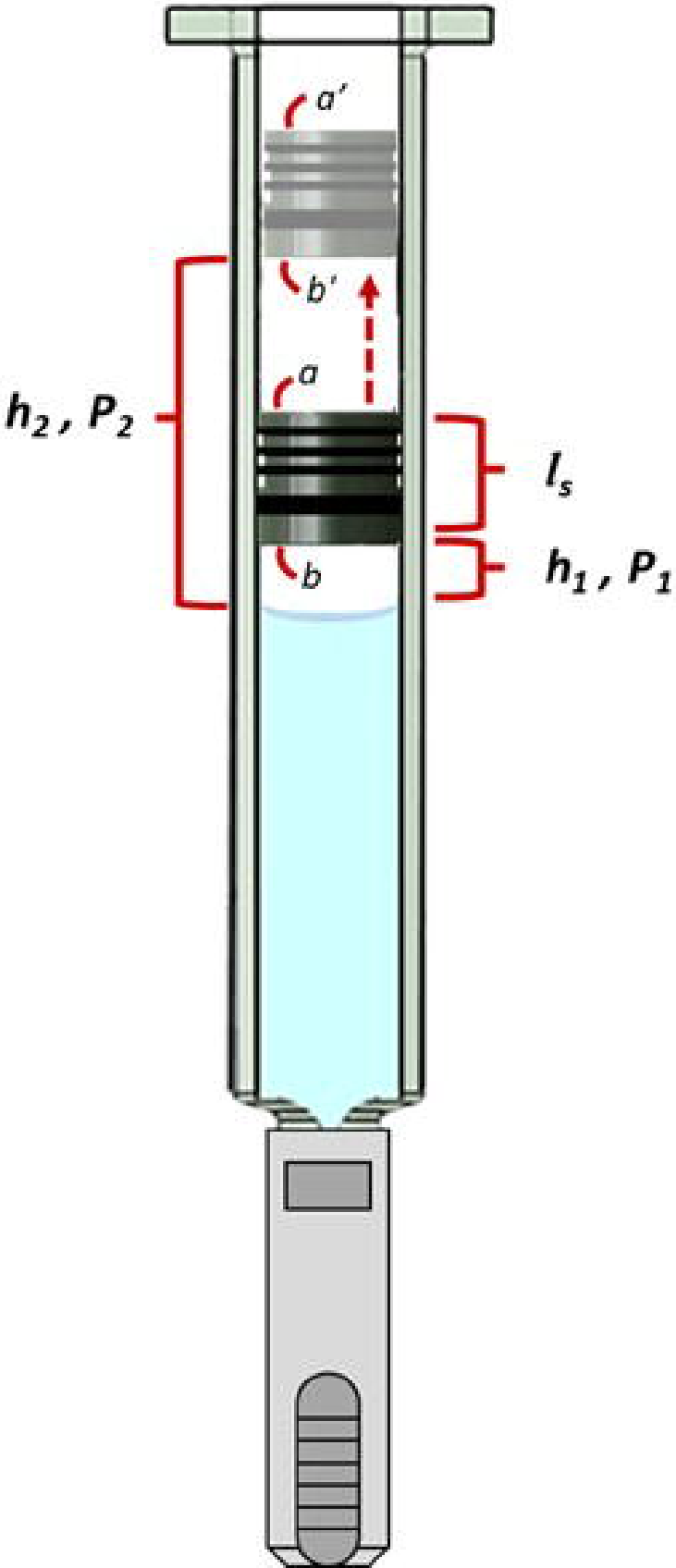


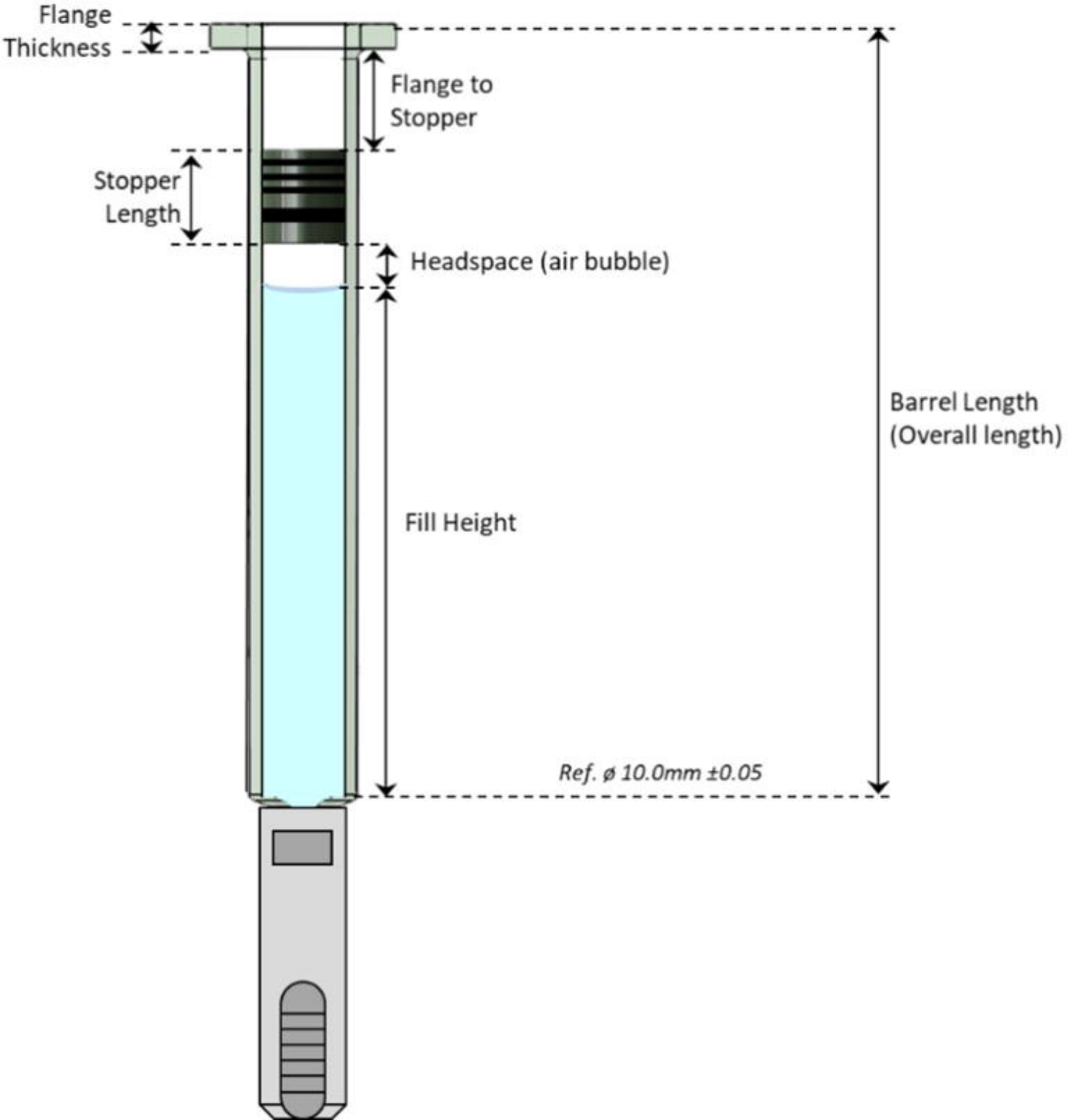

$l_s$ = mobile sterile barrier

