How to Succeed in the Search for Nothing:

Effective Swabbing Techniques for Cleaning Validation

Introduction

Searching for nothing would seem to be an absolute waste of time — unless you are responsible for cleaning validation. In that case, success is deliciously ironic since you can say, "I found nothing and that's good news."

We should start at the beginning. Those involved in the manufacture and quality control of pharmaceuticals and biotechnology products are aware of the need to prove that the production equipment and the manufacturing environment are sufficiently clean such that the next lot of product will not be contaminated by materials from the previous lot, i.e., that cross contamination will not be an issue. The procedures and documentation for that proof represent what is known as cleaning validation. Essentially, one wants to prove with a high degree of certainty, that any residues of drug product from a manufacturing lot and any residues of cleaning agents used to remove those drug residues, are below acceptable limits. We are not exactly searching for nothing (as in a zero value), but for extremely low values of residues — both drug product and cleaning agent residues.

Cleaning Validation

Cleaning validation can be considered a three-step process involving:

1. The cleaning and rinsing of the process surfaces
2. Sampling to detect any drug or cleaning agent residues that might still remain on those surfaces, and
3. Analyzing the sampled materials with the appropriate instrumentation.

Steps 1 and 2 are manual, sometimes tedious procedures, but only if they are done properly, they permit accurate results to be reported in Step 3. The cleaning of surfaces (what cleaning agents to use, how to do the cleaning, etc.) and the analysis of the sampled materials are not our focus here. For this discussion, we will look only at Step 2 — the procedures that enable one to sample a cleaned surface with a high degree of reproducibility, to ensure that what is reported in Step 3 truly represents the condition of the sampled surface.

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Figure 1. A polyester knit swab used for surface sampling. A notched handle allows for easy snapping the swab head into the vial.

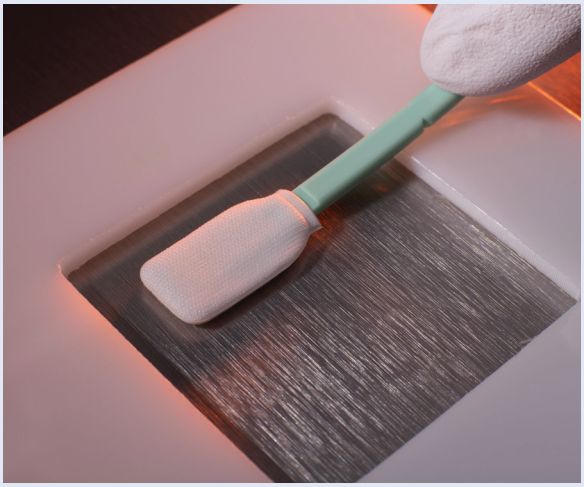

Figure 2. A template for surface sampling

Though it may seem intuitively obvious, one does not begin the cleaning validation process until there is an absence of visible residue on the surface. Residues can be visible at surface concentrations of between 1 and 4 µ/cm^2. The simple rule is that if you can still see residues on the surface, forget about any sampling activities, you have not finished Step 1 — the cleaning activities.

Sampling Surfaces with Swabs

Assuming the surface is free of visible residue (i.e., that the cleaning stage is properly completed), the challenge is to sample surfaces in a reproducible manner, such that any (invisible) residues, present in extremely small amounts, are collected and delivered to the instrument for measurement. The best type of swab for sampling is one with a head made of laundered polyester knit fabric (Figure 1), since the material provides the lowest levels of releasable particles, the highest recovery and the lowest background when total organic carbon (TOC) measurements are employed as the analytical technique. To sample the surface, the swab is moistened then drawn across the surface in a thorough and reproducible manner to collect any residue into the polyester knit fabric swab head. The swab head is then deposited into a suitable collection vial, and the residue is extracted for subsequent analysis.

It is worth devoting a moment to the technique for moistening a swab, since errors in technique here will lead to inconsistent results. There might be a temptation to simply saturate the swab head with high-quality (e.g., TOC-grade) water to do the residue collection. This will cause problems, since the excess liquid on the swab head will simply spread the residue over the surface to be sampled and will not allow the residue to be picked up reproducibly into the swab fabric. For best results, the swab should be damp, but not saturated. This is best accomplished by immersing the head into a container of high-quality water, and pressing both sides of the swab head against the side of the container a few times to expel any air trapped in the fabric to allow the water to fully penetrate the fabric. Then, the swab head is raised out of the water and the flat sides of the swab are drawn across the rim of the container to expel excess water and leave the swab head moist.

