**September 2014**
**Cleaning Validation Limits for Lyophilizers – Part 2**

This is the second part of a three part Cleaning Memo series on lyophilizers (freeze dryers). Last month, we discussed some general issues, but focused on vial lyophilization. This month the focus will be on lyophilization of bulk materials, which typically are on (or in) trays. Many of the same issues related to transfer of residues from surfaces to manufactured products that were discussed last month will also apply here, so it is preferable to have read that Cleaning Memo before reading this one.

The major difference between bulk tray lyophilization and vial lyophilization relates to accessibility of the product to residues that may be airborne. Remember that last month we said that one of the major routes of contamination from chamber surfaces involves loosely adherent surface residues that become airborne. So, depending on the nature of the trays, there may be differing degrees of risk.

If materials (liquid or a semi-solid paste) are placed on open stainless steel trays, there are two concerns. One is that product may more readily (as compared to the partially stoppered vial situation) become airborne. If product is swept out of the lyo chamber, then the major issue is yield of product. If product from one tray is deposited onto product in another tray, then there is no concern about cross-contamination (assuming the same product is in all trays). However, if the situation is such that each tray represents a certain lot, then lot integrity may be an issue. There may be ways to minimize this, with covers of some type. However, that should be included as part of the design of the lyophilization cycle.

A second concern, and the one more related to cleaning validation, is that residues of a previous product on cleaned surfaces may become airborne. This is a situation where, compared to the partially stoppered vial situation, there is a higher probability of airborne residue (from lyo surfaces) depositing on product. For clarification, I am not saying it is a high probability; I am just saying the probability is higher in this case as compared to vial lyophilization. That said, it is also the case that residues on shelves may be less likely to become airborne. Why? Because with tray lyophilization, there may be a greater of occlusion of shelf surfaces due to the surface area of the tray (in contact with the shelves) as compared to the combined surface areas of the vials.

A third concern is that if surface residues become airborne, they are more likely to deposit on the top of the materials being lyophilized. What that means is that, unless there is a subsequent step to homogenize the residue within the total amount of product (such as by milling), a small portion of next product may be preferentially containing that residue. In one sense, this is not unlike vial lyophilization, where airborne residue would not evenly deposit in each vial.

A fourth concern with stainless steel trays is that they should be cleaned and reused. Therefore, the internal surfaces of the trays are direct product contact surfaces. Other things being equal, these trays represent a higher level of risk of cross-contamination. Also, realize that any contamination that transfers from the tray surfaces to the next manufactured product may be likely to preferentially contaminate only a portion of the subsequent product next processed in that tray.

It is possible to avoid some of these concerns with tray lyophilization by using certain disposable plastic tray systems, such as Gore's Lyoguard trays. With these trays, the possibility of airborne residues contaminating the product is remote. The Lyoguard tray is plastic, composed of polypropylene with an upper surface of expanded-PTFE. It is the expanded-PTFE which is permeable to air and water vapor, but not to particles or to

bacteria. These trays have a screw-cap opening on one end for addition of product to be lyophilized. Because the trays represent a "closed" system (that is, closed to particles and bacteria; obviously it has to be open to air and water vapor), exit of product inside the tray or entrance of outside particulate residues is essentially eliminated.

Because such trays are single-use (disposable), there is no concern about contamination of the next product from the plastic tray itself (another advantage of these single-use or disposable systems, at least from the perspective of cleaning validation).

This brings us to the issue of setting limits for cleaning processes for the lyophilizer. Here we must distinguish between the indirect-product-contact surfaces of the lyophilizer and the direct-product-contact surfaces of stainless steel trays. Certainly for the stainless steel trays, the internal surfaces should be treated as product contact, with limits based on the surface area and "batch size". It may also be prudent to include an additional safety factor to deal with the cumulative effect of residues from both the direct product contact surfaces and the indirect product contact surfaces.

With the use of the Lyoguard-type trays, the situation is different. Well, it's different from the perspective of the trays themselves, because they are disposable. While it might be possible to make a case for still cleaning the lyophilizer, but not performing cleaning validation, that probably won't fly. While a case can be made for residues not entering the disposable trays, another possible concern is residues on the outside of the trays and possible product contamination of the product during removal of product from the trays after lyophilization. It is for this reason that cleaning validation should still probably be done, albeit with perhaps just a visually clean criterion.

It should be remembered that there is not one definitive approach for either vial or tray systems. However, this Cleaning Memo and the previous one should provide issues for consideration in a risk assessment.