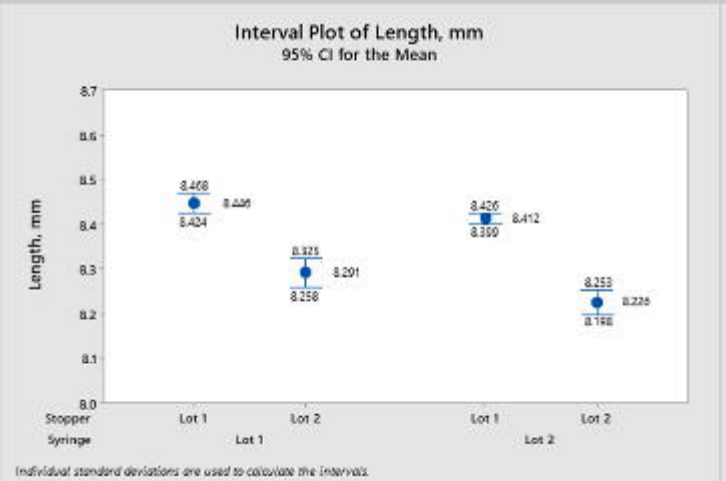
$a$ = proximal end of the stopper at $h_1$, $P_1$
$b$ = distal end of the stopper at $h_1$, $P_1$

