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Conductivity vs. pH vs. TOC
for Final Rinse Monitoring: Part 1

“Monitoring” is a term that is used in different ways by different companies. For some, monitoring is part of validation maintenance in which I repeat one or more validation protocol runs on a regular basis (such as yearly or every two years). For others, monitoring is the actual sampling and testing I do in my validation protocols (I monitor these swab locations, for example). My preference for the term monitoring is to refer to the activities related to the collection of data I do on every cleaning event after successful completion of the cleaning validation protocol. The purpose of collecting that data is to provide evidence that my cleaning process is still in a "state of control" (or to provide evidence that it is trending out of control, or even to provide evidence that it is out of control). In this sense, monitoring is also part of validation maintenance (or part of “continued process verification”, if you prefer that term from the FDA process validation guidance). So, at least for this Cleaning Memo, that’s the sense in which I am using the term “monitoring”.

For this discussion, I’ll focus on monitoring data that could be collected for a CIP cleaning process, and specifically monitoring data on a chemical property of the final process rinse. [I could collect microbiological data also, but unless I have a “rapid” method, that data may not be available for an extended time and I may have to continue manufacturing another product “at risk”.] Furthermore, I’ll limit my discussion to analyses I could perform on that final rinse. Those three are pH, conductivity, and TOC (Total Organic Carbon). Why would I choose monitoring (in the final process rinse) one of these parameters over the others (although it is clearly the case that I could monitor two or even all three parameters)?

Let’s deal with pH first. If I am cleaning with a cleaning solution that has a high pH (such as 11-12, perhaps due to the presence of caustic in the cleaning solution) or a low pH (such as 2-4, due to an acid in the cleaning solution), pH would be a measure of the completion of the rinsing process. As I approached closer to a baseline pH (7.0 or whatever my baseline water might be, realizing that I might be at a slightly lower pH due to pickup of carbon dioxide from the air during the CIP spraying process), I would have confidence that my rinsing process was effective. The disadvantage of using pH as a monitoring tool is that pH is a logarithmic scale. The difference between a pH of 7.0 and a pH of 6.0 is a tenfold difference in the concentration of hydrogen ions. Furthermore, measuring pH in more-or-less “pure” water is highly variable (it the reason KCl is added to the test sample in the Stage 3 USP conductivity measurement to more accurately measure the pH of the sample). So, pH can be used, but as discussed next, I would prefer to measure conductivity.

Conductivity is a measure of ionic species present. This includes acids, bases and neutral salts (such as sodium phosphate). It may also include ionic surfactants and ionic degradation products. At low levels, conductivity is measured in units of microSiemens per centimeter ($\mu\text{S}/\text{cm}$). Let me note here that sometimes the inverse of conductivity, or resistivity, is measured in such situations. Particularly in the medical device field, the level of ionic species in water is measured as resistivity. Units for resistivity are ohms-cm (or megaohms-cm). For simplicity, I will just use conductivity.

The nice thing about conductivity measurement is that it is a linear measurement (at least within a defined region). Therefore, a water sample with a conductivity of 4 $\mu\text{S}/\text{cm}$ has twice the number of ions as a water sample with a conductivity of 2 $\mu\text{S}/\text{cm}$. If I had a 10-fold increase in the number of ions, I would go from a

value of 2 $\mu\text{S}/\text{cm}$ to a value of 20 $\mu\text{S}/\text{cm}$. This linear relationship allows for discrimination in terms of levels of ions present. Note that conductivity does not necessarily tell me the mass concentration of ions present. For example, if I had two solutions with the same conductivity, and one solution was just lithium chloride and the other was just potassium chloride, the mass of those species (in ppm, for example) would be different due to the difference in molecular weight of the ionic species.

There is one additional benefit to measuring conductivity rather than pH. If I am in a situation where I am cleaning first with an caustic solution followed by an acidic solution, then it may be that as I measure pH I see the water sample is essentially neutral. However, if what has happened is that I have merely neutralized the caustic with the acid, then the result will be a neutral salt. However, if I were to measure conductivity, I could pick up the presence of significant amounts of that neutral salt and realize that rinsing was not complete.

Both pH and conductivity can be measured with online instruments (preferable for routine monitoring) and by a grab sample of the final rinse which is taken to a laboratory instrument for measurement (that instrument may be on the factory floor or may be in a separate laboratory).

This brings us to measuring TOC in the final CIP rinse. TOC is a measure of the any soluble organic species (usually expressed as ppm or ppb of carbon in water). In a final rinse sample, TOC may be due to the active (the API), excipients, processing aids, degradation products and/or cleaning agents (as well as to the baseline water). TOC is usually a linear response to organic carbon concentration. One concern about measuring TOC in the final rinse is that it is best done by an offline measurement. While some TOC instrument suppliers talk about measuring TOC online, I have yet to see convincing data to say that reliable real-time data for cleaning processes can be generated online (although I'm open to change on this).

A second concern with TOC is that in most situations, conductivity is going to be a more sensitive measurement in that the practical limit of detection will be lower. What I mean by this is that it is likely that as rinsing continues, a baseline TOC value will be achieved before a baseline conductivity value is achieved. This will particularly be the case for cleaning systems involving alkaline or acidic cleaning solutions. Where this may not apply is where I am cleaning an injectable product with water alone (which is not likely to be a situation where I would use conductivity as a monitoring tool).

The purpose of this Cleaning Memo is to discuss issues and differences among these measurements for monitoring the final rinse in a CIP cleaning process. The purpose is not to require one or the other (that's a decision you will make based on your understanding of your cleaning process).

Next month I'll continue on Part 2 of this topic, and cover some additional issues regarding use of these three techniques for monitoring of a cleaning process.