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Cleaning Validation Limits for Lyophilizers – Part 1

This is another topic that I have presented on numerous times (the first time was at a technical conference in Zurich in 2000), but which has never evolved into a formal Cleaning Memo. The internal surfaces of lyophilizers (freeze dryers) are what I generally call "indirect-product-contact surfaces". For clarification, I generally divide surfaces into three categories:

> Direct-product-contact surface (DPCS): A surface which may directly contact manufactured product, for which there is generally a reasonable expectation of transfer of residues to the product.
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> Indirect-product-contact surface (IPCS): A surface which does not directly contact manufactured product, but which is in close proximity to open product and where there is a reasonable possibility of transfer of residues to product, usually by a vector such as air or an operator.
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> Non-product-contact surface (NPCS): A surface which does not directly contact manufactured products, and which is not in close proximity to open product.

Realize that these are generally the categories I use; others may define them in different ways. Also realize that using the same categories, some may place certain surfaces in different categories. For example, some companies may consider a tank for buffer preparation as an IPCS, because that surface does not directly contact product containing the drug substance. I will generally classify it as a DPCS because that residue in the buffer tank will clearly transfer to the next product via the manufactured buffer. Note, however, that although we may classify the buffer tank differently, residues will clearly transfer to the next product via the manufactured buffer. Note, however, that although we may classify the buffer tank differently, we will generally handle it the same in terms of how limits are set.

With that introduction, we now get to the issue of interest, which for Part 1 is how limits are set for a lyophilizers for vial lyophilization (next month we will cover bulk lyophilization).

Getting back to classification of surfaces, internal surfaces of a lyophilizer are generally considered indirect-product-contact surfaces. That is, at no time in the lyo process is GMP product (that is, "good" or "saleable" product) in direct contact with the internal surfaces. Yes, product may contact the shelves because product is spilled onto the shelves by a vial falling over during loading of the lyo, or product may contact the shelves because of a broken vial at some time during the lyo cycle. However, the product that contacts the shelves via those mechanisms is not product that is part of the approved lot. So, it is not appropriate to say residues on the shelves can directly contact manufactured product. For clarification, the product that contacts the shelves via a spill or broken vial is relevant for cleaning validation, but how it is relevant is not as a product which can pick up residues from the shelves, but rather as a residue which can indirectly transfer to vials of the next manufactured product.

Before we get to limits, let's discuss ways that residues on cleaned lyo surfaces can transfer to the next manufactured product. The most logical manner is airborne transfer. As vacuum is pulled in the lyo, air currents may dislodge residues on surfaces, those residues may become airborne, and those airborne residues may deposit into the vials. A secondary mechanism is that residues could become airborne during repressurization of the lyo, and potentially deposit in vials. A third mechanism is residues on the bottom of shelves becoming dislodged during shelf movement, causing the residue to drop and potentially fall into vials.

It can be reasonably argued that while these are possible mechanisms, they are not likely mechanisms. One reason is that partial stoppering of the vials doesn't create an easy pathway for residues to enter the vials. Secondly, during chamber evacuation any residues on surfaces that become airborne are likely to be pulled in the direction of the evacuation port. The path to an opening in any partially stoppered vial is likely to be a tortuous path. And, at the same time the air in the vial is being pulled upward and out, thereby reducing the likelihood of air (containing any loose airborne residues) entering into a vial. Third, during chamber repressurization, any loose residues on the chamber surfaces would have already become airborne; and furthermore, as the vials become stoppered, the likelihood of transfer into vials becomes close to zero. Fourth, unless shelves are moving during the evacuation process, any residue which becomes dislodged is likely to only fall straight down, which is not a pathway into the partially stoppered vials.

Another issue in terms of lyophilizers is that most problematic are residues that are loosely adherent. Tenacious residues are not as likely to become airborne. Note that this is the inverse of what is most critical for a DPCS. For a DPCS it is those residues which are most tenacious that are of most concern. And ironically, it is those loosely adherent residues (on an IPCS) which can readily be removed just by flowing water. Another issue related to this is that lyophilized products are generally made to be reconstituted by water alone for patient use. This suggests that any residues on surfaces before cleaning can be readily removed by cleaning with water alone (which is one reason that water alone is generally the only cleaning solution used for lyophilizers).

Note that so far we have considered residues of manufactured product. Another concern is residues of glass, which may occur if vials crack or break. The situation here is that manual intervention may be required to remove glass residues from the shelves. Furthermore, it is not likely that glass particles become airborne in any way. Finally, those "nanoparticles" of glass (I have no idea whether these are realistically to be found in this situation) are likely to be removed just by flowing water.

Okay, now we are ready to discuss setting limits. Remember that we are talking about indirect product contamination, usually by an airborne route. How can we relate what is measured on chamber surfaces to potential contamination of product in vials. The answer is that it is very difficult to do. One reason is that if recontamination occurs, it is not likely to uniformly contaminate every vial in the chamber to the same extent. It may be that vials on the outside are more likely to be contaminated as compared to vials in the middle of a shelf. Put this in perspective. I'm not saying that vials on the outside are likely to be contaminated; the previous statement is made in comparison to vials on the inside. In both cases the chances of contamination in most situations is extremely low.

In my 2000 Zurich presentation, I presented several scenarios of setting limits based on assuming all residues on chamber surfaces become airborne, and then land in the partially stoppered vials. For example, one scenario presented a situation in which residues became evenly dispersed within the lyo chamber, and then positing the volume of each vial into which airborne residues could deposit. While such scenarios are possible to consider, they generally result in a conclusion that visibly clean is acceptable. However, there are some assumptions in those scenarios which may not be totally realistic (such as the possibility that every vial will be contaminated to the same extent). So while such scenarios may be interesting to consider, it is common practice to set limits for cleaning in vial lyophilization in one of three ways:

1.Surfaces must be visually clean.

2.Surfaces must be visually clean, and swab samples must be below a certain default value, such as 10 ppm TOC.

3.Surfaces must be visually clean, and surface residue levels must be no more than levels acceptable on adjacent DPCS.

The rationale for the third option is that an IPCS represent a lower risk as compared to a DPCS; therefore if the IPCS is held to the same criterion, the risk should be acceptable. We should remember that there is no ideal way to set limits in this situation. But, I believe these options provide adequate protection in most situations.

So, we have covered some basic issues for lyophilizers, and have had more discussion on the situation of setting limits for vial lyophilization. Next month (in Part 2) we'll cover issues in lyophilization of bulk materials.