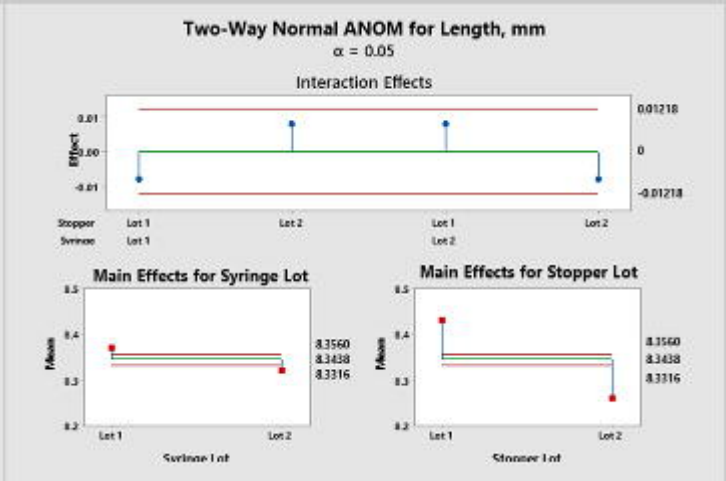
$a'$ = proximal end of the stopper at $h_2$, $P_2$
$b'$ = distal end of the stopper at $h_2$, $P_2$

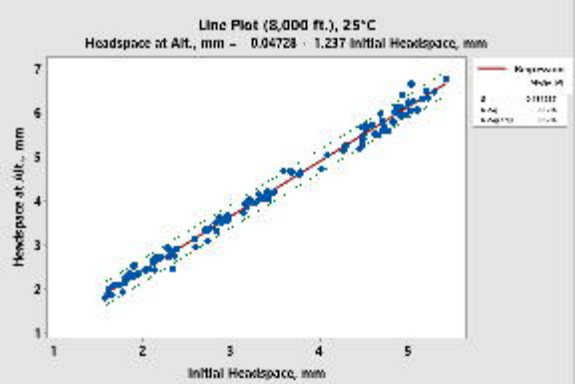
$h_1$ = height of headspace at initial pressure 1 ($P_1$)
$P_1$ = initial pressure

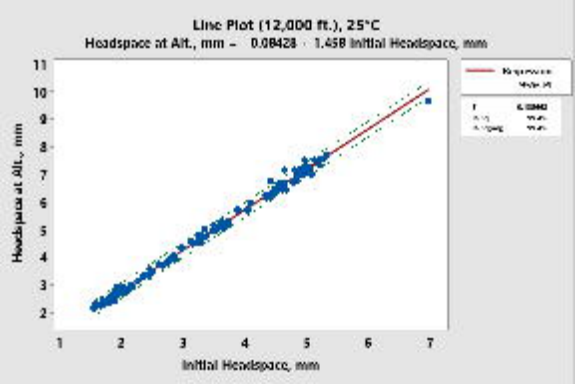
$h_2$ = height of headspace at pressure 2 ($P_2$)
$P_2$ = pressure at altitude

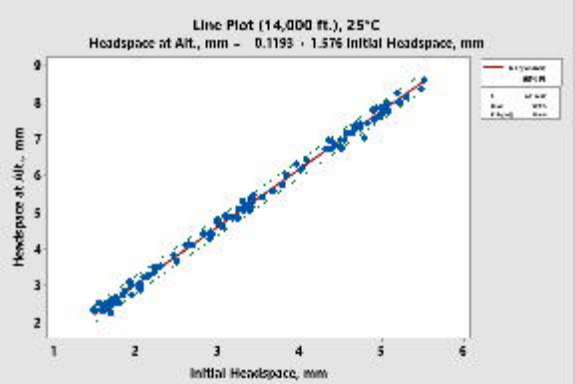

Flange
Thickness
Flange to
Stopper
Stopper
Length
Headspace (air bubble)
Barrel Length
(Overall length)
Fill Height
Ref. ø 10.0mm ±0.05

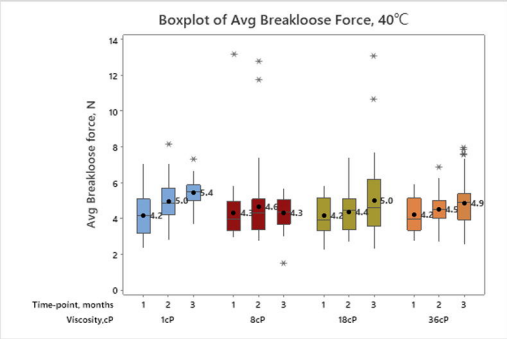

Interval Plot of Length, mm
95% CI for the Mean
Length, mm
8.7
8.6
8.5
8.4
8.3
8.2
8.1
8.0
8.468
8.424
8.446
8.325
8.258
8.291
8.426
8.399
8.412
8.253
8.198
8.226
Stopper
Lot 1
Lot 2
Lot 1
Lot 2
Syringe
Lot 1
Lot 2
Individual standard deviations are used to calculate the intervals.

