Title: Discussion of Vial Closures and Stoppering Force in Pilot Freeze-Dryers

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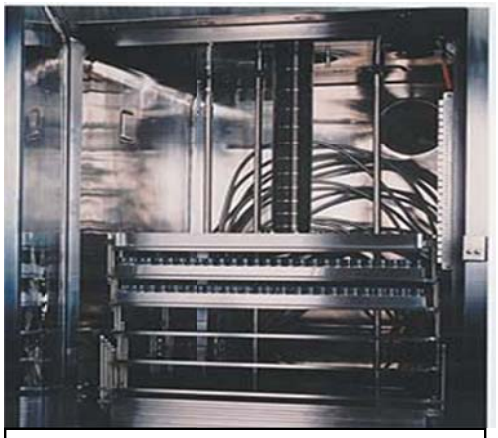
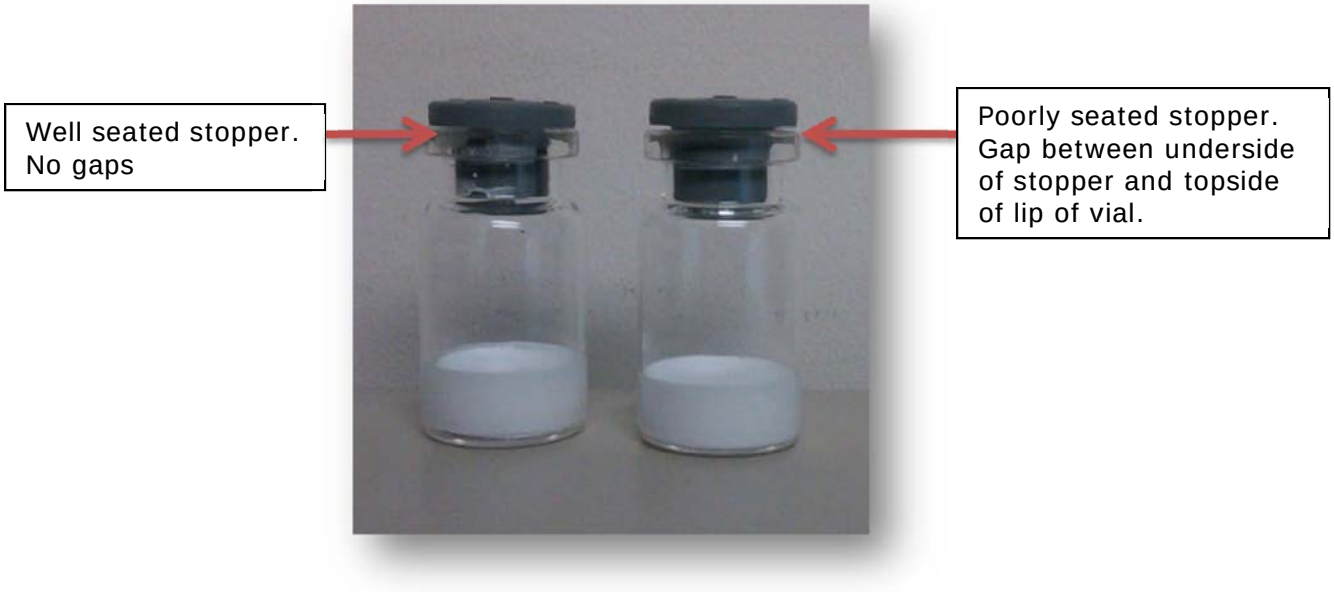
SP Scientific, as a supplier of Production and Research and Development freeze dryers over the last decades, has encountered various container-closure systems. On occasion, we are challenged with regard to equipment being able to properly seal a customer's selection of container-closure system which is typically a glass vial and rubber stopper that is pressed down into the vial during a stoppering step at the end of freeze drying. This became a more frequent problem as dosages and containers decreased in size because this configuration typically requires more force per square inch to create proper stopper seating in the vial. In addition, we have found that vials for R&D are not always processed as they might be for production and this may create a significant impediment to properly seating the stopper in an R&D freeze dryer due to an absence of lubricant that may be part of the processing of vials for production.

Most vials are stoppered in the freeze dryer at sub-atmospheric pressure, either with or without an inert gas layer over the product. The internal vial environment is at a lower pressure than the surrounding atmospheric pressure and an improperly seated stopper can easily lead to ambient atmosphere "leaking" into poorly stoppered vial. This may lead to oxidation damage or reabsorption of moisture (and hence decreased product quality and/or shelf life) because of a moisture rich ambient environment entering the vial through the leak spaces.



Vials being stoppered in a freeze dryer

As a result it sometimes becomes necessary to make sure that the force required to securely seat the stopper in a vial of your choice is compatible with the stoppering pressure being delivered by the freeze dryer you have chosen to use. The freeze dryer stopping assembly must provide enough force to fully seat the stoppers in the vials. Simultaneously the stoppering mechanism must be designed in such a way that it does not crush vials or cause the shelf assembly to warp under severe pressure.



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To answer the often asked question "Can my system stopper a full tray of the vials and stoppers I have selected?," it is important to be able to recognize the force needed for your particular container-closure system and to compare that to the stoppering pressure specification provided by the freeze dryer manufacturer.

The first step in this process will be to discover the amount of stoppering force that is required to fully stopper your container-closure combination. Although you might expect that the vial or stopper manufacturers should be able to tell you what is required to stopper, users often mix and match the container-closure system to meet their own specific needs. In addition, they may process the container-closure differently, depending on their own protocols. As a result it is a good idea to measure the pressure required to seat a stopper in your particular container-closure system.

