September 2007
TOC Analytical Method Validation

As given in the FDA's "Q&A on CGMP", one of the "requirements" for using TOC for cleaning validation purposes is to establish that "a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions." While it is somewhat easy to determine if the residue is organic (and thus contains carbon), it is another matter to determine that the residue can be oxidized under the TOC test conditions. This is typically why at least some level of method validation is done with organic residues and TOC.

Some may object and say that "TOC is a pharmacopeial method, and therefore separate method validation is not required." Certainly it is the case that TOC is a USP method. What that means is that TOC is a suitable method for measuring TOC in purified water (PW) and in water for injection (WFI). Does it follow that this means it is a validated method for measuring an organic active (such as acetaminophen) in water for a cleaning validation protocol? I don't think that is an appropriate conclusion, either from a scientific perspective or from a compliance perspective. Why is that the case?

One reason is that the levels that are acceptable in a cleaning validation protocol may be much higher than the nominal "500 ppb" level in the USP method. Note further that the USP method is in one sense a limit test; it basically is set up to tell you whether the test sample of water has a TOC value of not more than that of a 1.19 mg/L solution of sucrose. While many companies report out values (such as 53 ppb or 78 ppb) for their water systems, what the method really asks is how the TOC value for the test sample compares to the TOC value for the sucrose standard. Furthermore, if I have a limit for an active at 2.3 ppm in my rinse sample (or desorbed swab sample), what assurance do I have that a method that is designed for samples less than 500 ppb C can effectively measure at 2.3 ppm C? For example, just because a TOC instrument that utilizes oxidizing chemicals has adequate oxidizers to handle water at 500 ppb C, does that mean it has adequate oxidizers to handle 2.3 ppm C?

For these reasons, companies using TOC should consider validating their TOC method much as they would for a specific analytical method. If they are using TOC as a limit test only, then it should be validated with the residue much as a specific method would be validated if that specific method were used as a limit test. If they are using TOC as a quantitative test with a linear range, then it should be validated with the residue much as a specific method would be validated if that specific method were used as a quantitative test with a linear range. That is, accuracy and precision studies will be performed. Of course, there is no need to look for specificity, because TOC is a non-specific test (unless you really want to be technical and say that TOC is a specific method for organic carbon). In addition, measures of the limit of quantitation and limit of detection are performed differently for TOC as compared to methods like HPLC.

An additional reason to perform method validation is to assure that the residue has adequate water solubility to be measured at the residue limit (of course this applies only to TOC measurements in water systems, which is the predominant, if not exclusive mode, in the pharmaceutical industry).

Furthermore, when I use TOC as an analytical method for cleaning validation protocols, a USP "systems suitability" check may not be adequate to confirm instrument performance. Again, the issue gets back to what

the intended purpose of the USP "systems suitability" procedure is for. It is designed to check the suitability of the instrument for measuring TOC in PW and WFI. As discussed above, just because the instrument is suitable for measuring 500 ppb or less TOC in PW or WFI does not means it is suitable for measuring 4.7 ppm TOC in a cleaning validation sample. It is for this reason that I usually advocate running some check standards at or around the TOC residue limit in the sample with each set of samples (for example, one check standard at the beginning of the run and one check standard at the end of the run).

This discussion should not be considered a reason not to use TOC. TOC can be a valuable analytical technique if used properly. However, it makes no sense to adopt it because it is a pharmacopeial method without considering the ways in which it is being used beyond the compendial purpose.