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TOC Issues: Part 2 - Appropriate Blanks

This Cleaning Memo will address issues in the proper selection of blanks for TOC validation samples. In this situation, the purpose of sampling is to quantitate the organic residues that may be on the equipment product-contact surfaces after cleaning. The post-cleaning residues are one source of organic carbon on surfaces. Those organic residues may include the active drug, any excipients or process aids, the cleaning agent, and any degradation products. The proper use of TOC is to measure the organic carbon in the validation sample, and then express that organic carbon value as if it were all the target analyte (for example, as if it were all the drug active). While it is recognized that things such as excipients and cleaning agents may contribute to organic carbon of the validation sample, one cannot try to apportion the measured organic carbon to these various sources (See the FDA's Human Drug CGMP Note for the first quarter of 2002).

However, other sources of organic carbon in validation samples may include TOC from the sampling water itself, TOC from the swab itself (if swabbing is the sampling method), TOC from the sampling vial, and TOC from the air surrounding the sampling location. The total TOC resulting from these sources is called the TOC "blank". While some companies choose to define this as a "negative control" (and in some cases the blank may also serve as a control), it is better thought of as a blank. The "blank" value is subtracted from the "experimental" value to arrive at a corrected or net value. It *is* valid to measure this blank value and subtract it from the measured value to account only for the TOC due to the organic residues on the equipment surface. It should be noted that blanks that do not account for all the "interferences" are acceptable since they constitute a worst case whereby the net TOC (measured TOC minus blank TOC) is higher than the TOC due to residues on equipment surfaces.

What are appropriate blanks? Well, it depends on how one is sampling and the purpose of sampling. For swab sampling in a cleaning validation protocol, the appropriate blank is a swab placed in a sample vial just as the validation sample is placed in a vial. If the swab head is cut off into the vial for a validation sample, the same procedure should be used for the blank sample. The blank should also have the same amount of the same source ("same source" means from the same master container) of low TOC water as for the validation sample. The blank sample should be prepared at the same time and at the same location as the validation sample. Why at the same time? First, the same time means generally within a few hours of each other. The reason for this is that the extraction of organics from the swab itself (that is, from an unused swab) will generally increase with time. If the blank is prepared by the analytical lab, perhaps several days after the validation swab is taken, then the blank might be low as compared to a blank prepared at the same time as the validation sample. This will result in the net TOC being higher. While this is a worst-case and could be acceptable, the practice generally should be avoided (there are enough worst-cases involved in cleaning validation in general and in TOC analysis in particular such that one should not make it more difficult than it already is).

A second issue in preparing the blank sample is that it should be prepared at the same location where the experimental sample is taken. By this I mean that it should be taken on the factory floor rather than in the analytical laboratory. Why is this important? One reason previously given is the extraction time issue. However, a more critical issue is that the air surrounding the swab may contribute to the TOC of a swab sample. If that air contains significant organic vapors, then the swab sample may pick up additional organics due to that air. If the blank swab sample is prepared in the analytical lab, the organics in the air in the

analytical lab may be different from the organics in the air on the factory floor (depending on the specifics, one or the other may have a higher TOC contribution). To properly account for this, the blank should be prepared on the factory floor at the same time validation samples are taken.

I mentioned that sometimes blanks can also serve as controls. This last situation serves as an illustration of this. Suppose my validation sample has a high TOC value, but my blank also has an unusually high value. If it is possible that the sampler sprayed his gloves with isopropanol prior to sampling, the high result from the blank may help support that conclusion. On the other hand, if the blank had been prepared in the lab and was "normal", then I would lose that corroborating evidence to invalidate any high (and perhaps failing) TOC value of the validation sample.

In the preparation of the blank for the swab sample, one could better capture the effect of the air surrounding the swab by actually holding the swab over the sampled surface for a time replicating the actual swabbing of the surface, or even waving the swab over the sampled surface for a time replicating the actual sampling of the surface. In either case the swab should be wetted just as it is for the validation sample. This could be significant only where there are situations where the organics in the air may be significant (significant for purposes of swab sampling, that is).

When preparing the swab blanks, it is generally preferable to have more than one blank. For example, where a series of validation samples are to be taken for a given piece of equipment, it is ordinarily not necessary to take a blank for each swabbed location. It is generally adequate to prepare one swab blank sample at the beginning of a series of validation samples, one in the middle of those validation samples, and one at the end of the validation samples. The three blanks are then averaged together to provide an average blank value for subtracting from each validation sample.

For rinse sampling, the appropriate blank is a sample vial containing the sampling water (typically Purified Water or WFI) before it passes through the cleaned equipment in the final rinse cycle. There are several issues here. One is that when "pure" water is passed through "absolutely" clean equipment, it will ordinarily pick up trace organics from the air or from the "absolutely" clean equipment. Unfortunately, there is no way to account for this in a rinse sampling blank. What is usually done is to sample the recirculating water loop at a drop nearest the point of use for final rinsing. A sample here, in an appropriate vial, serves as a reasonable blank for rinse sampling (note that the blank is lower than "theoretical", and thus serves as a worst-case result). Some companies will also just use the TOC value of the recirculating water system for that time period as the rinse sampling blank. In one sense this represents a further worst case because it does not account for the TOC due to the sampling vial. Since this is a worst case, it also is acceptable. The only issue with this latter practice is that the two TOC values are taken on two different instruments (the recirculating water is taken on the on-line instrument while the validation sample is taken on a stand-alone lab unit). If equivalence of results can be demonstrated, then this practice is acceptable.

This Cleaning Memo addresses issues in the preparation of blanks for TOC rinse sampling and swab sampling. It should be remembered that from a compliance perspective, blanks with lower TOC values (or even the omission of blanks) are acceptable since they increase the net TOC. However, the use of more appropriate blanks (which account for all of the potential "interferences") should generally be preferred for a cleaning validation protocol.