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Sampling Recovery for Volatile Materials

The purpose of a sampling recovery study is to combine the analytical method and the sampling method to demonstrate that if that residue were present on the surface, the combination of that sampling method and analytical method could appropriately measure that residue. For purposes of this Cleaning Memo, I will first consider issues related to swab sampling. As is typically done for a drug active (the drug substance), a solution of that residue in a volatile solvent is applied to a coupon of the surface of interest, and that spiked residue is allowed to dry before swab sampling is performed. For most non-volatile actives, the dried residue left on the surface is representative of the condition of that residue that would be on the surface at the time of swab sampling (since swab sampling is generally performed on dry surfaces). It is generally not considered appropriate to spike the active in a volatile solvent and immediately (before it has a chance to dry) perform swab sampling. The reason for this is that it is highly likely that swabbing a wet surface (with the spiked solution of the active) will result in higher recovery percentages in a recovery study.

Okay, what if my residue itself is volatile? That is, if I perform a recovery study as is typically done, all (or a major portion) of that residue will be evaporated. That would result in having very low (and probably unacceptably low) recovery percentages. The issue here is that if the residue is truly volatile, and following the cleaning process there would be adequate conditions for that residue to evaporate, what is the concern? Well, the concern would be that something goes wrong and the conditions were not adequate to allow for adequate evaporation. Remember the situation with Roche's Viracept. With that product, a tank used to hold a starting material was cleaned with ethanol, and apparently the ethanol was not allowed to adequately evaporate. The result was a side reaction between the ethanol and a starting material to produce a genotoxic material. I should add that in this situation the cleaning process was not a validated cleaning process, so that consideration of testing for residues of ethanol was probably not done.

Other concerns with volatile residues are related to the fact that volatile residues could get into the working environment, leading to possible issues such as worker safety and interferences with TOC sampling for volatile organics. These other issues don't directly impact recovery studies, so they will not be covered in this Cleaning Memo.

However, this case of Viracept can be used to illustrate how to perform recovery studies for volatile residues. Remember that the objective of the sampling recovery is to adequately quantitate residues on surfaces if they are present. So, if I perform a recovery study by spiking the residue and then immediately performing my swab sampling, what is done is to demonstrate that I could measure residue if it were present. Clearly if I allowed adequate time for evaporation, there would be very low residues of any volatile residues on the surfaces. Therefore, doing a recovery study as is typically done (with drying of the spiked residue) makes no sense for volatile residues (other than to clearly demonstrate volatility of the residue). But, performing the recovery study by sampling immediately after spiking does demonstrate that I could measure the residue if it were present. Some companies may choose to perform a recovery study twice. The first study would be swabbing the spiked residue immediately after spiking, and the second would involve swabbing after a typical overnight (or equivalent) time of drying, which would demonstrate that with adequate conditions, the residue should not be measured (or would be measured with very low recovery of the originally spiked amount).

A further caution should be considered here. That is, if the analytical method is TOC, I may have to address some additional issues. For example, suppose I had a detergent with a volatile organic component and a non-

volatile organic component, and my main concern was the volatile organic component. If I spike the detergent itself and I sampled immediately after swabbing, I would measure recovery of both the volatile and nonvolatile organic components. For example, suppose the volatile and non-volatile components each comprised half of the total organic carbon present. If my recovery was 100%, I could reasonably assume that the recovery for each component was 100%.

On the other hand, if when I sampled immediately after spiking and the overall recovery was only 75%, it is at least theoretically possible that one component has a 100% recovery and the other has a 50% recovery. If I repeated the study and sampled after drying, I would have additional information. For example, if the overall recovery for sampling after drying was 75%, it is probable that I achieved 75% with each component. But, if the recovery after drying was only 50%, it is likely (assuming almost complete evaporation of the volatile component) that my original recovery (swabbing immediately after spiking) may be closer to 100% for the non-volatile component and 50% for the volatile component.

A few words about rinse sampling and recovery studies for volatile residues, because there are more complexities there. We will consider two situations, that of a separate sampling rinse and that involving sampling of the final process rinse. Furthermore, a separate sampling rinse could be done in one of two ways: either to allow the equipment to dry before my separate sampling rinse, or to follow my process rinse immediately with my separate sampling rinse (without drying in between). I sure you can see a possible difference here, in that with the separate sampling rinse done after drying, I have many of the same issues of volatility of the residue as with swab sampling.

The situation with sampling of the process rinse is slightly less complex. Providing that the volatile residue of interest is soluble or miscible in the final process rinse, performing a recovery study immediately after spiking is probably reasonable, in that there is no drying involved in actual manufacture (at least not before the separate sampling rinse). Note that while there may be drying before the cleaning process, that drying will only lower any volatile residue in the cleaned product which could transfer to the final rinse. If the volatile residue were part of the cleaning agent, then the volatility of that residue could only occur in the washing/rinsing process, which would make it not relevant to recovery from surfaces.