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Another Alternative for Rinse Sampling Limits?

Last month we discussed setting limits for rinse samples, focusing on limits for grab samples of the final process rinse (FPR) for CIP rinses. This month I'll cover (and critique) a different way for setting limits in that same situation. This approach is essentially based on estimating the amount of rinse water left behind in the equipment after the completion of the process rinse. It assumes that the only residue is that residue contained in the rinse water left behind on equipment surfaces (for shorthand purposes I will call this a calculation based on "Rinse Water Remaining", or RWR).

As in the method described last month, this method requires you to measure the residue in the last portion of the final process rinse. It then requires an estimation of the amount of rinse water left over in the equipment. Generally this estimate involves a worst case assumption about the thickness of water film that is left on equipment after rinsing. This thickness is multiplied by the surface area the water film could be on, to arrive at a volume of water (in cc or mL). Then the individual results from different surfaces are totaled, giving a total amount of water left in the cleaned system. This total amount of water can then be multiplied by the concentration of residue in the final rinse sample, to arrive at a total carryover of residue. This total carryover can be compared to what I call the L2 value (limit as "maximum allowable carryover") to determine whether the residues left after cleaning are acceptable.

Here is a mathematical presentation of what is done to estimate total carryover.

$$TC = [(SA1 \times T1) + (SA2 \times T2) + \ldots (SAn \times Tn)] \times Conc$$

Where:

TC is the total carryover of residue in the rinse water remaining
SAn is the total surface area in cm^2 of surface "n"
Tn is the thickness (in cm) of the water film for surface "n"
Conc is the concentration (in ppm or µ/mL) of the residue in the final rinse sample

Note that in the use of this type of calculation, the values for thicknesses of remaining water left on equipment surfaces will vary, for example, with horizontal surfaces as compared to vertical surfaces. In addition, a rinse sampling recovery factor should be used in the calculation. The use of a recovery correction factor addresses the objection that some residue could be still on the surface, but not dissolved in the rinse water.

It should also be noted that the calculation can be revised for solvent rinses, by including a factor for the specific gravity of the solvent (it is assumed in the calculations above that for dilute aqueous solutions of residue 1.00 g equals 1.00 mL).

At first glance, this RWR calculation sounds reasonable. Are we missing anything? Before we answer that question, it should be recognized that this type of calculation (based on RWR) will result in lower measured residue levels than the method described last week (based on a grab sample of the FPR and an assumed volume of the final rinse). Why is that the case? Simply because the concentration of residue in a grab sample of the final process rinse will be the same in each case, but the volume that is used to convert that concentration to the total amount will always be greater with the final rinse calculation given last week. That

sounds good, because it will be easier to meet a calculated L2 limit using the RWR method.

It is necessary, however, to ask what is the relationship between the total amount based on a RWR calculation as compared to a total amount based on a SSR calculation, since the separate sampling rinse (when corrected for recovery) most appropriately determines the total amount of residue left on the surfaces after the final process rinse. Last month we discussed how the limit based on a grab sample of the FPR and an assumed rinse volume was a worst case (that is, greater than) the total amount based on a SSR calculation. The next question is "What is the relationship between the total residue amount based on the RWR determination (the subject of this Cleaning Memo) compared to the total residue amount based on the SSR determination?" This is something that is more difficult to establish, and it is not obvious from a theoretical calculation.

We might expect the results to be same, that is, the total amounts based on a RWR determination and a SSR determination would be the same (although because estimates of the film thickness of water remaining should be "worst case" estimates, we might expect the total amount from a RWR determination to be higher than a total amount from a SSR determination). However, it would be helpful to actually see some data to confirm this. One option is to perform a final rinse, collect a sample of the final process rinse, make a determination of the assumed rinse water residuals, and calculate a total amount of residue left behind. Following the final process rinse, a separate sampling rinse could be preformed, with that separate rinse collected, residue concentration measured, and the total amount of residue determined. If the RWR determination (total residue amount) is the same or greater than the SSR determination (again, total residue amount), then the RWR determination represents a worst case and can be used. If the RWR determination results in a total residue amount significantly below the SSR determination, then perhaps this suggests something is awry in the RWR determination. For example, the assumptions about how much water remains on different surfaces might be too low in the RWR determination. It would certainly make me feel more comfortable with this type of calculation to see some kind of actual confirmation of comparative results before such a calculation should be widely accepted.

The purpose of this Cleaning Memo is to not to proscribe nor prescribe the RWR determination for measuring residues in cleaning validation. Rather the purpose is to describe the technique (which some companies have used), to explain its rationale, and suggest testing that can be done to confirm it applicability. Also, this Cleaning Memos is probably not for novices in cleaning validation; it is probably better to get some basics down before issues in this Cleaning Memo are considered.