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The 500 ppb TOC Myth

A question I get a lot relates to the acceptability of setting limits, and particularly rinse limits, based on the pharmacopoeial "specification" of 500 ppb TOC. Let me clarify that I am aware that the actual pharmacopoeial specification is not 500 ppb, but rather that the test sample have a response in the TOC instrument no greater than the response of a solution of sucrose containing 500 ppb TOC. So, while the specification is not precisely 500 ppb TOC, as a practical matter we typically refer to it as a 500 ppb specification.

Okay, what is the problem with setting limits at 500 ppb TOC? The main issue is the section of the FDA cleaning validation guidance that deals with "rinse samples", which states "… it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests) rather than test it for potential contaminates." While the FDA does not clearly state the rationale for such a statement, here is my interpretation of why this statement is made.

Suppose I am doing a CIP rinse sample, and the incoming final rinse water has only 50 ppb TOC. My final rinse sample has a TOC content of 450 ppb TOC. Clearly the rinse water has picked up a net of 400 ppb carbon from the equipment (either from the equipment surfaces or from the air in the equipment). If that carbon is from an older drug active like ibuprofen, the chances are the value of 400 ppb will be acceptable if I do a traditional carryover based on 0.001 of a dose. If that 400 ppb carbon is due to a highly hazardous API (that might be mutagenic, for example), then chances are the value of 400 ppb carbon will be unacceptable (based on a ADE carryover calculation). To find out if that TOC net value of 400 ppb is acceptable or not, I should really do a carryover calculation based on the dose or toxicity of the cleaned API, the dose of the next drug product, the batch size of the next drug product, the shared surface area, the sampling parameters (sampled area and rinse sampling volume), the sampling recovery percentage, and finally the percent carbon of the cleaned active.

If that carryover calculation results in a value higher than 500 ppb TOC, then I can (but am not required) to use the more stringent criterion of 500 ppb TOC in the rinse water. On the other hand, if that carryover calculation results in a TOC limit of less than 500 ppb TOC, what is the rationale for using a less stringent criterion of 500 ppb TOC? (As a third case, I suppose it is theoretically possible that my carryover calculation results in a rinse limit of exactly 500 ppb TOC; in that case, my carryover limit and the pharmacopoeia limit will be exactly the same, and I would be justified using the 500 ppb limit.)

We should also realize that limits higher than 500 ppb carbon may be acceptable. The 500 ppb criterion is the requirement for water in the recirculating loop. It is typically measured by an inline instrument that depends solely on UV light for oxidation, which may be adequate for Purified Water or WFI, but may be inadequate for higher TOC values. If a carryover calculation results in a value above 500 ppb, what is the rationale for adopting that lower level for a cleaning validation limit? However, it may be appropriate in such cases to set action levels or alert levels more conservatively, even below the 500 ppb TOC value, for routine monitoring (as part of "continued process verification"), provided those levels are based on process capability studies.

The situation is slightly different for bulk biotech manufacture, where limits are typically not based on carryover calculations (See PDA Technical Report #49 for the best explanation of setting limits for bulk biotech manufacture). Sometimes I hear that the reason for setting limits based on 500 ppb here is that it is the same level allowed for TOC as that allowed by contributions of carbon from the water. While that sounds nice, it is misleading. If a water system is allowed to contribute 500 ppb TOC and the cleaned equipment is also allowed to contribute 500 ppb, then the total amount allowed must be 1000 ppb. Of course, this is an overstatement of what actually happens. In the first place, water systems (Purified Water or WFI) are more likely to actually contribute less than 100 ppb TOC. Second, just because the final rinse has a carbon content of 500 ppb, that does not means that cleaned equipment will contribute 500 ppb TOC to the next product. Why is that the case? There are two basic reasons.

The first reason is that the 500 ppb is the concentration in the final process rinse. Once that final process rinse leaves the equipment, the contribution of equipment surfaces to the next product is less than 500 ppb. If you really wanted to get a better idea of the contribution of TOC to the next product, make a "placebo" of the next product using just water alone, and measure the TOC increase due to processing (I realize that manufacture with just water is not a true placebo, but using a true placebo when measuring TOC contribution is generally not feasible).

A second (and related) reason is that if one is performing a CIP final rinse, the volume of that final rinse may be only 10% or less of the equipment volume. What is the impact of this fact? Let's take an example of a 1000 liter vessel. If a final rinse is about 100 liters, but the batch size of the subsequent product is 700 liters, then using worst case assumptions, that 500 ppb TOC in the final CIP rinse represents a possible contribution of only 500/7, or 71 ppb TOC. The reason this is a worst case is related to the first reason I gave previously.

A modifying factor in this situation for bulk biotech manufacture is that setting a limit at 500 ppb for only one equipment may mean a possible contribution much above that for a situation where there are a series of equipment items in an equipment train. Of course, further considerations for bulk biotech involve the fact that we are dealing with degraded fragments of the native protein (which presumably have less toxicity concerns than the native protein itself), the clearance of degraded proteins due to upstream cleaning processes by subsequent downstream purification processes, and by the fact that there may other organic carbon sources which would contribute to the TOC value.

The purpose of this Cleaning Memo is to help clarify what is means to set a cleaning validation limit based on compendial water specifications of 500 ppb TOC.