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Cleaning Validation Limits for Lyophilizers – Part 3

This is the third part of a three-part Cleaning Memo series on lyophilizers (freeze driers). So far, we have covered some general issues, and then focused separately with more detail on vial lyophilization and then tray lyophilization. This month we will cover the regulatory basis for doing cleaning validation of lyophilizers.

If (has been discussed in previous Cleaning Memos) the likelihood of contamination from lyo chamber surfaces is remote, why does everyone seem to perform cleaning validation? One possible reason is cleaning validation for lyophilizers seems to be assumed in the 1993 draft guidance from the FDA entitled "Guide to Inspections of Lyophilization of Parenterals". Here are several statements from that document, with my comments following each statement:

> "In order to minimize oil vapor migration, some lyophilizers are designed with a tortuous path between the vacuum pump and chamber. For example, one fabricator installed an oil trap in the line between the vacuum pump and chamber in a lyophilizer with an internal condenser. Leakage can also be identified by sampling surfaces in the chamber after lyophilization for contaminants. One could conclude that if contamination is found on a chamber surface after lyophilization, then dosage units in the chamber could also be contaminated. It is a good practice as part of the validation of cleaning of the lyophilization chamber to sample the surfaces *both before and after* cleaning." [Emphasis added]

Notice that the context of this statement about sampling before and after the cleaning process is related to leakage of oils/fluids during the lyophilization process itself (and not residues remaining after the cleaning process). The concern seems to be that if such leakage occurs during the evacuation phase, those oils/fluids could become volatilized and contaminate the product manufactured in that cycle. Notice the concern here is not particles, but vapors. And, I would expect it be the case that vapors (as compared to particles) could more likely enter into open vials.

Notice also that the statement calls for testing surfaces both before and after the cleaning process. Ordinarily in cleaning validation, there is no need to test for residues before cleaning; it is a reasonable assumption that in most cases surfaces will be soiled after the manufacturing process. This seems to be inherent in an FDA Human Drug CGMP Note of the 2nd Quarter 2001, where the question is posed "Must a firm quantify the amount of residue on equipment surfaces in support of validating the cleaning procedure?" The answer given is "In validating the original cleaning procedure, a firm need not quantify the level of chemical contamination remaining after manufacturing a product and before cleaning during validation exercises." Why is there a different approach for lyo cleaning from other types of process cleaning? I can't answer for the FDA's logic, but it does seem reasonable based on the concerns expressed. In the case of the lyo example, the concern is not how cleaning might affect the next product. Rather the concern is identifying a problem which might have occurred during manufacture of the previous product with that might affect the quality of that previous product. I think the logic here is that those leaked oils/fluids could be adequately removed by the subsequent cleaning process. In that case, the potential for contamination of that previous product might not be discovered at an early time if surfaces are only examined after cleaning. Note also that the lyo validation guide was written over 20 years ago, so that concern about leakage may have been addressed by lyophilizer manufacturers (but to put things in perspective, the FDA cleaning validation guide was also written in that same year).

Here is a second statement from the FDA lyophilization guidance:

> "Generally, lyophilizers should be sterilized after each cycle because of the potential for contamination of the shelf support rods. Additionally, the physical act of removing vials and cleaning the chamber can increase levels of contamination."

Note that the concern here with a requirement for sterilization is microbiological contamination. Furthermore, the focus seems to be the shelf support rods. The implicit assumption is that microbial contamination could somehow enter the vials, either during the evacuation/venting cycles or during the movement of the shelves as the stoppers are fully seated into the vials at the end of the cycle. Whether that is a reasonable assumption or not, I hesitate to offer an opinion. However, it seems to be an implicit assumption for most pharmaceutical manufacturers, since lyo chamber sterilization is a common practice.

The FDA makes this assumption clear in this next statement:

> "*Obviously*, the lyophilizer chamber is to be sterilized between batches because of the direct means of contamination." [Emphasis added]

My earlier statement about pharmaceutical manufacturers making the same implicit assumption about the possibility of microbial contamination may be wrong. It just may be that based on this third statement (the "obviousness" of the need for sterilization), firms may feel it is not worth arguing when a clear statement like this is made.

It may seem like we've gotten off-track somewhat by a discussion of sterilization of the lyo chamber. However, I think not. The assumption of the need to sterilize the chamber clearly leads to the related assumption that the chamber must be cleaned (and that cleaning must be validated). Why do I say this? Very simply, if it is the case that the lyo chamber should be sterilized in between lyo cycles, then the reason is that somehow microorganisms can transfer into partially stoppered vials. If that does occur, it is a reasonable assumption that those contaminating organisms are not "free floating" microorganisms, but are rather microorganisms contained in or on particles of some sort. This is the assumption in cleanrooms, and there is no reason to believe the situation is different for lyo chambers. Therefore, if during the lyo cycle microorganisms can contaminate product in vials, it is reasonable to assume that particles can contaminate that same product. And, furthermore, those particles may be residues left after cleaning. If that seems like reasonable logic, then that perhaps is the best explanation as to why it is appropriate to do cleaning validation for lyophilizers.

Just for clarification, when I referred to particles contaminating the product in vials, I am not necessarily referring to insoluble particles that could complicate use of products in an injection. If the particles left after cleaning are residues of the previous product, then it is likely those residues are water soluble, and would be dissolved once that subsequent product were reconstituted.

One final clarification. It is sometime argued that any residues left after cleaning in a lyo would be degraded by the subsequent sterilization process. While that might be true, it does not address the issue of "why do cleaning validation?" Clearly, we don't want to say that whatever the amount of residue left behind, it will be dealt with by the sterilization process, so we don't have to do cleaning validation (that is, we might clean, but don't have to validate that cleaning). I believe we are in a situation where if we believe sterilization is required, then it makes sense that we should also validate the cleaning before that sterilization cycle.