PREFILLED SYRINGES

A Rational Approach to Determining the Maximum Allowable Gas Bubble Inside a Prefilled Syringe to Minimize Stopper Movement & Protect Product Sterility

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ABSTRACT

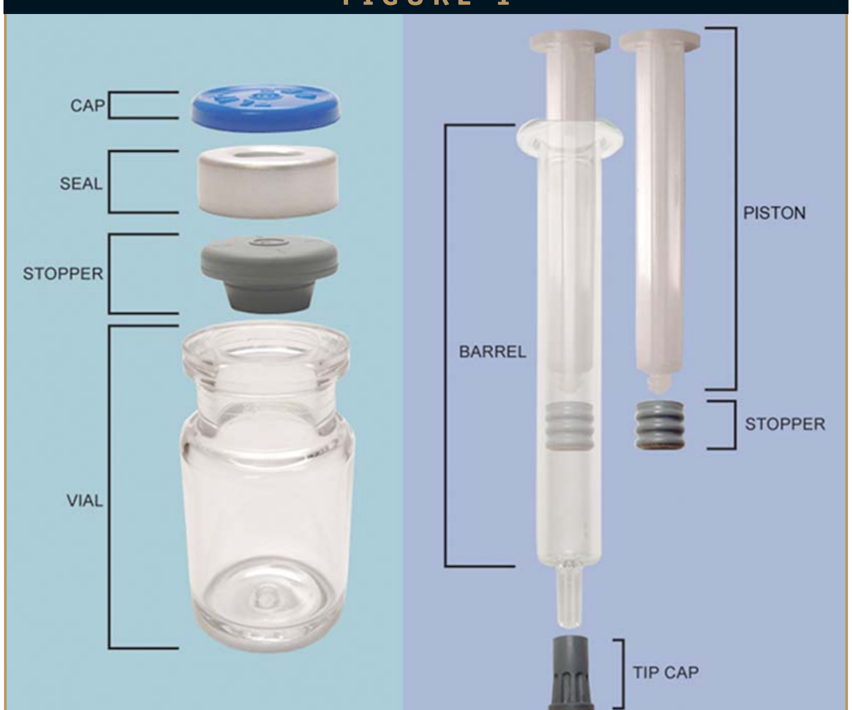
Prefilled syringes are a fast-growing alternative to vials in the parenteral product market due to the many advantages they offer relative to vials. These include reduced overfill requirements, ease of use, more accurate dosing, decreased waste, and enhanced product differentiation.

Conventional syringe-filling processes typically leave a large air bubble in a syringe that can negatively impact product sterility and package integrity. Using a series of equations and hypothetical scenarios, this article will demonstrate the potential impact of a bubble on stopper movement during periods of reduced atmospheric pressure. It will also propose a rational approach for determining the maximum allowable size of a gas bubble inside a prefilled syringe taking into account several critical factors. After weighing some of the alternatives for limiting stopper movement during shipping as well as one additional benefit of bubble-free filling, this article will make the case that reducing or eliminating the bubble inside a prefilled syringe is a preferred means for ensuring product sterility while enhancing the benefits of a prefilled syringe.

INTRODUCTION

The internal environments of a glass vial and a glass syringe have a number of features in common, as shown in Figure 1. Both presentations are essentially glass cylinders that are sealed by an elastomeric closure, or stopper, and both contain a gaseous headspace, or bubble. However, there is one noteworthy difference. A vial's stopper is held in place by a crimp, while a syringe's stopper is designed to move in order to allow injection of the drug product. This freedom of movement, when coupled with a gas bubble (which is not intrinsic to a syringe but is a byproduct of sub-optimal filling processes) can potentially cause significant challenges with regard to package integrity and product sterility, particularly when the syringe is exposed to repeated changes in atmospheric pressure, such as during shipping. Reducing or eliminating the

FIGURE 1



Comparison of a vial and a syringe. Both are essentially glass tubes sealed with an elastomeric closure and contain a gas headspace.

bubble inside the syringe would limit stopper movement, potentially enhancing sterility assurance of the product.[1]