The manner in which the swab is used to sample the surface, i.e. the swabbing pattern, is critical to ensure accurate and reproducible collection of residues. For easily accessible surfaces, a template with a 5 cm x 5 cm opening can be used to sample the same surface area each time (Figure 2). As with wiping, linear, overlapping strokes in one direction over the surface to be sampled will ensure that the residue is collected into the moist swab head. Figure 3 shows a typical sampling pattern employing 2 swabs. The first side of the first swab is swiped horizontally 10 times over the template opening, then the swab is flipped over and the second side is swiped vertically 10 times over the same surface. This swab is deposited into the collection vial (Figure 4). The first side of the second swab is swiped diagonally upward 10 times, then flipped over and the second side swiped diagonally downward 10 times. The second swab is deposited into the same collection vial. In this manner, the surface has been swabbed a total of 40 times, and there is a reasonable expectation that any residue on the surface has been transferred into the two swab heads. It is not required to use two swabs; often one will do.

Operators can verify that their technique for dampening the swab heads and swabbing surfaces is appropriate through replicate recovery experiments of known challenges dispensed onto sample surfaces. Ideally, one would like to recover 100% of the challenge, but recoveries may be limited to 75%-80%, depending on the sampling conditions and the residue. It must be recognized that the swab head may not get everything off the surface and that the extraction liquid may not get all of the residue out of the swab head. Indeed, a 90% efficiency at each stage, produces an overall recovery of only 81% (i.e., 0.9 x 0.9).

Pre-cleaned vials and swabs are available commercially that provide TOC background levels of <10 ppb and <50 ppb TOC, respectively. This may be important if very low levels of residues are sought, since one never wants to report at an analytical value obtained by subtracting two large numbers to produce a small difference.

Conclusions

So the search for nothing really involves (1) good cleaning and rinsing protocols, (2) proper swabbing techniques to ensure that any residues left on the surface are collected into the swab, and (3) pre-cleaned vials and swabs for minimum background levels.

Rigorous attention to detail & technique will enable success in finding nothing.

[For step-by-step Cleaning Validation guide, watch this video]

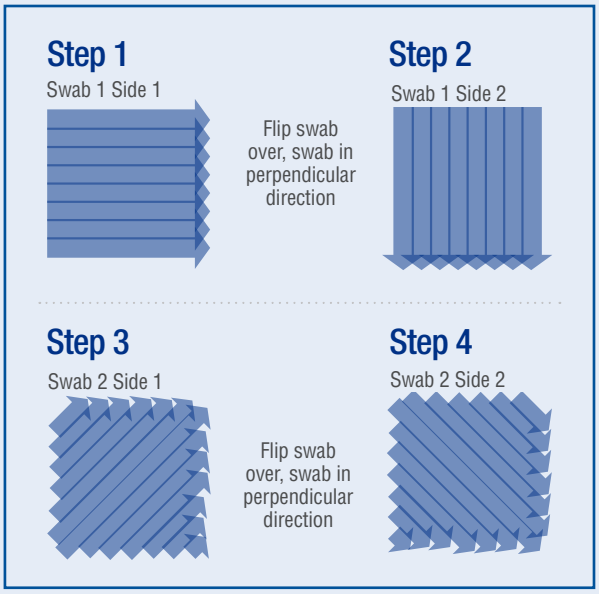

Figure 3. Step-by-step swabbing patterns for using two swabs.

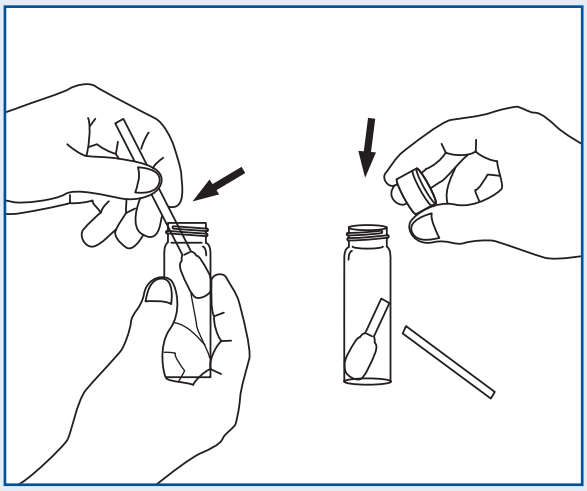

Figure 4. A notched swab handle simplifies separating the swab head from the handle. Only the head should be extracted for TOC measurement.

Figure 5. Cleaning Validation Kit TX3343

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