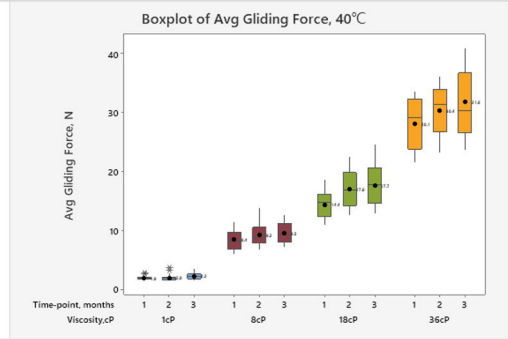

Two-Way Normal ANOM for Length, mm
α = 0.05
Interaction Effects
Effect
0.01
0.00
-0.01
0.01218
0
-0.01218
Stopper
Lot 1
Lot 2
Lot 1
Lot 2
Syringe
Lot 1
Lot 2
Main Effects for Syringe Lot
Mean
8.5
8.4
8.3
8.2
8.3560
8.3438
8.3316
Lot 1
Lot 2
Syringe Lot
Main Effects for Stopper Lot
Mean
8.5
8.4
8.3
8.2
8.3560
8.3438
8.3316
Lot 1
Lot 2
Stopper Lot

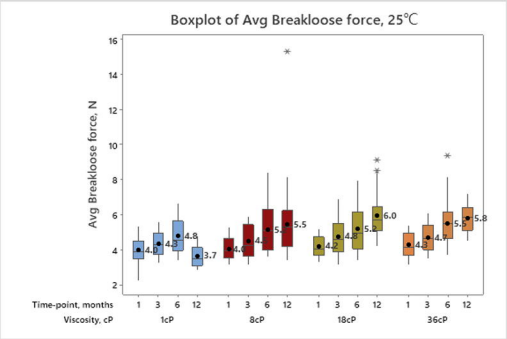

Line Plot (8,000 ft.), 25°C
Headspace at Alt., mm = 0.04728 + 1.237 Initial Headspace, mm
Headspace at Alt., mm
Initial Headspace, mm
1
2
3
4
5
6
7

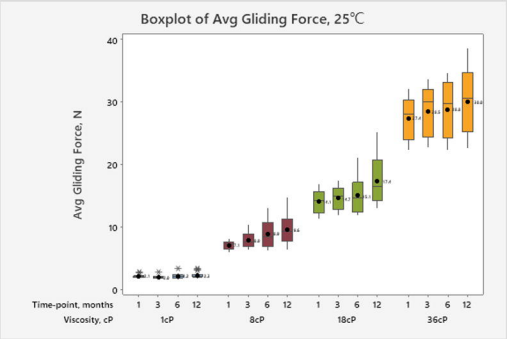

Line Plot (12,000 ft.), 25°C
Headspace at Alt., mm = 0.08428 + 1.458 Initial Headspace, mm
Headspace at Alt., mm
Initial Headspace, mm
1
2
3
4
5
6
7
8
9
10
11

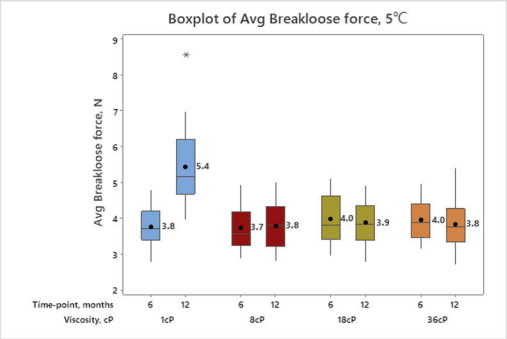

Line Plot (14,000 ft.), 25°C
Headspace at Alt., mm = 0.1193 + 1.576 Initial Headspace, mm
Headspace at Alt., mm
Initial Headspace, mm
1
2
3
4
5
6
2
3
4
5
6
7
8
9