In a preliminary study of the impact of a bubble on stopper movement in a prefilled syringe, three syringes were placed inside a Hypak vacuum chamber. One syringe contained a 2.5-mm bubble, one a 5.0-mm bubble, and yet another contained no bubble at all. Next, a vacuum was pulled at 8 inches of mercury and then again at 15 inches while the syringes were closely monitored for signs of stopper movement. The procedure was then repeated five more times, with a new set of syringes each time, to substantiate the initial findings, which included the following:

- In the syringes containing a bubble, the stopper was seen rising into non-sterile areas of the syringe barrel each time the vacuum was pulled.
- In the syringes containing no gas bubble, however, the stopper was not seen rising at all.
- The size of the bubble inside the syringe made a difference in the amount of stopper movement. The syringes filled with a 2.5-mm bubble experienced less movement than the syringes filled with a 5.0-mm bubble. When the vacuum was released and the pressure returned to original levels, the stoppers in the syringes containing a bubble returned to their original position with no indication that they had moved.

Due to the difficulty of controlling for all of the variables that affect stopper movement in a prefilled syringe, a series of equations were devised to show, on a theoretical level, the relationship between the size of the gas bubble and stopper movement. Using Boyle's Law, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to changes in pressure, and the amount of stopper movement that occurs as a result of that expansion and contraction was calculated.

TABLE 1

Gas Bubble Size	H_{sb} = 6.2 mm Approximate Elevation (1,000s ft)	H_{sb} = 4.3 mm Approximate Elevation (1,000's ft)
0.5 mm	21	19
1.0 mm	16	14
2.5 mm	13	7
5.0 mm	7	<5

Approximate elevation (in feet above sea level) at which a stopper will have moved 1/5 H_{sb}.

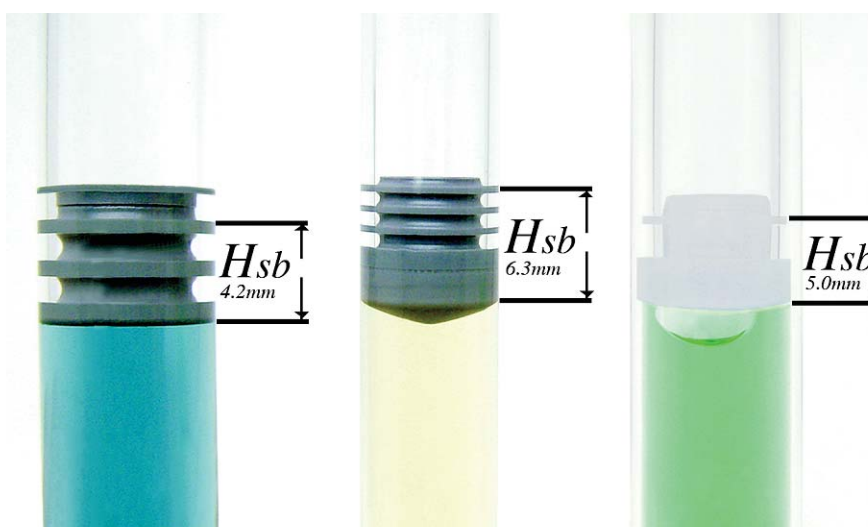
Plugging these calculations into a hypothetical situation in which a syringe is shipped multiple times from the manufacturer to the end-user, a rational approach was developed for determining the maximum allowable size of a gas bubble inside a prefilled syringe. Among the factors taken into account were stopper height, the elevations to which a syringe will likely be exposed and the consequent changes in pressure which it will undergo, as well as the number of times a syringe will be subjected to reduced atmospheric pressure.

STERILE BARRIER HEIGHT: H_{SB}

In a prefilled syringe, a sterile barrier is created in which the stopper is in intimate contact with the glass barrel of the syringe, as shown in Figure 2. The sterile barrier height, or H_{sb}, spans the entire distance from the uppermost to the lowermost point of stopper contact and represents the limit of upward stopper movement, which the stopper can undergo before product sterility is potentially compromised.

