October 2011
Limits Below the LOD in Rinse Solutions – Part II

This Cleaning Memo continues the thought processes in Part I (the September 2011 Cleaning Memo) by discussing applications to CIP rinsing. If you remember, the situation is this. I have established limits in my rinse sample based on carryover calculations, and the limit is X ppm. However, my analytical method can only detect down to a level of 3X ppm. Therefore, it appears that I can't really establish, based on a rinse sample, that I am meeting my acceptance criterion. The principle given in Part I involved situations where a series of discrete rinses were utilized in a dump and fill operation. The solution was not to measure the target in the final rinse, but to measure it in a prior rinse (where it is more likely to be above the LOQ). Then using known dilution information in going from one rinse to the next, determine what the target residue value should be in the final rinse.

It may be helpful to review Part I before you continue, because Part II assumes you are familiar with the general concept from Part I. I do not repeat all the conditions and caveats given in Part I in this Cleaning Memo, although most of them do apply to the CIP rinse situation.

Furthermore, usually when I present a somewhat unorthodox approach like I did in Part I, I will get some emails objecting to what I presented. Surprisingly, I have received no comments on the September Cleaning Memo. One possible reason for that could be that my presentation was so brilliant. However, I suspect the more likely reason is that so many of you were just coming back from vacation/holiday.

In any case, Part II will be a discussion of the application of those dilution principles to a CIP rinse. Before I present the details, I want to remind you that the carryover calculation limits for a final grab sample of a final CIP rinse should be based on the principles given in my Cleaning Memo of October 2005. That calculation involves estimating a worst-case limit based on an assumed separate sampling rinse, and then holding the grab sample of the final process to that same criterion (as a worst case).

So, let's assume that I am doing a series of three discrete pulse rinses following the washing step with a detergent. In between each pulsed rinse, I let the rinse solution drain from the equipment. Furthermore, in this first example, let's assumes that the first two pulsed rinses are recirculating, and that the last pulsed rinse is also recirculating. In this situation, I would measure my residue in the second rinse, and then based on dilution to the third rinse, extrapolate to a value in that final rinse. However, I need to be careful about what I measure for the second rinse. What I measure depends on whether in a recirculating rinse the residue is evenly dispersed throughout the rinse. In other words, does the first portion of the rinse give essentially the same value (within experimental error) as the last portion of that rinse as it drains from the equipment. If that is the case (which is expected for a recirculating rinse), then I can measure the residue in the second rinse (any portion as it exits from the equipment), and extrapolate what the value would be in the next (the final) rinse.

How would I determine the dilution factor? Can I use the same principle discussed last month, where I make a worst case estimate of the thickness of a film of water that could be left on various equipment surfaces (vertical walls, horizontal bottoms, etc.) as well as possible hold-up volumes (perhaps due to drains, dead legs, ports, etc.), to come with a volume of residual rinse solvent. Well, that might be possible, but the estimate of residual volume following draining in a dump-and-fill operation will not necessarily be the same volume following draining in a CIP rinse. Part of the reason is that the time frame involved for draining is different

(while the time after the completion of the rinse may be the same, significant drainage occurs during the drainage from the upper part of the vessel in the dump-and-fill operation. Therefore, the better estimate of the dilution factor is an experimental study, where I measure a marker in the second rinse and the final rinse, to determine the dilution factor. That marker might be any species (or even general property like conductivity) that I can quantitate in both rinses. With that dilution factor, I can then measure the target residue value in the second rinse, and then extrapolate to a value in the third (or final) rinse.

Let's now take a second case, where the first two pulsed rinses are recirculating, and then the last pulsed rinse is non-recirculating (that is, once through to drain). In this situation, I would measure my residue in the second rinse, but how do I determine the dilution factor? In this situation, the second rinse (recirculating) is not the same as the final rinse (non-recirculating). Furthermore, it is entirely possible that the residue value in the final, non-recirculating rinse, is not uniform throughout that rinse (it might slowly decrease from a sample taken at the beginning of that rinse as compared to a sample taken at the end of that rinse). I have to be a little more creative here in how (and where) I sample the two rinses for my marker. If the marker in the second rinse is uniform (the same in all parts - beginning, middle and end - as it exits the equipment), I can take any sample of that second rinse. However, for the final rinse, I probably don't want to take a sample from the final portion of that final rinse to measure my marker. In one sense, I might argue that it represents a realistic situation, since for my residue estimation, I am interested in the dilution that occurs in going from the second rinse to that final portion of the final rinse. However, my preference is to be a little conservative, and perhaps measure the marker in the middle portion of the final rinse. Another approach might be to use a composite sample (or average), of the samples from the beginning, middle, and end of the final rinse. Either option would provide a "worst case" of the dilution factor in going from the second rinse to the final portion (the grab sample) of the final rinse.

A third case for CIP rinses involves the situation where each of the three rinses is non-recirculating. This means that in the protocol, my sample for measuring the target residue (here I am not talking about the marker) is a grab sample of the final portion of the second rinse. I then need to determine a dilution factor in going from the final portion of the second rinse to a final portion of the last (third) rinse. This might be a valid case where I measure the marker (remember I am talking about the marker, not the target residue) in a sample from the final portion of the second rinse and a final portion of the last (third) rinse. However, my preference here would also to be somewhat conservative (because of the variances in timing of the final grab sample collection in a non-recirculating rinse) to use a middle portion of the final rinse as the marker value to determine my dilution factor. Remember that a smaller dilution factor represents a more conservative (or worse-case) situation.

Some of the issues related to variations or additional determinations of dilution factors discussed last month also apply here. For example, in the situation where each rinse is a recirculating rinse or where each rinse is a non-recirculating rinse, I might also determine the dilution factor from the first to the second rinse as well as the second to the third rinse; this is just a check to confirm that my assumptions about the dilution are correct. This additional check will not work if the most common situation, where the initial rinses are recirculating and the final rinse is non-recirculating. The reason it doesn't work (that is, the reason I would not expect the dilution factors to be about the same) is that the comparisons are different (one involves a "recirculating to recirculating" comparison, and the other involves a "recirculating to non-recirculating" comparison).

Let me also make clear that in any situation involving a non-recirculating rinse, what is "sampled" in that rinse is different from what is "sampled" in the recirculating rinse. In the recirculating rinse, I am collecting residues from the CIP supply line, the manufacturing equipment, the CIP return line, and the CIP skid. In a non-recirculating rinse, I am only collecting residues from the CIP supply line, the manufacturing equipment, and perhaps (depending on the location of the actual sampling port) the CIP return line.

Let me also emphasize (and this also applies to the situations discussed in Part I) that the marker I choose for measurement in the last two rinses must be something that is present in the washing solution, and then is reduced as rinses occur. When I say "present in the washing solution", I don't mean in the cleaning agent alone. I mean in the combination of cleaning agent and production soils that are dissolved, solubilized or emulsified in that cleaning agent solution. For example, if the cleaning solution involves potassium or sodium hydroxide, perhaps the potassium ion or sodium ion is chosen as my marker. I could also utilize conductivity in that situation, realizing that I also need to account for the baseline conductivity of the water used for dilution of the cleaning agent.

Finally, the good news about CIP cleaning and rinsing is that I am less likely to use this approach in a protocol. The reason is that, other things being equal, my rinse limits for CIP cleaning should be much higher than rinse limits for a similar "dump and fill" (also called "agitated immersion") cleaning.

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.