

**April 2005**  
**Cleaning Validation for Packaging Equipment: Part 2**

This is a continuation of last month's Cleaning Memo. In that Cleaning Memo, I discussed the criticality of cleaning for primary packaging equipment. That this is important is evident from the fact that the principle involved (non-uniform contamination of the next batch) is mentioned in the FDA cleaning validation guidance. This month I will focus on issues related to limits and worst-case challenges.

As discussed last month, one issue that makes primary packaging equipment critical is that it is possible that residues on some or all surfaces of the primary packaging equipment may preferentially transfer to a small portion (such as the first portion) of the next product packaged. It would be prudent to set limits based on this worst-case assumption (that transfer of residues can preferentially occur into a small portion of the next batch). When limits are set based on Maximum Allowable Carryover principles (the conventional method for finished drug products), it is necessary to ask two key questions. The first is "What surface area of equipment has the likelihood of transferring residues preferentially?" In other words, because residues from these surfaces can preferentially contaminate a small portion of the next batch, it is possible that residue limits should be more stringent for these surfaces. The second question is "What portion (amount or percentage) of the next batch could possibly be contaminated at this higher level (due to preferential desorption or release from the equipment surfaces into a certain portion of the next manufactured product).

What is a reasonable surface area to consider for preferential contamination? Well, it depends on the nature of the equipment. For example, for tablet filling involving a hopper bowl and slats, it is reasonable to assume (as a worst case) that residues on the cleaned bowl and slats may preferentially transfer to the first part of the next filled batch of tablets. Therefore, the surface area used for this special calculation would only involve those specific surface areas. For a liquid filling operation, a similar judgment must be made, including the filling needles, the associated filling hoses (which could be omitted if they are "single use") and valves, and any other surfaces that could be associated with preferential transfer of residues.

What is a reasonable batch size? Remember that this is the initial portion of the next batch that could be preferentially contaminated from residues on the surfaces discussed in the prior paragraph. This is also a judgment call. For a tablet filling operation involving a hopper bowl, this batch size might be on the order of a half a hopper bowl full of tablets. Certainly one could take an extreme approach and say something like "This batch size is represented by a single layer of tablets on the hopper bowl surfaces." While that may be the case if tablets were perfectly rectangular solids and actually filled the hopper bowl in that manner, in most cases tablets have a rounded shape, and transfer of residues from the hopper bowl to tablets will require more than a single layer of tablets. In doing this for a liquid filling operation, it may be appropriate to use as a "batch size" the volume of the portion of equipment selected for preferential contamination of the next batch. In other words, there has to be a reasonable correlation between the surface area selected and the batch size selected.

In doing this calculation, since the batch size is in the numerator, the smaller the "batch size", the lower the residue limit. And, since the surface area is in the denominator, the larger the "surface area", the lower the residue limit. One may be tempted to overestimate the batch size to make the limit higher. However, remember that the estimated batch size has to reasonably relate to the equipment surface area.

Once those estimates are made and the surface area limit for the packaging equipment is calculated, there may be one of two results. One is that the surface area limit is the same or greater than for surfaces which transfer equally to all portions of the next batch. In this case, continue with cleaning validation with one surface area limit for all equipment. The second is that the surface area limit is smaller than the limit for surfaces which transfer equally to all portions of the next batch. In this case, continue with different cleaning validation limits for different parts of the equipment train.

In either case, the only concern is whether there is a possibility that you were overly aggressive in estimating how much of the next batch could be preferentially contaminated. In other words, while you estimated that it was the first 1000 mL that could be preferentially contaminated, perhaps it is actually only the first 100 mL. One way to deal with this possibility is to determine how much of the filled product is initially discarded as the filling line is started up. If the amount is 1000 mL (continuing with the same example), then there is no concern about preferential contamination because you have discarded the first 1000 mL of product. On the other hand, if the amount discarded is less than the amount that could be preferentially contaminated, then one option is to redo the calculation with the smaller batch size in the limit equation. Realize that if this is done, you may also have to adjust downward your estimate of the surface area that can preferentially contaminate the next batch.

Particularly if the calculation and your actual experience show that you can deal with this issue of non-uniform contamination by discarding the first quantity of filled units, your cleaning validation may not have to be changed. It is only if this is not the case that you may have to continue with cleaning validation using a more stringent residue limit. If that is the case, the cleaning process for the filling equipment may need to be more robust.

A final issue to be discussed is how to handle the case where you may have to deal with crushed tablets or capsules. How are these dealt with in a validation protocol, since these clearly represent worst cases? Normal production may not include these cases for every run. If that is the case, then one option is to specify that the three cleaning validation runs will be on the first three packaging runs in which crushed tablets or capsules occur. Some may not like this option, because it means that there may be more than three packaging runs before the cleaning process is validated. Another option is to deliberately cause a crushed tablet or capsule to occur on a packaging run, and to force this on the first three packaging runs. A third option is to introduce a cleaning process which has a separate step for cleaning following a crushed capsule or tablet (particularly after a crushed liquid- or gel-filled capsule). This process may just involve precleaning (perhaps with alcohol and a clean wiper to avoid the issue of detergent residues) until the affected area is visually clean. This will allow packaging runs to continue. At the end of the packaging run, then the equipment is cleaned by the routine cleaning procedure. [Note that the precleaned area certainly is a critical location for swab sampling.] If during the first three packaging runs, such an event as a crushed liquid capsule does NOT occur, then following completion of the run, certain equipment parts could be intentionally soiled with broken capsules. The cleaning should then include the cleaning for the broken capsule followed by the routine cleaning procedure. A time delay between the two cleaning procedures may be included if it might affect the overall results. It should be emphasized that the issues discussed in this paragraph do NOT change the residue limits; these issues only deal with one aspect of worst-case challenges during cleaning validation.