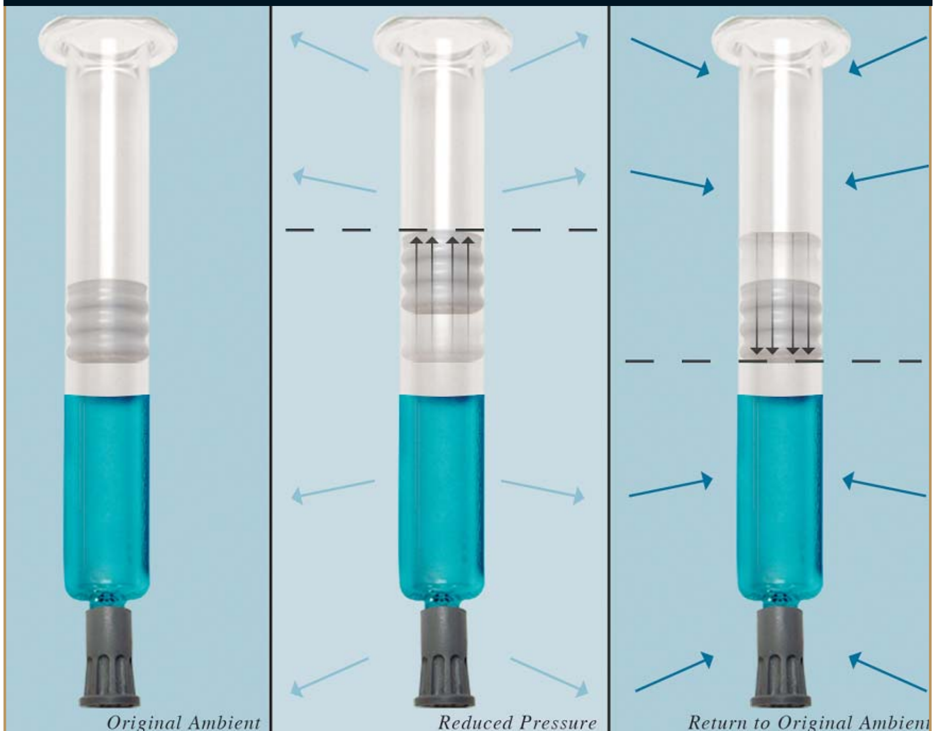
A gas bubble sealed inside a prefilled syringe acts like a spring, expanding and contracting with changes in temperature or external ambient pressure. If the external ambient temperature increases or pressure decreases, the gas bubble expands, pushing the stopper up until the pressure in the syringe is equivalent to the external pressure. When the external ambient pressure and/or temperature return to their original levels, the gas bubble in the syringe contracts until the pressure in the syringe is equal to the external pressure. This causes the stopper to return to its

FIGURE 2



Syringes and stoppers. The distance from the uppermost to the lowermost point of contact between the stopper and the syringe is known as the sterile barrier height or H_{sb}.

FIGURE 3



A gas bubble will expand or contract under changes in ambient pressure. This expansion/contraction will cause stopper movement in a syringe with no visible evidence that the stopper has moved when external conditions are returned to their original levels.

original position, leaving no visible evidence that the stopper has moved (Figure 3).[2]

If the stopper in a syringe moves more than the distance of H_{sb}, it can pull microorganisms or contaminants from the non-sterile portion of the syringe into the drug product, potentially causing a sterility failure. This same phenomenon could occur when a stopper moves less than the distance of H_{sb} if it moves multiple times and the sum of all stopper movements exceeds H_{sb}, as demonstrated in Figure 4.

PRESSURE & THE VOLUME OF A GAS BUBBLE

The amount of change in the volume of a gas bubble is relatively small over the reasonable temperatures to which a syringe might be exposed (total range of approximately 40ºC); however, the volume change due to pressure changes alone can be significant, as demonstrated in the calculations that appear further on.

Assuming that temperature remains constant, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to pressure changes can be calculated using Boyle's Law (Equation 1).

Equation 1.

$$P_1V_1 = P_2V_2$$

Where P_1 = pressure condition 1, V_1 = volume condition 1, P_2 = pressure condition 2, and V_2 = volume condition 2. The volume (V) of a cylinder, such as a syringe, is given by Equation 2.

Equation 2.

$$V = \pi r^2 h$$

Where r = internal radius of the syringe barrel, and h = height of the gas bubble/air gap (assuming the bubble spans the entire diameter of the syringe). If Equation 2 is substituted for V in Equation 1, and both sides are divided by πr^2, the result is as Equation 3.

