cleaning validation: verifying the performance of a validated cleaning process

what you need to know

The use of total organic carbon (TOC) in cleaning validation (CV) has become a widespread best practice throughout the pharmaceutical industry as an analytical method to verify the performance of a validated cleaning process and associated critical cleaning parameters.[1] Instead of focusing on product-specific analytical methods, many industry-leading companies have changed to TOC for this application because it provides a simple way to ensure that a validated cleaning process is still in control. While product-specific methods like High Performance Liquid Chromatography (HPLC) and Enzyme Linked Immunosorbent Assay (ELISA) are sometimes useful for supporting the design or development of a cleaning process, TOC has significant advantages over these methods throughout the design, validation, and continuous verification phases of a CV program.

the challenge

Historically, many companies have had a very product-focused view of cleaning validation. This approach has led to incremental risk, cost, and complexity. While a product-focused view can prove that an individual compound or API did not carry over to the next batch, it cannot necessarily prove that a cleaning process is in control over time. This is because product-specific analytical methods only verify that specific compounds are removed—a focus primarily of the design phase of a cleaning process. A non-specific method like TOC can enable a user to continuously verify that a cleaning process is in control and that the cleaning process completed successfully by detecting all potential organic contamination. The FDA's *Guide to Inspections - Validation of Cleaning Processes* highlights an example of an inadequate CV program that focuses only on the absence of previous compounds, rather than verifying the performance of the cleaning process as a whole.[2]

business impact

Cleaning processes are designed to make compounds more cleanable or soluble. This may have the unintended effect of forming degradants or potentially leaving residual cleaning agents on the surfaces of equipment that could carry over to the next batch. Continuous reliance on product-specific methods for these processes could in some cases lead to:[3]

- Labor-intensive method validation that could take years to design, develop, and complete.
- Complex testing for cleaning process validation.
- Delayed product changeovers due to prolonged verification samples that leads to low equipment use.

solutions and recommendations

Compared to product-specific methods such as HPLC, TOC offers simpler method development and allows users to test not only for product removal, but also removal of excipients, degradants, and cleaning agents. Considerations when implementing TOC may include:

- Upgrade or replace existing methods for new cleaning processes using TOC to verify critical cleaning process parameters (TACT).
- Fully validate any new TOC method when switching from HPLC/ELISA for validation or continued verification sampling.
- Unlock hidden cost savings by using TOC exclusively on the production floor to sample, analyze, and report results in near real-time for continued verification.

Through its Sievers* product line, SUEZ offers the M9 Laboratory and Portable TOC Analyzers. These robust TOC Analyzers meet global regulatory requirements and are able to measure residual organic compounds remaining after the completion of a validated cleaning process. The instruments are highly effective for recovery testing, method and process validation, and swab or rinse sampling for equipment qualification or continued verification. Sampling materials (swabs and vials) and TOC reference standards are also available to support a cleaning validation program.

industry guidance

In 2010 and 2012, the Parenteral Drug Association (PDA) issued Technical Report No. 49: Points to Consider for Biotechnology Cleaning Validation and revised Technical Report No. 29: Points to Consider for Cleaning Validation.[5] The reports were created by a team of European and North American professionals from the FDA, cleaning chemical specialists, and drug manufacturing experts to encourage a new focus and a change of thinking when it comes to cleaning validation. Although the title suggests a unique manufacturing process, the PDA CV Taskforce notes that the report is applicable to traditional pharmaceutical or API manufacturing processes. Lastly, the technical report highlights the widespread use of non-specific methods such as TOC as offering major benefits for measuring how well a cleaning process is designed, validated, and will be continuously verified:

> *"A specific analytical method (HPLC/ELISA) for products (or APIs) is not usually an appropriate technique to determine whether the cleaning process is effective." – Anurag Rathore and Destin LeBlanc*[4]

> *"We agree that TOC is a great measurement tool for how well our cleaning process was designed, validated, and performing over time (verification)." – Baxter, Member of the PDA CV Taskforce*

> *"TOC may be used for all stages of cleaning validation, including design/development, validation and continued verification. It can also be used for validation maintenance as well as for investigations." - PDA Technical Report No. 29, page 57*[5]

It is important to note that continued verification includes the ongoing validation costs associated with ensuring the cleaning process is within control over time.[6,7] Continued verification also eliminates the need for "re-validation," unless there are major deviations in the design of the cleaning process.[8] Design and validation phases are typically only done once.

our promise

As the pharmaceutical regulatory environment continues to shift from legacy approaches to a focus on risk mitigation and continuous quality assurance, SUEZ will provide support through its Sievers product line of instruments and specialized services for the industry.

References

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8. Sievers Instruments (2010). *At-line TOC Reduces Cleaning Verification and Product Changeover Costs by 92% for Pharmaceutical Manufacturer*. Application Note 300 002014.

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