Cleaning Memo for June 2020
Another “Worst Case” Product Grouping Idea

I frequently teach that the solubility of the active, when used alone, is not the most appropriate way to select the “hardest to clean” product in a product grouping approach. Note that I sometimes refer to the “hardest to clean” as the most ”difficult to clean”; so for purposes of this Cleaning Memo consider them interchangeable. Sometimes that approach is fine. For example, if I manufacture sterile injectables with all formulation components other than the active (API) soluble in water, and if I clean with water alone, it is reasonable to conclude that the product with the active with the lowest solubility in water is the most “difficult to clean”. On the other hand, for oral solid dosage forms, such as tablets, it probably is not reliable to depend on the solubility of the active alone for determining the “hardest to clean”.

Why do I say that? Well, it is a simple factual matter that the excipient components for tablets do affect the difficulty of cleaning. Those excipients may be designed to speed up dissolution (as in orally dispersible tablets) or they may be designed to slow down release of the active (as in extended release, or ER, tablets). So, the question to answer is “what else can be considered to address those differences?” For example, it may be possible to say that ER tablets are more difficult to clean that immediate release and orally dispersible tablets, and therefore my first “cut” in a staged approach is to say the ER products in the group are the hardest to clean. Now, I just consider the ER release products, and among those ER products I now select the product with active with the lowest solubility. Will that work? Well, it’s a step in the right direction, but how do I know that the excipient formulation among the different ER tablets are equally difficult to clean. Perhaps I might say that the excipient formulation components are essentially the same, and therefore solubility of the active is the deciding parameter. So, I will need to work on those criteria to conclude that the excipient formulations are equally difficult to clean. I suspect you get the idea here of making sure you have a sound basis for selection of the “difficult to clean” product in a group.

Okay. Here is a proposal for an alternative method. For oral solid dosage forms like tablets, a common test is a “dissolution time” procedure. This is a test to evaluate the rate and extent of release of the active in tablets. The test apparatus is described in USP <711>. While the apparatus is designed to provide in vitro data for release of active that hopefully correlates with in vivo release when taken by a patient. It essentially involves placing a “dissolution medium” in a vessel with a stirrer, placing the product in the dissolution medium, and taking samples at time intervals to measure (by techniques such as HPLC) the amount of the released active at each time interval. Now, how can this procedure be modified and used for determining the most ”difficult to clean” product?

Obviously the “dissolution medium” is preferably the cleaning solution, which might be water alone or an aqueous formulated detergent formulation at the cleaning temperature. The product is then added to the “dissolution medium” to run the test. Samples of are removed at various intervals and analyzed for the active. That data can then be plotted.
with time on the X-axis and the total amount released on the Y-axis. If two products are compared, then some result can be compared to determine which product is more difficult to clean. If release is a linear function, then perhaps rate of release could be used. Another option is to avoid the rate of release issue and just set the criterion as time to achieve 95% release of the active (or another suitable percentage).

There are some concerns you might already have for testing tablets directly by this method. What if one is a 250 mg gross weight tablet and the other is a 500 mg gross weight tablet? That might not be a reliable comparison. Two tablets of identical weight but with different shapes (e.g., oval versus spherical) might also be problematic. In those cases a direct comparison would not be appropriate. I would have to do something different. That might be preparing in the lab tablets of the two different formulations at the same gross weight and with the same physical shape. Or it might not be testing the tablets, but testing the powdered formulation before the tableting step. After all, when I clean equipment it is not generally the tablet itself that is being cleaned, but some powder from an earlier step or from the (uncoated) tablet itself. Realize here I might have to develop data comparing the powdered formulation before and after the addition of a lubricant (such as magnesium stearate) to more accurately define the relative differences between different products at different processing stages (if such difference exist).

Now, let me emphasize this is just an idea. I have never seen this done, nor have I seen it proposed before. So don’t adopt this with trying it out and seeing if seems reliable. I would encourage any reader who tries it to let me know their experience. If this method does, in fact, provide a more reliable and justifiable way to select the most difficult to clean product for a grouping approach, we should share that information.

Now, there may be some objections. One is that rather than use this method, why not just use a simulated cleaning situation in the lab to make the comparison. After all, a simulated cleaning method not only gives the relative difference in difficulty of cleaning, but also gives in some sense an absolute determination of the cleaning conditions (assuming the lab cleaning method reliably translates to a realistic situation on the factory floor). My reply is that “I agree”. However, that option has been around for a long time and doesn’t seem to be so widely adopted. It may be that a modification of the dissolution testing is something that tablet pharmaceutical manufacturers are familiar with and already have the needed apparatus. Modifying the procedure for a comparison of active release may be more straightforward as compared to designing a lab cleaning method. The second part of my response is that a lab method like the “beaker test” makes a numerical comparison difficult, because in a lab cleaning study the evaluation is made after the combination of the washing step and the rinsing step, which really adds two elements to the interpretation if residues on the test coupons are measured analytically.

A second objection might be that when companies select the most “difficult to clean” product, they also consider the “most toxic” (i.e., the active with the lowest limit), so they are not really using solubility of the active alone. I have written earlier (see the Cleaning Memo of November 2017) on why toxicity is not related to difficulty of cleaning, but rather to the difficulty of meeting low residue limits in a protocol. That, of course, is why
for a product grouping approach I generally recommend selecting the most "difficult to clean" product in the group, but in the protocol evaluating the “most difficult to clean” product at the lowest limit of any product in the group.

Furthermore, you might ask if this type of evaluation could be applied to other formulation types. That’s conceivable. For example, it might be able to be adapted for ointments by evaluating a fixed amount (and with fixed shapes) of ointments. It also may apply to liquids if instead of testing the liquid itself, we tested the dried material, which may better simulate the dried material which could be left on the equipment at the end of an extended dirty hold time. However, at this time the more sensible place to start an evaluation of this technique is with oral solid dosage forms.

This suggestion is not presented as a panacea for all the issues we face in selecting the “most difficult to clean” product in a grouping approach. However, it seems to offer an advantage as compared to just relying on the solubility of the active.