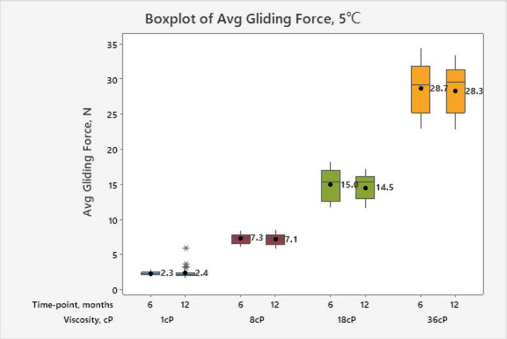

Boxplot of Avg Breakloose Force, 40℃
Avg Breakloose force, N
0
2
4
6
8
10
12
14
4.2
5.0
5.4
4.3
4.6
4.3
4.2
4.4
5.0
4.2
4.5
4.9
Time-point, months
1 2 3 1 2 3 1 2 3 1 2 3
Viscosity,cP
1cP
8cP
18cP
36cP

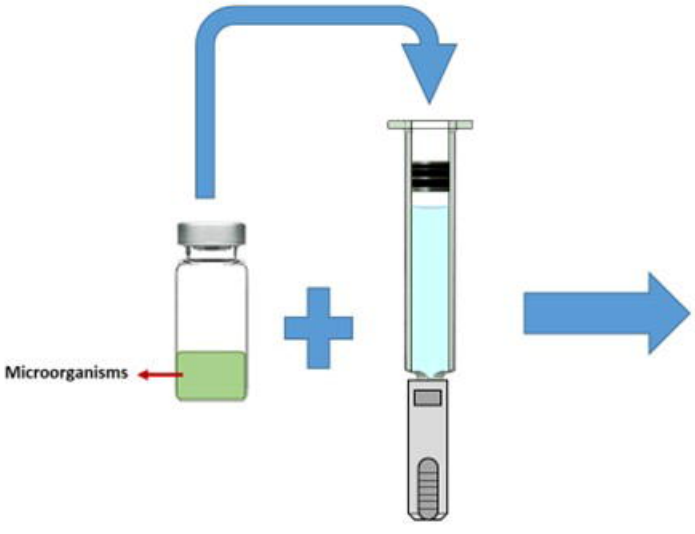

Boxplot of Avg Gliding Force, 40℃
Avg Gliding Force, N
0
10
20
30
40
Time-point, months
1 2 3 1 2 3 1 2 3 1 2 3
Viscosity,cP
1cP
8cP
18cP
36cP


Boxplot of Avg Breakloose force, 25℃
Avg Breakloose force, N
16
14
12
10
8
6
4
2
4.1
4.3
4.8
3.7
4.0
4.4
5.1
5.5
4.2
4.7
5.2
6.0
4.3
4.9
5.5
5.8
Time-point, months 1 3 6 12 1 3 6 12 1 3 6 12 1 3 6 12
Viscosity, cP 1cP 8cP 18cP 36cP

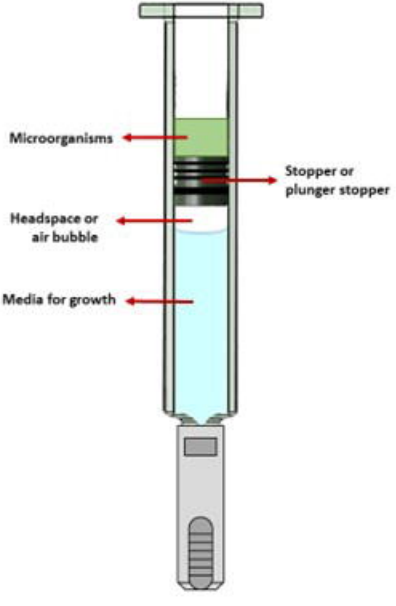

Boxplot of Avg Gliding Force, 25℃
Avg Gliding Force, N
40
30
20
10
0
Time-point, months 1 3 6 12 1 3 6 12 1 3 6 12 1 3 6 12
Viscosity, cP 1cP 8cP 18cP 36cP


Boxplot of Avg Breakloose force, 5℃
Avg Breakloose force, N
9
8
7
6
5
4
3
2
5.4
3.8
3.7
3.8
4.0
3.9
4.0
3.8
Time-point, months
6
12
6
12
6
12
6
12
Viscosity, cP
1cP
8cP
18cP
36cP


Boxplot of Avg Gliding Force, 5℃
Avg Gliding Force, N
35
30
25
20
15
10
5
0
28.7
28.3
15.4
14.5
7.3
7.1
2.3
2.4
Time-point, months
6
12
6
12
6
12
6
12
Viscosity, cP
1cP
8cP
18cP
36cP




The microorganisms are placed at the back side of the stopper/plunger for testing.



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