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Dealing With Preferential Transfer of Residues

Often in dealing with a specific issue for someone, I will think that I have previously written a Cleaning Memo on that subject, and I can just refer the person to that publication. Sometimes, however, I am surprised in that while I have presented numerous times on that topic, I don't have a Cleaning Memo specifically addressing that issue. Starting this month I will try to remedy that problem.

"Preferential transfer of residues" is a topic that I have covered often in my standard seminars. Another way that I have referred to this topic is "non-uniform contamination". By "non-uniform contamination" I do not mean that on the cleaned equipment that there are different levels or amounts of a given residue on different surfaces within that equipment. That generally is the case, and is part of the basis for selecting "worst case" swab locations. What I mean is non-uniform contamination of the next product. That is, residues from certain areas of the cleaned equipment may transfer to a small portion of the next product made. That is one reason I have tried to use the term "preferential transfer of residues", so as not to confuse the issue.

Preferential transfer of residues is not something new. It was addressed in the 1998 PDA Technical Report #29 ("Points to Consider for Cleaning Validation") and was called a "critical site". It was also addressed in the 1993 FDA cleaning validation guidance, in section VI.a. that discussed placebo batches:

> "One cannot assure that the contaminate will be uniformly distributed throughout the system. For example, if the discharge valve or chute of a blender are contaminated, the contaminant would probably not be uniformly dispersed in the placebo; it would most likely be concentrated in the initial discharge portion of the batch."

While the context of this comment is placebo batches, it does illustrate one situation where residues may preferentially transfer from a surface to a small portion of the next batch. It should be noted that in the example given, if the product is subsequently blended after passing over the discharge chute, the issue of preferential transfer may be addressed by that subsequent blending step.

The two most common examples of preferential transfer involve vial filling and tablet manufacture. In vial filling, residues on the cleaned filling needles and the associated filling equipment are not likely to transfer equally to product in every vial that is filled, but are more likely to transfer to the first few vials that are processed. With a tablet press, residues on the cleaned dies and punches are also not likely to transfer evenly to all tablets produced. Rather residues are more likely to be transferred to the first few tablets manufactured (although it is also possible that residues from the prior process may be trapped on surfaces by residues from the new product being processed).

How does one deal with this issue? The good news is that you may already have dealt with it. For example, in liquid filling of vials, it may be that you already process a certain initial amount of product (either flushing it to drain or filling vials that are discarded) that is not "saleable" product. The key in this situation is to confirm that the current practices do not produce some vials with unacceptable levels of residues of the previous product. One way to do this is to measure residues in the initially produced vials to see if they are below calculated limits. This is generally not a preferred approach because you have to measure residue of the

previous active in the new product (and we know that measuring residues at low levels in water or a solvent is difficult enough without having to address a new possible interference source). One possible modification of this approach is to fill vials with water (or another solvent) rather than product, so that the analytical task is more likely to be achievable.

A better approach for this vial situation is to make a worst-case calculation of how much product must be processed and discarded to deal with possible preferential transfer. Here is the information needed to determine this:

L1: Calculated limit in next product (in µg/g or µg/mL)
L3: Calculated limit of residue per surface area (in $\mu g/cm^2$)
SA: Surface area involved in preferential transfer (in cm^2)
AV: Amount filled per vial (in g or mL)

Then, the number of required discarded vials (assuming all discarded product is in filled vials) is:

$$\text{No. of discarded vials} = \frac{(L3)(SA)}{(L1)(AV)} \qquad \text{(Equation I)}$$

If you first discard some product before filling vials, the amount of product to discard to deal with preferential transfer is:

$$\text{Amount of discarded product} = \frac{(L3)(SA)}{(L1)} \qquad \text{(Equation II)}$$

This calculation assumes that residues will come off in the first amounts of product filled and/or processed. If it comes off evenly then preferential transfer is not an issue. If it comes off randomly (say only after 100,000 vials are filled), there is no logical way to deal with this situation (although it is not a likely scenario).

In this type of evaluation, if you determine that preferential transfer is dealt with after processing X vials (or after Y grams of product), then as long as the standard practice is to discard that number of initial vials (or that amount of processed product), then you have addressed this issue of preferential transfer.

If the number of vials or amount of product to be discarded is more than your current practice, then you have two options. One option is to discard more product or vials. A second option is to make the L3 limit just for the equipment involved in preferential transfer (that is, the equipment involved in the surface area value you used in the calculation) more stringent than the rest of the equipment. For example, suppose your overall L3 value is 2 $\mu g/cm^2$ and the calculated number of vials to discard is 50. But you normally discard only 35. In this option you would establish the limit for the equipment involved in preferential transfer at a lower value. If that lower value were half (1 $\mu g/cm^2$), then the required vials to discard would be only 25. Since you normally discard 35, you have adequately dealt with the preferential transfer. If you know how many vials are discarded, you can also determine the L3 limit required for the surfaces involved in preferential transfer by using the following equation (which is derived by solving for L3 in Equation I above):

$$L3 = \frac{(\text{No. of vials discarded})(L1)(AV)}{(SA)} \qquad \text{(Equation III)}$$

Similar types of calculations can be performed for the tablet press example. However, there may be other things that should be considered. In many cases, the dies and punches used for a given product may be dedicated to that product. In that situation, the surface areas of the dies and punches would not be included in the surface area involved in preferential transfer. Note, however, that there may be other surfaces in the tableting process which could contribute to preferential transfer.

There are other situations which are technically similar, but are handled differently. For example, in tablet filling equipment, the hopper to hold tablets may be filled multiple times during a run. In that case, it is likely that residues from the cleaned tablet filling equipment would be transferred to a large degree to the first hopper full of tablets. In this case, one does not discard the first hopper of tablets that are processed. The approach here is to set limits using a smaller batch size of product (for example, using as the batch size the mass or number of tablets in one full hopper).

The purpose of this Cleaning Memo is for me to have a document to refer individuals to when I am asked questions about preferential transfer.