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Revisiting Rinse Sampling Recovery Studies

The purpose of rinse sampling recovery studies is to address the “baby and bath water” question posed by the FDA. The question is this: “If you have bathed your baby, and you want to know if the baby is clean, what do you do, look at the baby or look at the bath water?” Well the obvious answer is that you look at the baby. The problem with that answer for pharmaceutical manufacturers is that there are circumstances where it is difficult or impractical to look at the baby; we want to look at the bathwater. In order to have a rationale why looking at the bath water is acceptable, we must perform rinse sampling recovery studies. Such studies tell us that if the residue were on the equipment surfaces (the “baby”), we would be able to quantitatively measure them in the rinse water (the “bath water”).

Depending on how the rinse is performed, there are several variations on how to perform these studies (see the October 2002 Cleaning Memo). However, the main issues to address for this Cleaning Memo are to explore what we are really measuring in a typical rinse recovery study. What is involved in a rinse recovery study is to spike a surface with a solution of the target residue (I’ll use the active as an example), allow the surface to dry, and then simulate the rinsing process in one of several ways. My question is the extent to which this rinse in a recovery study simulates the rinsing process in the execution of a cleaning process in a protocol. I’ll cover two situations, both involving an aqueous CIP rinse procedure. One is a rinse sample that is a grab sample of the final portion of the final process rinse; the second is a separate sampling rinse after completion of the process rinse.

We’ll cover the second case first. In the situation where I complete the process rinse, and then perform a separate sampling rinse, the recovery study is a reasonable approximation of the separate rinse sampling situation. That is, in the separate sampling rinse, regardless of whether the equipment is dry after the final process rinse, the separate sampling rinse could conceivably remove any of the active that is still on equipment surface. So in that case, applying the active and allowing it to dry represents either a realistic case (if the equipment is dried after the process rinse) or a worst-case situation (if the equipment is not allowed to dry after the final process rinse).

Now let’s cover the other situation, where what I am doing in sampling is to take a grab sample of the final process rinse. How does this relate to what I do for my recovery study? Well, it all depends on what is occurring during the process rinsing procedure. If I have designed my cleaning process in a robust manner, all the active that previously was on equipment surfaces should be either dissolved, emulsified or suspended in the washing solution. I then allow that washing solution to drain from the equipment and begin my rinsing process. As I continue my rinsing process, what is happening is that I am diluting out the concentration of the active in the wash solution, such that as the rinse proceeds, the concentration of active in the rinse solution decreases. If my assumption about the effectiveness of the washing process is correct, then there is no (or very little) active left on the equipment surfaces themselves at the end of the washing process (other than what is in the wash solution itself). I generally have not designed my rinsing process to remove residues from the surface itself. So what actually happens in the rinsing process is a dilution of the concentration of the active. So how does this relate to my rinse recovery study, where I am placing dried active on a surface and simulating the rinsing process? Well, it does replicate it. However, what I do in a rinse recovery procedure (with dried active on the surface) is to provide a worse-case as compared to the actual situation. Therefore any recovery

percentage I obtain in a recovery study can be used as a rinse sampling recovery.

Now, let's look at the second situation, where I perhaps have not designed my cleaning process so well. In this situation, most of my active may be dissolved, emulsified, and/or suspended in the wash solution, but some may remain on the equipment surfaces themselves. In this case, as I proceed with my process rinse, I am certainly diluting out the active in the wash solution. It may or may not be further serving to remove actives from surfaces themselves (that is, removing active that is on the equipment surfaces at the beginning of the process rinse. [Certainly if I thought water alone would be effective in significantly removing the active, I might use water alone for cleaning; that situation, however, confounds the difference between the washing solution and the rinse itself, since water alone would be used in each.] In this situation, the active I measure in the final process rinse is a combination of both the active diluted from the washing step and active removed from the equipment surface during final rinse. I think the important point here is that even if I have not designed my cleaning process well, a rinse recovery study involving dried active on a surface is also a worst-case approach to measuring residual active. A side note here is reiterate a point I have made frequently about rinse sampling. That point is that in a CIP process, a grab sample of the final process rinse is a worst case measure of the residues that can transfer to the next product, because it represent what is present in the rinse solution during the final rinse, not what is left on the equipment after completion of the final rinse (but that is a related, but different issue from the focus of this Cleaning Memo).

I realize that I have covered several issues here. However, there are two more things to remember about any sampling recovery study (swab or rinse). First, is that recovery studies are generally done for a specified residue. But, in actual fact, there may be other residues present when I sample for that given residue in a cleaning validation protocol. For example, when I do a recovery study for the active, I spike the active and nothing else (okay, except for the volatile solvent). But, in a cleaning validation protocol, there may also be cleaning agent and/or excipients present in the sampling situation. While this is a possible objection to just spiking the target residue, in many cases it is impractical to spike excipients with the active (such as for solid oral dose products). Furthermore, if TOC is the analytical technique and if multiple potential residues are spiked, the recovery measured might be intermediate between the recovery percentages of each spiked residue.

Secondly, in some cases, such as in biotech cleaning validation, I may do a recovery study with the bulk active. However, because I am cleaning with hot, aqueous alkaline cleaning solutions, the residues that exist at the end of the cleaning process are actually degraded fragments of that bulk active. Since those degradants are generally lower molecular weight and more polar, they should be more water soluble. Higher water solubility should give higher recovery percentages (assuming I am sampling with water, which is usually the case in biotech manufacture). Therefore, recovery studies done on the bulk active should represent a worst case.

The focus of this Cleaning Memo is to help provide a rationale for why doing rinse recovery studies the way they are typically done in the pharmaceutical industry is applicable to realistic rinse sampling procedures in protocols.