Water Technologies & Solutions
application note

USP <661> compliance and total organic carbon (TOC) analysis

introduction and challenge

The pharmaceutical industry is heavily dependent on plastic packaging materials to bring products to market. This packaging comes in the form of bottles, disposable bags (such as those used for intravenous solutions, blood and blood components), pre-filled syringes, etc. and may include many materials (myriad polymers and additives). Ultimately, it must be demonstrated that these packaging materials and their materials of construction do not interact with the therapeutic products in such a way to alter their suitability for use.

The USP <661> chapter was recently revised to become more comprehensive in scope. This has allowed the regulation to separately cover the materials used in packaging and the packaging system (which may comprise several materials).

total organic carbon (TOC) regulations per USP

USP mandates testing of TOC in Purified Water (PW) as well as Water for Injection (WFI). This is comprehensively documented in USP Chapter <643>. The limit for TOC in both PW and WFI has been set for 0.5 ppm.

On May 1, 2016 USP made a major revision to General Chapter <661> and reintroduced the chapter as "PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION". In addition, two subsections were written:

- *<661.1> Plastic Materials of Construction*
- *<661.2> Plastic Packaging Systems for Pharmaceutical Use*

In addition to the delineation of materials and systems, a wider range of testing methodologies and technologies were presented, including TOC. This was done to understand the materials that compose the packaging systems, as well as the packaging themselves. As such, this has far-reaching effects, as the revised chapter will now apply to:

- Manufacturers of finished dosage pharmaceuticals
- Manufacturers of plastic bags, vials, IV kits, etc.

Primary responsibility for compliance to this regulation resides with the owner of the regulatory approval for the packaged drug product.

USP <661> subsections

There are two subsections to chapter <661>:

<661.1> *Plastic Materials of Construction.* This subsection is designed to ensure that the individual materials are characterized for suitability of use. This is dedicated to individual plastic materials.

<661.2> *Plastic Packaging Systems for Pharmaceutical Use.* This subsection is designed to ensure that the entire system, which consists of one or more materials, is characterized for suitability of use.

expected evaluations of <USP> 661

Material Screening

- Evaluation of ingredients as probable extractables and potential leachables

Controlled Extraction Study

- Worst-case controlled extraction (simulation) study to determine the extent to which extractables may become probable leachables

Product Assessment

- Actual-case measurement of confirmed leachables in the therapeutic product in the pharmaceutical packaging/delivery system intended for the commercial market

TOC limits per <USP> 661

USP	Applies to	TOC Specification*
<661.1>	Individual plastic materials	≤ 5ppm
<661.2>	Plastic packaging system	≤ 8ppm

* TOC Specification is a differential and requires blank correction

other requirements for TOC to comply with USP <661>

TOC analyzer performance:

- Should have a limit of detection of 0.2 ppm
- Should have a demonstrated linear dynamic range from 0.2–20 ppm

Sievers* M9 TOC Analyzer and compliance to USP <661>

The Sievers M9 TOC Analyzers offer time-tested dependability with fast analysis. The analyzers reduce the time to TOC results by 50%, enabling increased productivity.

Designed to facilitate compliance within a heavily regulated environment, Sievers TOC Analyzers exceed both regulatory and analytical requirements. The broad linear range allows for excellent low-level sensitivity for ultrapure water samples and high-level capability for cleaning validation samples.

With its Linear Range of 0.03 ppb to 50 ppm, the Sievers M9 TOC Analyzer meets the USP <661> requirements for detection limit as well as dynamic linearity range. All Sievers TOC Analyzers also comply with USP <643> for PW and WFI.

ISO/IEC 17025 and ISO 17034 accreditations ensure Sievers standards are consistently produced, controlled, and audited. The following standards are available to support the analyzers and USP <661> compliance:

- Accuracy/Precision, 8 ppm (STD 77013)
- Accuracy/Precision Set, 5 ppm (STD 99011)
- USP <661> Linearity Set (STD 99012)

A linearity protocol and spreadsheet for reference can be provided on request.

These standards, combined with Sievers investigative Failure Analysis Reports (FAR), provide traceability and enable expedited Out of Specification (OOS) investigations.

The Sievers M9 TOC Analyzer is offered in Laboratory and Portable models for ease of use. The analyzer offers compliance with USP <643>, USP <645>, USP <661>, USP <1225>, 21 CFR Part 11 and others, including globally equivalent standards.

References

USP General Chapter <661>
USP Subchapters <661.1> and <661.2> USP 661 Briefing:
http://www.usp.org/sites/default/files/usp_pdf/EN/meetings.pdf

Find a contact near you by visiting www.sieversinstruments.com and clicking on “Contact Us”.

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