Cleaning Memo for September 2019
Cleaning Validation for Homeopathic Drug Products

In order to discuss a possible approach to cleaning validation for homeopathic drugs, I first need to clarify what constitutes a homeopathic drug. "Homeopathy" is a practice in which a substance which causes disease symptoms at high levels is thought to have curative effects of those same symptoms at very low levels. A homeopathic drug is one where the substance is prepared in a more concentrated form, and then diluted down to a very low level. That low level is one where the substance may not be able to be analyzed in the final product. It is for that reason that homeopathic drugs are exempt from the FDA requirement for "laboratory determination of identity and strength of each active ingredient prior to release for distribution". Furthermore, while homeopathic drugs in the USA are not evaluated by the FDA for safety and efficacy, the manufacture of those drugs is subject to the CGMPs.

Which brings us to the issue of cleaning validation. The conundrum is that if it is *not* practical to have laboratory analysis for the "active" drug in the homeopathic drug itself, on what basis can we determine that the level of the "active" left behind in cleaned equipment does not affect in some way the subsequently manufactured homeopathic product. It probably is not acceptable just to say that at those very low levels it doesn't matter. It also probably is not acceptable to say that adequate further dilution assures removal, because performing recovery studies to demonstrate that fact are also not possible due to analytical limitations. Trying to establish ADE/PDE values probably won't work because it is likely that the ADE/PDE values are already above the levels of the active in the homeopathic product itself.

Which brings me to one possible approach (or at least the best approach I could think of). In this approach, I propose something similar to a dose-based calculation that allows 0.001 of the minimum daily dose of cleaned active in the maximum daily dose of the next homeopathic drug. Okay, I know you are probably thinking that that approach will not work for the same reason I gave above, namely that even lower values would not be measurable in any reasonable analytical test. And you would be right!

However, what I generally propose is not to analytically measure the homeopathic active itself, but to measure some other chemical species (which I will call a "marker") in the product. That other chemical species might be an organic salt (where I might measure an ionic species such as sodium ion or phosphate ion), or it might be the preservative in a formulation (assuming that these products are liquids rather than solids). So how would that help? Well, I would contend that *if* there is a reasonable expectation that the active would be reduced in the cleaning process by an equivalent percentage as compared to the marker, then analytically measuring the "marker" to show that the marker would be present in the next product at a level of no more than 0.001 of the minimum "dose" of the marker would be acceptable for residues of the active. In general, since the homeopathic drug active is prepared by dilution, it is reasonable that at first pass the reduction by cleaning/rinsing of the product should result in at least an equivalent percent reduction of the drug active and the marker.

That said, I can envision that there may be cases where the solubility of the drug active in the drug product is enhanced by presence of a marker or another chemical species, resulting in the active possibly not being reduced proportionally to the marker. Another concern might be if the drug product is dried on equipment surfaces, such that the *dynamics* of removal of the drug active were significantly less than that of the marker. There may be other specific situations that should be evaluated in individual cases.

I should say that I have no idea of this approach would be acceptable to regulatory authorities. However, I suspect that most regulatory authorities would focus on other concerns for homeopathic drugs, even though the December 2017 FDA draft guidance on homeopathic drugs includes " significant violations of current good manufacturing practice requirements" as one area of focus. The key word is whether implementing a cleaning validation program based on this approach would be a *significant* issue.

Needless to say, issues related to control of residues of cleaning agents, microorganisms and endotoxin are still concerns to be addressed as part of a cleaning validation program for homeopathic drugs.