Cleaning Validations: Alternatives for monitoring non-soluble compounds

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Cleaning validations are becoming more of a regulatory requirement across the pharmaceutical industry, requiring manufacturing companies to ensure their equipment is being cleaned to a satisfactory level. This leads to companies developing and validating cleaning methodology, while also keeping cost in mind. One such approach to evaluate and monitor cleaning processes at a lower cost is to develop a non-specific total organic carbon (TOC) cleaning validation method.

Advantages to using a TOC approach is that a TOC method is not specific. The instrumentation will measure all organic carbon in the sample solution whether the carbon is contributed by the active in the drug product, from cleaning agents, from other excipients or even from contamination. Therefore, because the source of carbon in the sample cannot be determined, one must assume that all carbon measured in the solution is due to the compound of interest. This approach is beneficial when monitoring products that may degrade while being cleaned as the total amount of carbon present doesn't change. Other advantages to TOC methods are that they are relatively easy to develop and cost-effective to perform.

For cleaning validations, although TOC being non-specific is viewed as an advantage, it can also be viewed as a disadvantage. If it is critical to monitor an individual compound, whether it is an API or a residual cleaning agent, a TOC method cannot meet the method requirements. In addition, TOC samples are very susceptible to contamination by direct physical contact or through volatiles in the air. One has to be careful with how the glassware and equipment is cleaned and handled during sample preparation if a TOC method is going to be used. Even when all precautions are taken to eliminate contamination, there is always background TOC present at low levels. Background TOC contribution can be determined by analyzing blanks. Swab blanks or water blanks are analyzed alongside swab or rinse samples. The results from the blanks can be used for background subtraction when calculating total carbon in samples. Organic solvents cannot be used as rinse solutions because they will drastically increase the amount of carbon on the equipment surfaces and thereby artificially bias sample results. Another disadvantage to utilizing TOC is that all compounds to be monitored need to be water soluble. Or do they?

Historically, if a compound was rendered by the Merck Index to be only slightly water soluble, TOC was immediately ruled out as an option. Eurofins BioPharma Product Testing has developed methods utilizing TOC for compounds that are not fully water soluble. In order for a compound of interest to be TOC compliant, compounds only need to be slightly soluble in water. For example, if a maximum contamination limit (MCL) is set to 10 ppm, the compound only needs to be soluble at 11 ppm in water to be measured in the range of interest. This is a very interesting concept that is growing in popularity across the industry.

Sensitivity is always a concern when dealing with only slightly soluble compounds. The typical concentration detection range for TOC analysis is approximately 100 ppb to 2000 ppb. However, if solubility is limited, the concentration range is usually restricted to an even smaller range of approximately 100 ppb to 500 ppb for performing appropriate spike recovery studies. One limitation that must be determined during method development, is if the

compound of interest has sufficient solubility in water to accurately perform spike recovery studies and still maintain the sensitivity required to be detected within the allowable range of the instrumentation? This question may not be answered until suitable laboratory work is performed.

Another consideration for the use of TOC is that sufficient carbon needs to be present in the sample matrix. Many cleaning detergents on the market today do not contain any carbon, thereby eliminating the possibility of TOC detection.

When deciding whether or not TOC is the right approach for detection during a cleaning validation, one needs to understand that swab and rinse procedures must have the ability to collect the residue of interest from a surface with only the assistance of a non-organic diluent. Although water is preferred, sometimes greater surface recoveries are obtained for swab samples by using a weak base or a weak acid as swabbing solvents. When collecting swab samples with alternative solvents, TOC instrumentation may require higher oxidizer and/or acid rates to effectively analyze the sample. This methodology should be determined during method development.

If TOC is determined not to be a feasible approach, other modes of detection such as UV-VIS, CAD or ELSD may be evaluated. UV-VIS can be used on compounds that contain a chromaphore and CAD or ELSD can be used for compounds that contain a nonvolatile or semivolatile analyte.

In Summary . . .

Here are some key factors to evaluate when determining if TOC is the correct approach for a cleaning validation:

- Is the carbon content of the sample great enough to be detected once the sample is appropriately diluted?
- Is the compounds solubility in water above the concentration of the desired MCL?
- Does the method need to be compound specific?
- Can acceptable surface recoveries be achieved by rinsing or swabbing with water or swabbing with water, a weak acid or base