Equation 3.

$$P_1h_1 = P_2h_2$$

Where P_1 = pressure condition 1, h_1 = height condition 1, P_2 = pressure condition 2, and h_2 = height condition 2. Thus in Equation 4, the theoretical height of the gas space in the syringe at a given external pressure can be determined based on the initial conditions (condition 1).[2]

Equation 4.

$$h_2 = P_1h_1/P_2$$

The percentage of total stopper movement beyond the initial sterility barrier (H_{sb}) can be calculated by subtracting the initial height (H_1) from the height calculated in Equation 4 (H_2) and dividing the result by Hsb, as shown in Equation 5.

Equation 5.

$$\text{Percent } H_{sb} = 100*(H_2 - H_1)/H_{sb}$$

Figures 5b and 5c show the percentage of H_{sb} that a stopper will move in syringes with an H_{sb} of 6.2 and 4.3 mm, respectively, and initial bubble sizes ranging from 0.5 mm to 5 mm, the most common size range for a bubble. The points on the x axis in Figures 5b and 5c represent feet of elevation rather than absolute pressure to demonstrate the effect that reduced pressure (due to changes in elevation) will have on a syringe. These points were determined using a conversion of 1 inch Hg vacuum equal to 1000 feet of elevation (Figure 5a).

The *y* axis in Figures 5b and 5c represents the percentage of H_{sb}, which the stopper in a syringe will move, while the red line at 100% shows the point at which the stopper will enter a non-sterile area of the syringe, potentially compromising product sterility.

In the example in Figure 5b, in which H_{sb} is 6.2 mm and the initial bubble size is 2.5 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 23,000 feet. When the initial bubble is 5.0 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 20,000 feet.[2]

Because the cargo hold of an airplane is generally maintained at a pressure equal to 8,000 feet of elevation, and ground elevations during shipment do not often exceed 10,000 feet, a stopper is not likely to move more than H_{sb} in a single exposure. However, during shipment, a syringe could possibly be exposed to reduced pressure on several occasions which, taken together, increases the potential for total stopper movement to exceed H_{sb}.

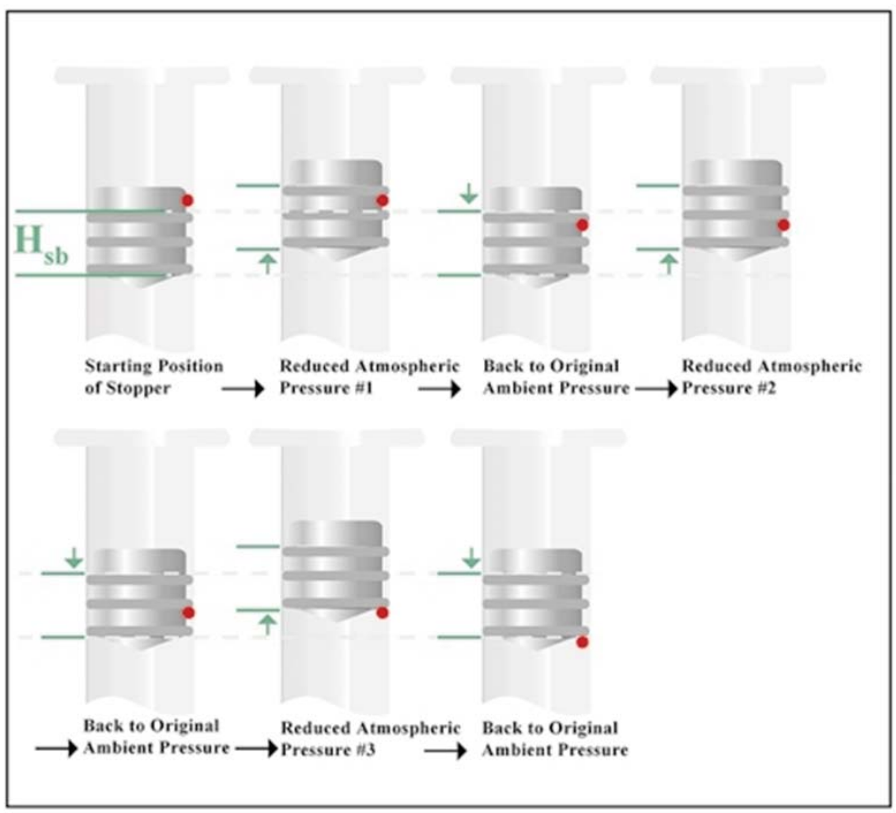
Consider, for example, a syringe that is shipped from a CMO's manufacturing site to the sponsor company's facility to a distribution center and finally to the end-user's site, for a total of three shipments. It is possible that one or more legs of the product's journey could involve more than one flight, creating additional opportunities for the stopper to rise and fall. Under those conditions, it is conceivable that a syringe could be exposed to changes in pressure on five occasions, resulting in five up and down stopper movements. In that case, a stopper would only need to rise 1/5 H_{sb} each time to potentially pull non-sterile material, such as silicon, or other contaminants into the product causing a sterility failure.

