

# Time to switch to TOC?

Penny Bristol, of Ionics Instruments, argues that as most pharmaceutical laboratories have TOC analysers for regulatory reasons, then the same instruments might be used for cleaning validation (CV) purposes to save analysis time and the replacement costs of more specific analysers

In applications where detecting the overall absence of contaminants becomes more important than determining the actual compounds present, TOC can prove to be a more cost-effective, sensitive and rapid method than more specific analytical techniques. Moreover TOC can deal with unanticipated compounds. One area in which it is gaining growing use is for cleaning validation testing in the pharmaceutical/biotech industries.

## Specific versus non-specific

Which analytical techniques are best for monitoring system cleanliness? Techniques broadly fall into two primary categories: specific and non-specific.

In cleaning validation the most commonly-used specific method, i.e. one that detects a unique compound in the

presence of potential contaminants, is High Performance Liquid Chromatography (HPLC). The most common non-specific method is Total Organic Carbon (TOC), where all organic or carbon-containing species, regardless of the classification of these species, will be detected by a single total organic carbon analysis.

Often in cleaning validation applications it is necessary to establish limits based upon more than one target residue. TOC, as a non-specific assay, can detect a variety of residues in a single test. HPLC, a specific assay, dictates that only one anticipated residue could be detected for a given test. In a

cleaning application with multiple compounds of interest, including active ingredients, excipients and cleaning agents, a specific method would require many individual assays to be performed, with the potential to overlook and therefore miss detecting some cleaning agents or unanticipated contamination. TOC analysis allows for all of these ingredients to be detected, and in a single analytical test that will detect the carbon concentration contributed by all ingredients.

Methods of analysis for TOC analysers vary. Some are better than others for TOC determination in cleaning validation ►



Sievers 800 TOC auto-sampler

**Table A: TOC and HPLC Recovery of Compounds Considered Water Insoluble<sup>6</sup>**

Active	Solubility (Merck Index)	Actual Solubility	(as TOC)	Recovery (HPLC)	Recovery (TOC)
Sulfacetamide	Sparingly Soluble	>10,000 ppm	>5,000 ppm	91.0%	93.1%
Sulfabenzamide	Substantially Insoluble	300 ppm	127 ppm	71.2%	78.0%
Sulfathiazole	Substantially Insoluble	600 ppm	254 ppm	82.4%	86.5%

Recovery from coupons at 4µg/cm<sup>2</sup> level (-2 ppm TOC in 20ml sample)

applications. For purposes here, all key features, data and attributes are in reference to TOC models that use UV/Persulphate oxidation such as the Sievers 800 TOC analyser<sup>1</sup>, which uses membrane conductometric detection techniques. Such analysers have been shown to offer advantages over HPLC in the areas outlined below.

