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Limits Below the LOD in Rinse Solutions – Part III

This Cleaning Memo continues the thought processes in Part I and Part II, but goes beyond just the consideration of dealing with issues relating to the LOD/LOQ of the analytical method being too high. What I'm doing in Part III is discussing something related, but somewhat different. In the previous Cleaning Memos I discussed cases where the primary issue was not being able to measure the residue in the final rinse because of the LOD/LOQ of the analytical method. In this Cleaning Memo, I am assuming that the LOD/LOQ limitation is not present. I am further assuming that the the issue is that I want to set limits based on a separate sampling rinse, but I don't want to have to perform the separate sample rinse. That is, I want to measure residues in the *final process rinse*, and then extrapolate (or estimate) what that value might be in a *separate sampling rinse* if one were actually performed (but it is not).

In this situation, what I could do is set my limit for my target limit for a separate sampling rinse as if it were done. Then I measure the amount of the target residue in the final process rinse. I then take that value in the final process rinse, and extrapolate it to a value in the (unperformed) separate sampling rinse. I finally compare the extrapolated value in the separate sampling rinse to my calculated value for the separate sampling rinse.

Sounds easy enough, but there are certain requirements for doing this. First, I need to have a dilution value from the final process rinse to the separate sampling rinse. In order to do that, we will use the same principles that have been discussed in previous Cleaning Memos. That is, for my process rinses, I need to have at least two *discrete* rinse steps (such as pulse rinses) that are exactly the same, and that are also exactly the same as my *proposed separate sampling* rinse.

So, I first calculate my acceptance criterion for the separate sampling rinse using carryover calculation principles. Note for this calculation that I need to know the volume of solvent (organic solvent or water) that would be used for the separate sampling rinse if it were done. This volume should be the same volume used for the last discrete process rinse (actually, I could be more clear by saying it is the same volume used for each of the last two discrete process rinses). Let's assume that calculated rinse limit is 3.0 ppm. Now under the *conventional* way of setting limits for a sampling situation where I am analyzing a sample from the aggregate final discrete process rinse, I would say that the sample from the aggregate final discrete process rinse must meet the acceptance limit of 3.0 ppm. However, I know that is overkill (so what else is new in pharma processing?), because the residues left over after completion of the final process rinse (which is what I am really concerned about) would be lower. But I don't want to do it the conventional way; I want to extrapolate to a value that would be in the final process rinse if it were used. So under this extrapolation, the residue value in the final discrete process rinse could be above 3.0 ppm, but my extrapolated value could be below 3 ppm (thus demonstrating the equipment is acceptably clean insofar as this residue is concerned).

So, once I have my limit in the assumed separate sampling rinse calculated, in the protocol I then measure the residue in the last two discrete process rinses (these can be "dump and fill" rinses or can be recirculating CIP rinses). I then calculate the dilution factor in going from the penultimate rinse to the ultimate rinse. Using the assumptions I have made about the nature of the rinses, I then utilize that dilution factor to extrapolate from the residue value in the final discrete process rinse to my assumed separate sampling rinse. If the value of the residue is 47 ppm in the penultimate process rinse and 3.8 ppm in the ultimate process rinse, the dilution factor

in going from one rinse to the next is 45.6 divided by 3.8, or 12. I then use that same dilution factor to extrapolate from the value in the ultimate rinse (3.8 ppm) to a value in an assumed separate sampling rinse. That value of 0.32 ppm (or 3.8 ppm divided by 12) is then compared to my acceptance criteria in the separate sampling rinse. If the acceptance value is 3.0 ppm in the assumed separate sampling rinse, then I have met my acceptance criteria for that residue.

If this approach is of interest to you, I should remind you to revisit the September and October 2011 Cleaning Memos for some of the caveats in using an approach based on extrapolation of values in rinses. One key one to remember is that this approach depends on having a thorough washing step such that the target residue is adequately dissolved, suspended and/or emulsified in the washing solution; this helps assure that sequential dilutions using the same rinse processes give the same dilution factor. If the measured residue is still on equipment surfaces, then sequential dilution factors may not be the same. Of course, if this is an issue, it can be overcome by a more aggressive washing step or steps.

The purpose of the Cleaning Memo is not to advocate for the use of this method for measuring residues in cleaning validation protocols. The objective is to present it as an alternative, and to present considerations in its possible use.