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Solvent Reflux Sampling Recovery

A general principle for cleaning validation protocols is that if you utilize a certain sampling technique to measure residues that are then compared to acceptance criteria (limits), then it is necessary to perform a sampling recovery study to confirm that the sampling method appropriately measures residues if they were present. This is covered by the statement in the FDA cleaning validation guidance (Section IV.3), "The firm should challenge the analytical method in combination with the sampling method(s) used to show that contaminants can be recovered from the equipment surface and at what level, i.e. 50% recovery, 90%, etc." This is also explicit in the PIC/S guide (Section 7.10.3), "The analytical methods should be challenged in combination with the sampling methods used, to show that the contaminants can be recovered from the equipment surface and to show the level of recovery as well as the consistency of recovery. This is necessary before any conclusions can be made based on the sample results."

For swab sampling, the sampling procedure can easily be replicated in the lab using spiked coupons of representative surface materials. For rinse sampling, the sampling situation and parameters also can be simulated in the laboratory. For solvent reflux sampling, as is commonly done in small molecule API synthesis, it is also possible to simulate the sampling situation and parameters in the laboratory. In that simulation, a reflux flask with a condenser is set up, and either a spiked coupon is suspended inside the condenser, or the inside of the condenser is spiked directly (particularly if glass is the only surface, this may be acceptable). Recovery studies are conducted in much the same manner as other recovery studies, with the amount removed in sampling compared to the amount spiked. An acceptance criterion is established, based on whether the purpose is just to qualify the sampling method or the purpose is to use the recovery percentage to adjust ("correct") the limit or the protocol analytical data.

There is one other possible consideration for solvent reflux recovery. This is to assume a high recovery (>95%) based on well established scientific principles. What are those principles? Well, if the residue to be measured is readily soluble in the refluxing solvent, particularly at the temperature of condensation, then it can be assumed that under the conditions of refluxing for an adequate time, the residue would be removed from the surface more or less completely. What do I mean by "readily soluble"? What that would mean is that the solubility (of the residue in the refluxed solvent) is at least ten times (10X) higher than the expected concentration (assuming 100% recovery) in the solvent sump in a recovery study. In other words, if 100% recovery in a recovery study were to result in a concentration of 9.2 µg/mL in the solvent sump, I would want the solubility of the residue in the solvent to be at least 92 µg/mL. This also assumes adequate time to achieve solubility. The figure I would use is that the time of contact of condensed solvent with all parts of the equipment surfaces is at least fifteen (15) minutes. In other words, under those conditions of solubility (10X greater than the expected maximum concentration in the solvent sump) and a time of at least 15 minutes, I would expect essentially all the residue to be effectively removed and sampled.

The expected concentration in the solvent sump can be calculated by determining the limit per surface area (what I typically call the L3 limit), the surface area sampled during the recovery study, and the amount of solvent used for the study. Note that the ratio of solvent to surface area in the recovery study should be the same as the ratio of solvent to surface area in the production equipment (or should be a worst case in the recovery study, meaning less solvent per surface area). In addition, the contact time of 15 minutes is not the

time of refluxing; rather it is the time of contact of condensed solvent with all surfaces.
Under these conditions, it can be argued that, based on good scientific principles, a laboratory study to confirm recovery is not required.

Here are possible objections, along with replies, to this approach:

1. Objection: What if the residues on the surface are degraded materials?

   Answer: If the residues that are being sampled and measured are degradants, then either the recovery study needs to be done with those degradants or else (in the case of a rationale for not doing a recovery study) the applicable solubility criteria is the solubility of that degradant in the condensed solvent.

2. Objection: What if condensed solvent does not contact certain surface in the production equipment?

   Answer: This is not a recovery issue, but rather sampling issue. It is a problem whether a formal sampling study is done or not. If during the reflux sampling condensed solvent is not contacting a given surface, then the sampling needs to be revised.

3. Objection: This approach is generally not used for rinse sampling; what's different here?

   Answer: In conventional rinse sampling (flushing with water or solvent, for example), the contact time of the water or solvent with a given surface is limited (generally only a few minutes). Furthermore, in rinse sampling, the turbulence of flow is important in terms of recovery from surfaces. With solvent refluxing, the only mechanism of removal of residue from the surface is solubility. Therefore, with an extended time of at least 15 minutes at the temperature of the condensed solvent, complete recovery can be expected. Also, with solvent reflux "fresh" solvent is continually being applied the surfaces.

If this approach is used, a formal procedure needs to be set up, giving the rationale and requirements to utilize the approach. Furthermore, for each new residue, a report should be generated showing how those requirements are met for that residue and a given sampling situation.

This Cleaning Memo is designed to provide information and conditions for an alternative mode of dealing with recovery studies for solvent reflux sampling.