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Why TOC is Acceptable

A recent "publication" from the FDA hopefully put to rest the issue of using TOC for measuring residues for cleaning validation studies. The question was asked in the First Quarter 2002 Human Drug CGMP Notes, "Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?" The beginning of the answer was. "Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues. We think TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation."

That issue of Human Drug CGMP Notes then goes on to gives some "warnings" about using TOC appropriately and correctly.

1. Make sure the residue can be measured by TOC (that is, do analytical method validation).
2. Attribute all measured carbon to the target residue.
3. Limit the background (blank) carbon level.
4. Perform sample recovery studies.

In my training seminars on analytical methods, I sometimes say that if I were a pharmaceutical company measuring an active in a cleaning validation study, I would prefer a specific method (like HPLC) as compared to TOC -- other things being equal. Why? The answer is very simple. A specific method makes it easier for me to meet my acceptance criterion for the active.

Why is TOC a worst-case, then? First, it is important to remember that the residue limit for the active DOES NOT CHANGE depending on the analytical method. I may express the limit differently (micrograms of active versus micrograms of carbon, but they should be equivalent expressions). However, if I measure TOC, I am likely (in most cases) to pick up sources of carbon other than the active. These sources may include excipients, media, and cleaning agents. Therefore my measured carbon, which I MUST assume (see the FDA's point #2 above) is all active, will generate a value for the level of active either the same or (in most cases) higher than the number generated for the same sample using a validated specific method (like HPLC).

If TOC actually is a worst case (in that it make it more difficult to meet my acceptance criterion), why do people use TOC? When I stated I would prefer a specific method, one condition was that "other things are equal". Well in many cases, other things are not equal. For example, in biotech production, the active is usually degraded by cleaning with hot, aqueous alkaline cleaning agents. Therefore, a method that is specific for the native protein is not appropriate. This same situation may also apply to some "small molecule" drug actives. As a drug manufacturer, I may also prefer TOC because of the simplicity of method development, or because of the simplicity of use of one analytical technique for all actives in my facility. In other words, even though TOC represents a worst-case as compared to a specific method, there are many cases where it is actually simpler overall to use TOC.

In addition to following the FDA's cautions above, a key to using TOC is not setting limits for an active based on USP or other compendial water specification for TOC. It is still necessary to calculate the "medically safe" acceptable level of the active, and then express that medically safe level as TOC. If a medically safe level

(using the standard dose-based calculation) of a drug active in a rinse water sample is 620 ppb, and if the active contains 50% carbon, then the TOC limit for the active should be 310 ppb (and that is net TOC, which is the measured sample minus the blank). It is clear in this case that setting a default limit of 500 ppb TOC is not appropriate.

However, suppose the calculation above actually resulted in a limit of the active of 1400 ppb, with a corresponding TOC limit of 700 ppb. Couldn't one set a limit of 500 ppb on any rinse water sample and be below the medically safe acceptance limit? The scientific answer to that is "Yes, you could do that." The compliance answer is "Yes, you could do that, but I wouldn't advise it." The reason for not advising it is that setting limits based on compendial water specification ALONE is generally not permitted (see the FDA cleaning validation guidance). Setting a limit at 500 ppb thus becomes a red flag that might cause investigators to further look into whether or not this limit was set based on "medically safe" principles or whether it was based solely on compendial water specifications. In this case, if I would either set my limit at the calculated lint of 700 ppb, OR if I were to set a lower default limit, it would be 400 ppb or 350 ppb, not 500 ppb.

Unfortunately, the PIC/S guidance PI 006-1 (Section 7.10.2), which states that analytical methods "should be specific for the substance to be assayed", will continue to be an issue for people wanting to use a non-specific method. The best that can be said for this statement is that it is not calling for a "specific analytical method", but that it's requiring (similar to a statement from the FDA on the subject of rinse sampling) that the analytical method be a "direct measure" of the substance assayed. If this were the case, then TOC could be considered "specific for the substance to be assayed".

The purpose of the Cleaning Memo is neither to recommend nor discourage the use of TOC for cleaning validation. The purpose is to help clarify that it may be used, and to bring up issues so that when it is used, it is used correctly.