Table 1 shows the approximate elevations at which the stopper would exceed 1/5 of H_{sb} given several different sized bubbles. To prevent stopper movement as a result of changes in ambient pressure, syringes should ideally be filled without any gas bubbles. However, in practice, most syringe filling equipment does not have the capability to remove all of the gas in a syringe. When that is the case, the maximum acceptable size of a gas bubble for a given stopper in a prefilled syringe should be determined. This can be done by factoring in the differential pressure changes to which a syringe will likely be exposed, the number of times it will be subjected to reduced pressure, and the height of the sterile barrier.

DETERMINING THE MAXIMUM SIZE OF A GAS BUBBLE

Using the aforementioned equations, the size of the bubble that will lead to a movement of the stopper equal to 1/5 of H_{sb} can be calculated at a number of different elevations. For example, Figure 6 shows the results of calculations performed using elevations of 8,000 and 12,000 feet with a range of H_{sb} from 1 to 15 mm. In situations where H_{sb} is 4.0 and elevation is 8,000 feet, the maximum acceptable size of the gas bubble is approximately 2.0 mm. When the elevation reaches 12,000 feet, however, the maximum acceptable size of the gas bubble decreases to approximately 1.6 mm.[2] The aforementioned analysis is a worst-case scenario and does not take into account frictional forces and break loose forces. Frictional forces caused by the stopper rubbing against the syringe, and the break loose force, which is required to start the stopper moving, should reduce stopper movement. Break loose forces, which increase over the life of the syringe, would improve resistance to stopper movement the longer the product was in transit, requiring greater force to initiate the movement of the stopper. However, it is not unreasonable to assume that a newly filled prefilled glass syringe with silicon has very little break loose force. In fact, we have confirmed in our laboratories that standard, commercially available glass syringes and elastomeric stoppers with silicon show actual stopper movement that is approximately 75% of that which has been theoretically calculated in this article. We did not perform an extensive study of all factors that could affect glide and breakloose forces; therefore, we have used theoretical calculations to demonstrate

FIGURE 4



If the stopper moves more than H_{sb}, contaminants may be pulled into the sterile liquid. This effect can occur with multiple movements if the sum of all stopper movements exceeds H_{sb}.

several worst-case scenarios for stopper movement.

The aforementioned analysis is also based on the assumption that pressures are controlled at consistent levels throughout shipment when, in fact, the actual magnitude of reduced/increased pressure to which syringes are exposed is generally not known. Cargo is shipped by a variety of carriers, many of whom may not consistently control, measure, or report changes in pressure. Atmospheric pressure in a cargo hold could rise and fall during flight, and the drug manufacturer would not be aware of it upon inspection at the final destination.