## Current regulatory uses

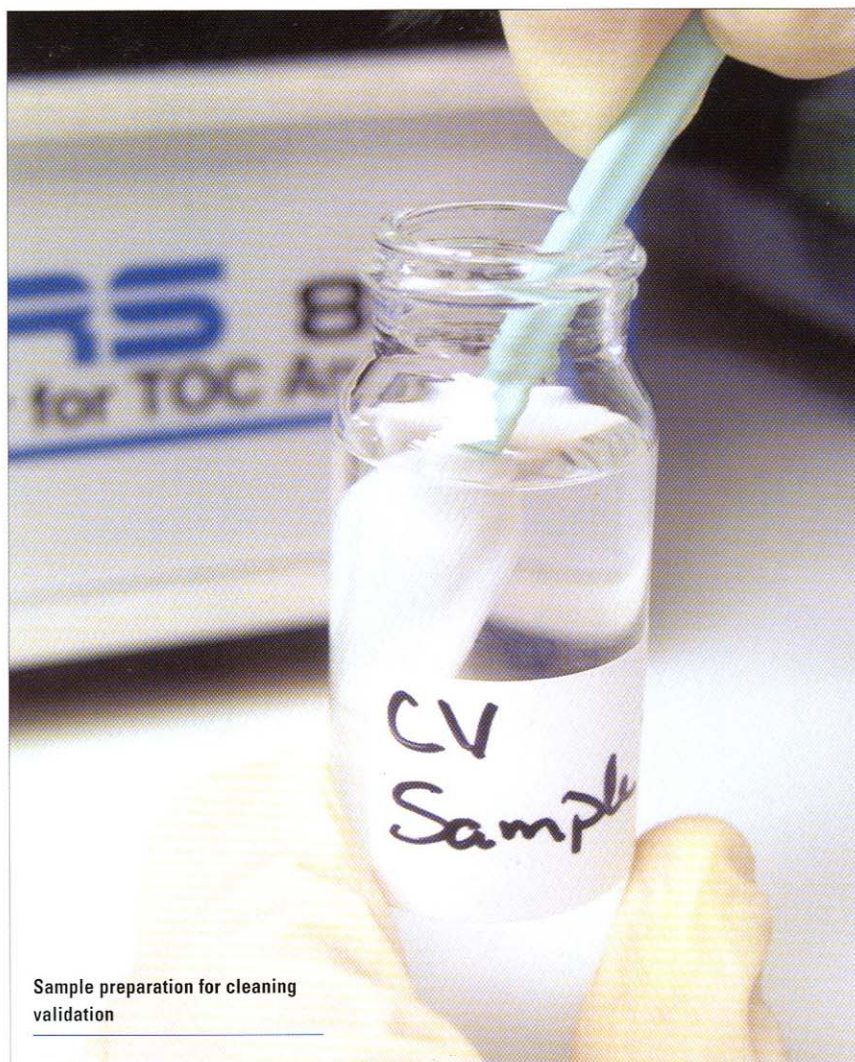
TOC analysis is already being used for regulatory purposes in the pharmaceutical industry<sup>2-6</sup>. The US Pharmacopoeia (USP), Japanese Pharmacopoeia (JP) and European Pharmacopoeia (EP) prescribe its use in various stages of pharmaceutical manufacture, such as WFI (Water for Injectables).

Due to these regulatory requirements, most facilities will have a TOC analyser in-house already. The additional expense of providing an alternative means of analysis for cleaning validation need not be incurred. Additionally, protocols developed for regulatory purposes need only be modified slightly to accommodate cleaning validation, and one cleaning validation protocol can serve at multiple locations throughout a facility.

## Comparison studies

TOC provides excellent sensitivity and product recovery. Multiple comparison studies have been performed to determine the effectiveness of TOC versus HPLC for cleaning validation applications. In one such study by Jenkins *et al*<sup>7</sup>, of all the analytical methods tested (among those, TOC and HPLC analysis), TOC analysis was the preferred method. Citing good recoveries in all cases for a number of compounds, TOC consistently performed as well as, or better than, HPLC. A strong argument was made for the use of TOC analysis in cleaning validation: "TOC has low-level detection, rapid analysis time, is low cost as compared to other methods, and can detect all carbon-based residuals."

As stated, TOC yields high sample recovery. Additionally, this is true even of those compounds that are generally thought to be insoluble in water. Studies have been



Sample preparation for cleaning validation

carried out to show that TOC methods can also be applied to carbon-containing compounds that have limited water solubility, and recovery results are equal to, or better than, those achieved by HPLC; see Table A<sup>8</sup>.

Also, TOC, as a non-specific method, can detect all carbon-containing components of the sample. Its increased sensitivity, as low as 0.05 ppb for some instruments enables users to detect contamination not possible via HPLC.

With TOC the user knows that the contamination of all of the reactive and non-

reactive compounds used in the manufacturing process will have been reduced to an acceptable level, including detergents and contamination generated from unknown or unanticipated sources. Although there is literature to suggest that surfactant analyses via HPLC is possible, often these analyses are performed on concentrated products. This results in high detection limits and limits of quantification, which may or may not allow for the detection of the products in the dilute form in which they are likely to be found in cleaning validation samples. Again, as TOC

is a non-specific method, it can detect all carbon-containing components of the detergent, and its increased sensitivity allows for detection of contamination not possible via HPLC. Additionally, the time-sensitivity associated with biotechnology products that degrade quickly is a concern for the labour and time-extensive HPLC tests.

As TOC evaluates all of the carbon contributing compounds for a given sample, from a contamination standpoint it provides the worst-case scenario. One cleaning validation strategy is to assume that all residues detected are due to the most potent or toxic potential contaminant, typically the active ingredient. When determining the carbon concentration, the worst-case assumption is used and all carbon is attributed to the most toxic material. If this determination yields results that are less than the previously established limits, then it should not be necessary to specifically identify the contaminant since the worst-case assumption was made<sup>9</sup>.