Step 1: The force required by the specific vial and stopper combination can be measured by using a force gauge. Simply press the stopper into the vial using the force gauge and record the reading. This value will be a lbf (or pound of force reading). ***For the purposes of this exercise let's say that your experiment indicates that each vial requires 2 lbf to stopper correctly***.

Wagner Force Dial, Model FDK, Wagner

The force values may be too low if only a single vial is tested. Stoppering a small group at one time improves the accuracy of the reading. Take the total force and divide by the number of vials tested to get the lbf (pound force) need to seat a single stopper in a single vial.

As you know vials when put in any kind of rectangular pattern – such as a freeze dryer shelf – don't simply line up in straight rows. If they did we would probably have a relatively easy time calculating the amount of force required from the system to stopper all the vials. The reality of the situation is that vials "nest" in trays in an irregular pattern and the pattern is a function of the tray's length and width characteristics. The number of vials per square inch of tray will vary based on not only the vial size but also the vial nesting characteristics.

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In step 2 we have to understand the size of the tray that will be used in the freeze dryer and we need to refer to the manufacturers specifications for the number of vials (of the size you are investigating) in a single tray. This will allow us to calculate the force we need to stopper a full shelf of vials (Step 3).

Step 2. Referring to the freeze dryer manufacturer's literature determine the size of the shelf and the number of vials per shelf. ***For the purpose of this exercise let's assume that the shelves are 11" x 21" and hold 545 of our vials (as specified by the freeze dryer manufacturer).***

Step 3. To determine the total force needed to stopper a full tray of vials the following simple equation is used:

Total Shelf Force Required = Require Stopper force [lbf/vial] * Number of vial [vial]
(*2 lbf*/vial) * (*545 vials*) = 1,090 lbf of force to stopper an entire tray.

There are three ways that a manufacturer may express the stoppering capabilities of their dryers. These are:

1. **Lbf. If the lbf of the freeze dryer exceeds the 1,090 calculated in step 3 your freeze dryer has sufficient force to stopper a shelf of vials**. The number of shelves in your dryer do not affect the total force need to stopper the vials. You will need 1090 lbf total force regardless of the number of shelves.
2. **PSI (pounds per square inch) of stoppering pressure exerted by the shelf.** In this case it is easy to take our exercise one step further and calculate the psi required to stopper our vials.

   Step 4: Calculate the surface area of the shelf. In this case

   Area = width X length
   = 11" X 21"
   = 231 in^2

Step 5: To calculate psi (pounds per square inch) required by the container-closure system

Psi required = lbf required / area
= 1,090 lbf/231 in^2
= 4.72 psi

As long as the freeze dryer manufacturer's specification is greater than 4.72 psi you should have no trouble seating the stoppers correctly.

3. **PSI of hydraulic pressure delivered by the stoppering mechanism pump.** In this case, in order to understand the pressure at the shelves themselves, additional information is required from the manufacturer and additional calculations need to be done.

   The additional information required, in this case, is the diameter of stoppering bore.
   Eg: The hydraulic fluid in the stoppering pump delivers 1000 psi. The stoppering bore diameter is 1.5".

   Area of stoppering ram [in^2] = (π) *(r^2)
   = (3.14) X (*1.5*/2)^2 = 1.766 in^2

   The force delivered by a 1.5" diameter ram when supplied with 1,000psi of hydraulic pressure is:

   Force Delivered [lbf] = P[psi] * A[in^2]
   = (*1,000 psi*) X (1.766 in^2) = 1,766 lbf
   PSI at the shelf = lbf/square inch of shelf
   = 1,766 lbf / 231 in^2 = 7.65 psi

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If your freeze dryer is equipped with a hydraulic gauge for the fluid in the stoppering ram pump you may make adjustments to the stoppering force available to you by changing the hydraulic pressure of the fluid by working these equations backwards to arrive at the hydraulic pressure required.

Most stoppering mechanisms for freeze dryers typically deliver somewhere between 8 to 12 psi but it is always advisable to get this specification from the manufacturer. If you have a container-closure system that requires more force than that offered as standard, the freeze dryer manufacturer may be able to provide you with additional stoppering force for your system. Since the 8 to 12 psi pressure range works for the vast majority of the container-closure systems available it may be more advisable to change your container-closure system versus having a system with additional stoppering force.

If additional stoppering force is needed there may be no alternative but to use fewer vials per tray. When this is done the stoppering force on each individual vial is increased. Caution should be used to make sure that the vials are evenly spaced throughout the tray when this approach is utilized.

These calculations also illustrate the fact that when stoppering fewer vials than a full shelf, proceed with caution. If, in this example, the freeze dryer delivers 1766 lb force and you only put 3 bottles on the shelf, those 3 bottles are each experiencing 588.6 lbs of force if the stoppering mechanism is fully engaged. Interestingly, this kind of force can be so great that this uneven stoppering approach (because of fewer vials) may lead to glass breakage but is even more likely to cause the stainless steel shelves to warp and twist—requiring total replacement. There have been instances where the force needed to stopper a full shelf was so great that the underside of the shelf above the vials would have a dimple pattern of impressions that coincided with the stoppers of the vials below. Always check with the freeze dryer manufacturer to get their recommendations for stoppering less than a full shelf of container-closure systems.

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