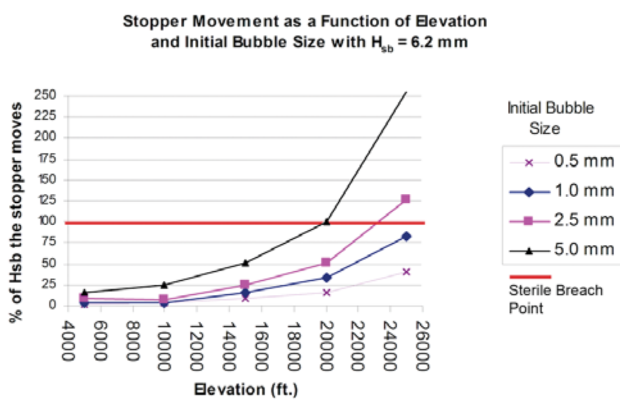
There are alternative means to prevent contamination due to stopper movement other than reducing the size of the gas bubble or increasing H_{sb}. For example, the stopper can be locked in place with a device placed inside the barrel, or the entire syringe can be sealed inside a sterile container (protecting the sterility of the barrel above the stopper), or the syringe can be placed in a holder that secures the plunger rod in place. However, each of these approaches adds cost and requires additional packaging and does not provide the added benefits of a bubble-free syringe.

FIGURE 5A

Elevation	" Hg Vac.	psi	torr
0	0	14.7	760
8,000	8"	10.7	555
10,000	10"	9.8	506
12,000	12"	8.9	455
15,000	15"	7.3	379
18,000	18"	5.9	302
25,000	25"	2.4	125
27,000	27"	1.4	74

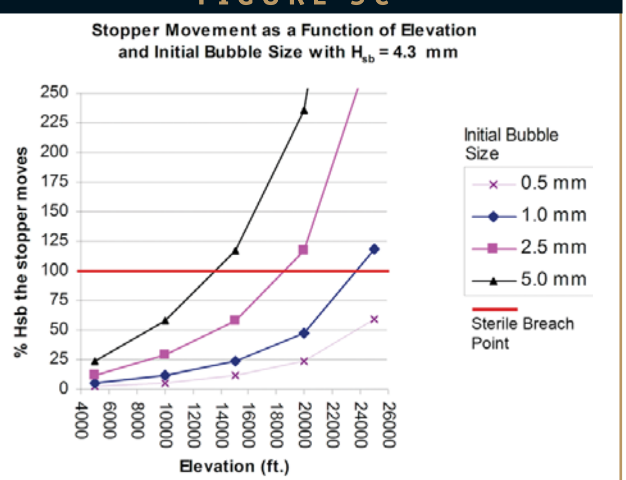
Conversion of 1-inch Hg vacuum equal to 1000 feet of elevation.

FIGURE 5B



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 6.2 mm.

FIGURE 5C



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 4.3 mm.

ELIMINATING PRODUCT LOSS

One added benefit of a bubble-free syringe is the reduction in the amount of product inadvertently lost during use. In a side-by-side analysis, 15 syringes were filled with gas bubbles of varying sizes, while 15 syringes were filled with no bubble. As the tip caps on each set of syringes were removed, the needles were watched for any sign of dripping or product leaks. In the set that were filled with a bubble, product was observed leaking from needle over 75% of the time when the tip cap was removed. Conversely, in the needles that were bubble-free, no product was seen leaking from the needle any time the tip caps were removed (Figure 7).[2]

This is because in a bubble-free syringe, there is no expansion and contraction of the bubble as a result of the small vacuum that is created when the tip cap is removed. Without a drip, there is added assurance that the end-user will receive the entire deliverable dose. There is also less risk that the administrator or end-user will be exposed to cytotoxic or potent compounds, as well as a reduction in product wasted.

CONCLUSION

Although, on the surface, syringes may appear very similar to vials, the freedom of stopper movement in a prefilled syringe, coupled with a gas bubble, will result in challenges to package integrity and product sterility when the syringe is exposed to changes in atmospheric pressure. A gas bubble is not intrinsic to a syringe but is the result of a sub-optimal filling process and therefore, can be reduced or eliminated using alternative filling methods.

Manufacturers go to great lengths to monitor and control the temperature to which products are exposed during shipping. Yet the same attention has not been paid to changes in differential pressures to which a product is exposed. Given that a number of today's parenteral products are shipped several times before reaching the end-user, undergoing several changes in atmospheric pressure and several potential movements of the stopper, such attention is warranted. Just as exposure to elevated temperatures may impact the shelf-life and efficacy of products, exposure to reduced pressure may potentially impact the sterility and safety of an injectable product in a prefilled syringe if one is not aware of the importance of reduced bubble size and stopper design.

