



Validating Cleaning Processes: Implementing Total Organic Carbon Analysis

General

Current trends in pharmaceutical manufacturing have seen increasing demand for rapid sample analysis time along with low detection limits for clean in place (CIP) samples. TOC analysis provides a quick, accurate screening alternative for critiquing CIP samples. Some qualities that make TOC a viable part of a cleaning validation includes:

- High sensitivity;
- High recovery of samples;
- Non-specific measurement;
- High throughput, no interferences (depending on TOC selected method !);
- Excellent linearity (depending on TOC selected method !);
- Precision (depending on TOC selected method !);
- Only one method is needed for all cleaning validation analysis;
- The TOC method is simpler to implement and easier to validate than chromatographic techniques, the method always produces a "**worst case**" result, assuming that all residue is the active substance.

Background

Medicines are primarily intended to promote good health; however, when residual compounds remain in the manufacturing process, potential for side effects from toxic levels of contaminants increases. For this reason, the FDA has recognized, with greater importance, that effective cleaning and sanitizing protocols are a proactive measure in preventing cross-contamination in pharmaceutical and cosmetic production.

As CFR sect 211.67 states, " Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety , identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

A good validation of the cleaning process should document at what point does the cleaning procedure fail when reducing to the worst-case scenario. Typical laboratories testing includes the development and implementation of analytical methods that test for residues of previously manufactured products, cleaning



detergents, chemicals, solvents, byproducts, degradants, and microbial contaminants (from wet environments after the cleaning validation).

Detergent selection

In addition to product residuals, detergent selection is a critical step in the development a cleaning validation. The FDA´s Inspection of Validation of Cleaning Procedure(July 1993) guideline states:

"As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no (or for ultra sensitive analytical test methods-very low) detergent levels remain after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus, they should be easily removable. Otherwise, a different detergent should be selected."

The chemistry of the detergents should be investigated before use in cleaning different surfaces. Some surfaces are intolerant to certain pH solutions or compounds. Cleaning methods (Clean in Place, Clean Out of Place, Manual Cleaning, Immersion, etc.) may influence which detergent properties are desirable. Since most of the cleaning solution will contain water, the purity of the water being used should be determined. The effluent produced from the cleaning process should be investigated to assure that the facility is within the bounds of the submitted regulations.

Sampling Techniques

A cleaning validation may consider various sampling techniques to assure effectiveness of the cleaning process.

Technique	Description
Visual Inspection	Qualitative , Subjective
Rinse water Sampling and Analysis	Qualitative
Swabs for Surface Sampling and Analysis	Quantitative, Removes Adherents, Defined Sample Area
Swabs for Surface Sampling from Coupons	Quantitative, Similar Surface to Equipment

Table 1: *Common sampling techniques used in cleaning validations*



The FDA's guidelines (July 1993) state for sampling, "There are two general types of sampling that have been found acceptable. The most acceptable is the direct method for sampling the surface of the equipment. Another method is the use of rinse solutions."

Sampling of the rinse water is most careful in analyzing a large surface area or inaccessible areas. Whereas, the use of swabs (a direct method) can remove contaminants that may adhere to surfaces.

The swab technique typically involves moistening a polyester swab with purified water (acidified with phosphoric acid, if necessary) to wipe a measured area in a systematic manner.

Swabbing involves using wipe or swab that is moistened with high purity water (WFI) that is typically wiped over a defined area in a systematic multi-pass way always going from clean to dirty areas to avoid recontamination - ie. 10 side by side strokes vertically, 10 horizontally and 10 each with the flip side of the swab in each diagonal direction. For TOC analysis very clean low background swabs or wipes and sample vials such should be used.

Sampling Techniques and Acceptance Criteria

The FDA's guidelines (July 1993) require, "that the basis of any limits is **scientifically justifiable**." Acceptance criteria is typically set at 1/1000 reduction of the lowest therapeutic dose of the previous drug product (active ingredient in most cases) or the LD50 toxic dose of the cleaning solutions. If the calculated is larger than 10ppm carryover of the residual contaminates, then the limit is set at a more rigorous 10 ppm acceptance criteria (dependent on medical opinion/safety factor).

$$\text{Carbon \% in Residual Compound} = \frac{(\text{Atomic Weight of Carbon}) (\text{Number of Carbon Atoms per Molecule})}{\text{Formula Weight of Compound}}$$

$$10 \text{ ppm Residual Compound (mg/cm}^2 \text{ or mg/L)} \geq \text{TOC Limit ppmC (mg/cm}^2 \text{ or mg/L)} = \left(\frac{\text{Mass of Residual Compound (mg)}}{\text{Volume (cm}^2 \text{ or L)}} \right) (\% \text{ Carbon}) \left(\frac{1}{1000} \right)$$



Analytical Methods

Analytical Methods used in cleaning validation:

- Capillary Zone Electrophoresis
- Conductivity
- ELISA
- Gravimetric Analysis
- HPLC
- Ion Chromatography
- Light Microscopy
- pH
- Spectroscopic Techniques
- Thin Layer Chromatography
- TOC (quick results)
- Visual Analysis

Almost any residual compound can be detected if three non-analytical (screening) tests are in place for a cleaning validation. These three analytical methods include: **TOC** (for organic characteristics-carbon), **pH** (for acid/base characteristics) and **conductivity** (for ionic characteristics).

Therefore, these methods can determine contaminants from various sources (water quality, active ingredients, excipients, cleaning agent, etc..). **These non-specific methods assume that the entire residue is the worst compound (active ingredient)**. If the results are above the acceptance criteria, then an additional cleaning process can occur on the equipment.

K. M. Jenkins ("Application of Total Organic Carbon Analysis " PDA J. Pharm. Sci & Tech. , Vol. 50 No.1 , 1996, pp. 6-15) found in their study that a strong case can be made for the use of TOC analysis in cleaning validation, " TOC has low level detection, rapid analysis time, is cost-effective compared to other methods, and can detect all carbon-based residuals". It has been compared TOC, HPLC, TLC, spectrophotometric methods, TOC did as well or better analysis.