### Rapid analysis

TOC encourages high sample throughput because it is automated and has quick analysis times. Once samples have been collected and prepared, attended operation of the analyser is minimal. For example with an autosampler and appropriate software, more than two dozen 40ml samples can be

prepared and analysed sequentially, without an operator present. Coupled with faster analysis time for TOC, typically six minutes, greater sample throughput is achieved relative to HPLC while encouraging unattended operation of the analyser.

### Lower cost

TOC has a lower capital cost and cost of ownership. In general, the capital cost of a TOC analyser is significantly lower than that of an HPLC, up to 25%. As mentioned above, most facilities will have a TOC analyser in place for USP purposes. The same analyser can serve both USP and cleaning validation purposes, potentially eliminating the need for a capital purchase entirely. Additionally, operating costs for TOC analysis is a fraction of the cost, from 40 to 75% of that of a traditional HPLC. This does not account for the additional time required of HPLC for frequent maintenance and calibration; calibration of some TOC analysers need only be performed annually and routine maintenance is minimal.

Also to be considered is the ease of routine TOC analysis. It requires no special training and requires minimal method development, freeing the operator for other tasks. HPLC operation often requires specially-trained, higher-paid personnel, and unattended sample analysis is not possible.

TOC analysis for cleaning validation is becoming a more valuable, more frequently-

used tool<sup>7</sup>. Ease-of-operation and method development, lower cost, high sensitivity and recovery, and the ability to perform automated sample analysis all serve to make TOC an ideal analytical method in cleaning validation applications.

A library of technical/academic papers on TOC and other techniques for the medical, semiconductor and pharmaceutical industries is provided on Ionics Instruments' website [www.ionicsinstruments.com](http://www.ionicsinstruments.com)

### REFERENCES

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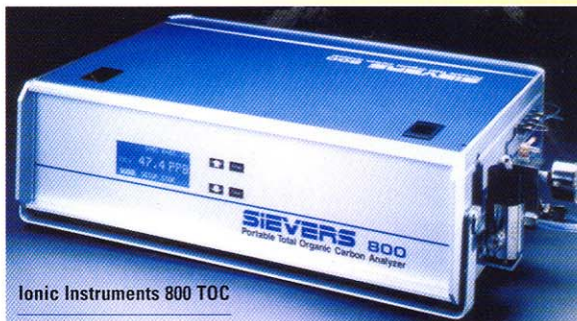
## TOC & semiconductors – a sensitive issue

TOC analysers used in chip manufacture need to be much more sensitive than their pharmaceutical counterparts in monitoring organic contaminants. SIA recommendations in the 1990s guided manufacturers of TOC water analysers to develop analysers that might measure TOC levels in semiconductor Ultra-Pure Water (UPW) to 1ppb and below.

However, conversely, this can lead to less efficient wafer manufacturing as too fine a measurement when working with extremely low TOCs can bring its own practical problems. Often chip manufacture processes respond to the slightest presence of organic contamination by automatically closing down part of the manufacturing line – imperative where there is contamination, but inefficient and inconvenient where interferences cause an artificially high TOC reading.

A major semiconductor manufacturer's studies recognised urea, trimethylamine and other organic nitrogen compounds as the source of interferences when measuring TOC. To overcome this Ionics Instruments introduced a new parameter, TOx. As well as TOC and conductivity/resistivity the PPT analysers have a separate channel to measure TOx organics containing halogens, sulphur, nitrogen or phosphorous, as these are principal offenders in creating false positive and false negative readings. The result is a higher sensitivity TOC (20ppt), yet less susceptible to interfering compounds.

Ionics Instruments also addressed the difficulties of measuring



Ionics Instruments 800 TOC

TOC in semiconductor reclaim waters. Here, very fast analyses are required to prevent unwanted organics re-entering the UPW system. The Model 800 Turbo was developed to provide TOC measurements every 3.5 seconds with a 3.5 minute instrument response. It can be hand-carried to different locations and installed in minutes. The Model 800 can also be used in 'Normal Mode' for higher sensitivities (to 0.05ppb), but in the more typical timescale of about six minutes.

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