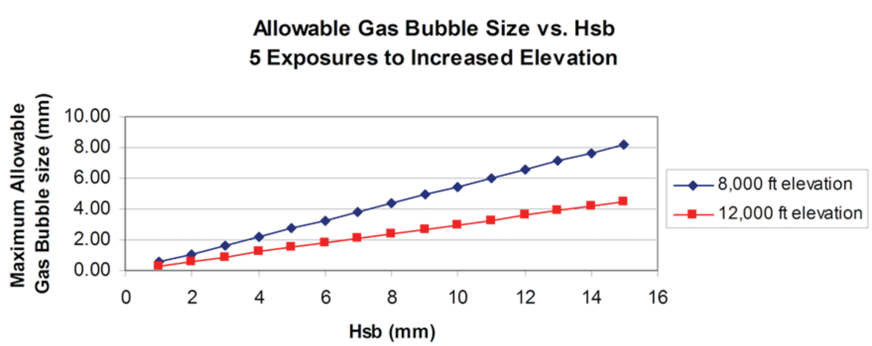
In this discussion, we have proposed one way to determine the maximum acceptable size of a gas bubble that can be left inside a syringe based on stopper height as well as other variables. There are alternative ways to protect prefilled syringes from contamination due to stopper movement, but these require additional packaging and do not offer the added benefits of a bubble-free syringe, such as enhanced dosing accuracy and safety as well as reduced waste due to the elimination of a product drip at the needle when the tip cap is removed.[3]

As prefilled syringes continue to find favor as an alternative to vials for many of today's parenteral products, reduced gas bubble filling should likewise become increasingly popular as an alternative to traditional filling methods and may one day become the industry standard.

REFERENCES

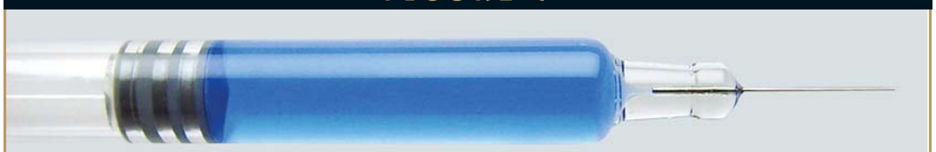
1. Harrison B, Rios M. Big shot: developments in prefilled syringes. Pharm Technol. 2007;31(3):50-56.
2. Kinney SD. Considerations on the size of the gas bubble in a prefilled syringe. Paper presented at the PDA Universe of the Prefilled Syringe Show in Berlin, Germany, November 27-28, 2007.
3. Kinney SD. Innovative Solutions Seminar. New Brunswick, NJ, October 30, 2007.

FIGURE 6



The data demonstrates that smaller gas bubbles and stoppers with larger H_{sb} reduce the risk of stopper movement exceeding 1/5 H_{sb}.

FIGURE 7



Gas bubbles in traditionally filled syringes, like the syringe on the bottom in this photo, can cause product to drip from the needle when the needle sheath or tip cap is removed. In a bubble-free syringe, like the one pictured on the top, there is no drip, decreasing waste and improving dosing accuracy and safety.

BIOGRAPHIES

Dr. Shawn D. Kinney, President of Hyaluron Contract Manufacturing (HCM), founded HCM in 1999 to provide aseptic manufacturing and filling services to the pharmaceutical, biotech, and medical device industries. Dr. Kinney earned his PhD in Chemistry from the University of Massachusetts at Amherst, a Masters in Medicinal Chemistry from Northeastern University, and a BS in Chemistry from the University of Massachusetts at North Dartmouth. Dr. Kinney has worked at Anika Therapeutics, Wyeth-Ayerst, and Millipore and has more than 20 years of experience in the pharmaceutical industry. He has extensive experience in the development of sterile formulation and filling processes, including viscous and difficult-to-fill products. Prior to founding HCM, he was responsible for the sterile formulation and filling of hyaluronate into prefilled syringes in his role as VP of Operations at Anika Therapeutics. Recently, Dr. Kinney has pioneered a new technology in online vacuum filling and stoppering (Bubble-Free Filling®) and has been granted a patent. He continues to oversee HCM's expansion and leadership in the aseptic contract manufacturing industry. He can be reached at shawn@hyaluron.com or (781) 270-7900, ext. 218.

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