August 2013
Conductivity vs. pH vs. TOC
for Final Rinse Monitoring: Part 2

Last month we discussed final rinse monitoring, and considered general issues related to conductivity, pH, and TOC. This month we cover some additional issues in final rinse water monitoring. For clarification, my use of 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.

First, let me state that the three measurements I covered last month are not the only things I might utilize for monitoring. For example, I could use an HPLC method that is specific for the active (API or drug substance). My preference is not to do this, except if I am dealing with a highly hazardous active (one that is genotoxic, mutagenic, teratogenic, etc.). The reason I generally prefer one of the other measurements is that the purpose of monitoring is not to say that my active is at an acceptable level. The purpose is to collect data 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). TOC, for example, provides a more reliable indicator of a state of control. The reason I might use a specific method for a final rinse sample for highly hazardous actives is reduce risk due to possible carryover of that active, particularly if the limit is very low.

I could also routinely collect bioburden data on the final rinse. This would only be done if microbiological contamination was a considerable risk. Note that unless I had a rapid method, the bioburden data might not be available until a week later; therefore, I would either wait until I had that data before I released the equipment, or I would release the equipment "at risk".

Secondly, if you really wanted to know what the best monitoring measurement in the final rinse might be, it is relatively easy to develop some data. Perform the cleaning process as you normally would. Then during the final rinse, collect samples at intervals. For example, if the final rinse is 5 minutes long, collect samples at 1, 2, 3, 4 and 5 minutes. Then analyze each sample by the analytical techniques that are being considered. For example, I might analyze each sample as to pH, conductivity, and TOC. What I might see is that in each case, I see a steady decrease that is attributable to the effectiveness of the rinsing process. TOC should start high and decline. Particularly if I am using an alkaline or acidic cleaning agent, conductivity should also decrease over time. For pH, again I might see a trend to move toward a neutral pH. By analyzing that data, I may be able to see if one technique is better than another. For example, suppose the TOC decreases to a baseline by 3 minutes, but it takes 4 minutes for conductivity to achieve a baseline. In this example (and it is only an example), I might prefer to utilize conductivity as my monitoring technique, because it appears more likely to detect changes in my cleaning process.

Just because you measure TOC and conductivity in a cleaning validation protocol does not mean that you are required to measure both for monitoring purpose. You certainly could, but it is not a requirement. As I have regularly stated in my training seminars, the purpose of measurements in a protocol are to determine that I am less than (or equal to, if you want to be technically correct) my residue limits; the purpose of monitoring is to determine that my cleaning process is in a state of control. While the purposes of data collection are different, I should perform my monitoring tests during the validation protocols. The reason I do that is because I want to establish values for my monitoring measurement so that, based on process capability, I can establish action

and/or alert levels for monitoring data. Note that if in a protocol I use TOC for rinse samples as the analytical measurement to determine whether my active is below the residue limit, I can also use TOC as a monitoring tool. I am collecting samples and analyzing them in the same way; it's just what I do with that data that is different. In one case I compare it to my protocol limit to see if it is acceptable; in the monitoring case I trend the data and determine whether the cleaning process is in a state of control.

Finally, when I say a test like conductivity or TOC is used to determine whether a cleaning process is in a state of control, it is not the only data I evaluate to come to that conclusion. Clearly I want to evaluate other data such as visual examination, training records, process parameters, etc. to come to a conclusion that my process is in a state of control. On the other hand, if all other data suggests I am in a state of control, but my conductivity data suggests I am not in a state of control, I want to do a careful investigation, first as part of my OOS (Out-Of-Specification) program, and then perhaps as part of my CAPA (Corrective And Preventive Actions) program.