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Measuring Residues of Volatile Solvents?

A common question for residues for pharmaceutical manufacturers is whether it is necessary to measure for residues of volatile organic solvents in cleaning validation protocols. While this question primarily arises with API manufacturers who perform solvent cleaning for manufacturing involving organic synthesis of actives, it also comes up in finished drug manufacture where a volatile solvent (typically isopropanol or ethanol) is used as a final rinse (perhaps after a water rinse).

This question has become even more germane because of the cleaning problem that led to the recall of Viracept by Roche. The cleaning problem was that ethanol was used as solvent for cleaning. Because it was left behind in a storage vessel for a reactant (perhaps because of not being allowed to adequately evaporate), the ethanol reacted with the reactant to form a genotoxic material, which was then carried through the manufacturing process at a relatively high concentration.

First, it clearly makes scientific sense to say that if there are adequate conditions to assure the complete evaporation of the volatile solvent, then there is no need to measure it in a cleaning validation protocol. How can that assurance be achieved? One way is by visual observation to see if surfaces are still "wet" with the solvent. The other is usually some technique, like an air or nitrogen blow, for a time to assure evaporation. Depending on the solvent, a "smell" test may also be used (perhaps to supplement one of the other methods).

Second, it also makes good compliance sense to perform a FMEA (Failure Mode Effects Analysis) on the cleaning process to determine what the consequences of inadequate evaporation would be. Would residual solvent lead to an unacceptable by-product residue (as in the case of the Viracept problem)? Would residual solvent lead to interference with a subsequent process step? There may be other questions that would be relevant depending on the specific situation. Of course, a conclusion might be that the solvent is a solvent that is utilized in the next manufacturing step, and that (other than possible effects of dilution), the residual solvent would have no effect on the quality of the manufactured drug active or drug product.

Third, despite this, one can expect some manufacturers and some regulators (and perhaps some consultants) to overact to the Viracept problem and want to measure residual solvent in any case. If that is to happen, the questions that can be asked are "How do I set limits?", "What analytical techniques can I use for residues?", and "What sampling techniques are appropriate?" Let's take these questions one at a time.

First, how are limits set? Let's assume for purposes of this discussion that the only concern would be residual solvent in the same or in a different API. In part this is a traditional question of "What is a safe level based on toxicity concerns?" One might be tempted to the use the limits for residual solvents in ICH Q3C. That ICH document, however, deals with residual solvents from a manufacturing process. While some can argue (as I sometimes do) that cleaning is part of the overall manufacturing process, I believe it is clear that the ICH Q3C is not meant to apply to residual solvents from cleaning processes of the previous drug active. If that were the case, the levels of solvents that could be left behind after cleaning could be significant since concentrations in the manufactured product of 0.5% are allowed for Class 3 solvents. Furthermore, ICH Q3C states that residual solvents are ones that "are not completely removed by practical manufacturing techniques". It can be argued for cleaning processes that one should be able to "completely remove" volatile cleaning solvents by "practical"

manufacturing techniques. Rather than invoke ICH Q3C, it would probably make better sense to do "traditional" safety-based calculations based on LD_{50} or NOEL values for such solvents.

Analytical techniques for solvents include things like gas chromatography, or Total Organic Carbon (assuming the solvent is an organic solvent containing carbon). Either technique should be able to adequately measure residue at expected residue limits. But when it comes to sampling, there may be differences. Why? If the sampling of the system is not surface sampling, but rather sampling of air (or nitrogen) as the system is flushed to evaporate the volatile solvent, then it makes sense to perform GC. On the other hand, if sampling is by swabbing, then unless the system is grossly wet with the residual solvent, you are unlikely to pick up much residual solvent with a swab. On the other hand, for swabbing TOC can be used if the swabbing is with water and if the solvent is water miscible. In this case, the use of equipment that measures non-purgeable organic carbon (NPOC) would not be appropriate (assuming the volatile solvent is purged in the NPOC system).

Of course, if swabbing were done, any swabbing for a recovery study would have to be done immediately after the surface was spiked with the solvent (since drying would cause evaporation of the solvent, and hence a low recovery).

If all this analytical and sampling discussion sounds like overkill, I agree. It is much simpler to have some kind of process control to effectively establish that evaporation is complete. Of course, this control should be in place for every cleaning process. It is also simpler to perform a FMEA and either establish that carryover of residual cleaning solvent has no effect on product quality or safety, or establish a detrimental consequence of residual solvent due to inadequate evaporation (which should then lead to measures to insure adequate evaporation).

The purpose of this Cleaning Memo is not to argue for one way or another for handling volatile cleaning solvents. Its emphasis is on understanding the cleaning process, and then making evaluations based on that understanding of possible concerns due to residual solvent being left on equipment surfaces. This is one of the key ideas behind a "risk-based" analysis.