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Additional Considerations in Recovery Studies: Part 1

Last month's Cleaning Memo suggested that swab recoveries were relatively straightforward. That is definitely true in comparison to recovery studies for rinse sampling- the swab procedure utilized in the lab recovery study is exactly the same as that used in the validation protocol, whereas the rinse sampling procedure has to be simulated in the lab. However, there are some key items in a swab and/or rinse recovery study that require careful attention to make sure the lab recovery procedure accurately represents recoveries obtained in the validation protocol itself. Those items include:

What to spike: The residue that is to be analyzed should be spiked. However, if the target residue is the drug active of a finished drug product, the question arises whether only the active itself is to be spiked, or whether the active should be spiked along with the various components in the finished drug product excipients. There is no magic answer here. Fortunately, when applied at low levels at the acceptance limit and below, there is probably little difference in the recovery percentage between the two situations.

One exception to this involves any procedure that involves TOC analysis of the active. For TOC analysis it is generally only feasible to spike the active itself. If the drug product contains any organic excipients, those excipients will contribute to the TOC value in the recovery study. For example, if a finished drug product contain 50% of its TOC from the active and 50% of its TOC from the excipients, then what does a recovery of 70% (as measured by TOC) represent if the drug product itself is spiked? Does it represent 70% recovery of the active and 70% recovery of the excipients, or does it represent 100% recovery of the excipients but only 40% recovery of the active? For this reason, it is preferable in this case to spike only the active (if TOC is the measurement technique).

This TOC exception can be complicated in the case of biotech actives. In most cases, it is difficult to isolate the active (for spiking) apart from the various organic stabilizers that might be utilized for the protein active. In this case, it makes better sense to spike the stabilized product (active protein plus organic stabilizers). Then one can make the assumption that the recovery of the active and the recovery of the organic excipients is essentially the same. One strategy to have more confidence in this assumption would be to actually perform two recovery studies. One study would involve spiking the drug product (the stabilized protein), and a second study would involve only spiking the product placebo (product minus the active protein). If the recovery with the drug product were 75% and the recovery of the placebo were also 75%, this is reasonable supportive evidence that the recovery of the active is also 75%.

Types of surfaces: Coupons used in the recovery studies should reflect the different material surfaces that will be sampled in the cleaning validation protocol. For example, if both stainless steel and PTFE are sampled in the protocol, then recovery studies should be made on both types of surfaces (stainless steel coupons and PTFE coupons). In most cases the recoveries on different non-absorbent surfaces will not be significantly different. However, until there is adequate published data (at least within certain classes of residues) to support the similarity of recoveries on different surfaces, it is prudent to perform recovery studies on different surface types.

Related to this issue is the quality of the coupon material and the quality of the surface. If the equipment

surfaces are 316L electropolished stainless steel, must the lab coupons also be electropolished 316L stainless steel. Here again, a safe harbor may be to use 316L electropolished coupons. On the other hand, the "electropolished" surfaces in the equipment might not be quite the surface quality of the laboratory coupons. A case can be made for using a rougher surface finish, on the assumption that a rougher surface may be a worst case (by giving the same or lower recoveries). One could also consider the use of 316 or even 304 stainless steel for lab coupons (rather than 316L), in that the recoveries will be very similar.

In considering whether one gets the same data, one must remember that swabbing a coupon is a form of "manual cleaning", and the results are not that precise. Variations of ±10% around a mean are not uncommon for different operators.

Uniformity of the residue: A third issue involves the uniformity of the spiked residue on the coupon surface. If one were spiking a residue at a level of 1.2 $\mu g/cm^2$, one would spike 120 μg of the residue onto a surface where 100 cm^2 is sampled. Must the residue be uniform? The more basic question is "Can the residue be uniform?" Assuming the residue is applied as a solution in water or another solvent, unless one is spiking a surfactant solution, it is very difficult to spread the spiked solution evenly over the coupon surface. The basic answer to the first question is that it probably doesn't matter if the dried residue is evenly applied or unevenly applied. One could make a case that unevenly applied residue is a worst case for removal; one could also make a case that uneven residue probably more appropriately reflects how the residue exists on the equipment surface as it is sampled in the validation protocol. The only caution with uneven application is that the person swabbing may be tempted to apply extra pressure where residue is seen; this should be avoided -- the purpose of swabbing recovery studies is to follow the swab SOP exactly, not to modify it based on special circumstances.

These are three issues that should be addressed in sampling recovery studies. These three apply equally to swab and rinse sampling. The discussion of additional considerations will continue in next month's Cleaning Memo.