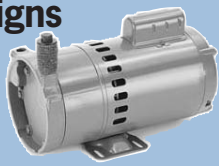


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Three lab tests
check
manufacturing
cleanliness

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A gravimetric analysis measures the weight of extracted residue. Concentrated extract is transferred to a crucible and evaporated. The crucible is reweighed, and the weight difference is the amount of extractable soluble and insoluble residue from the device.

How to tell if a device is really clean

There are several ways to check medical devices for their cleanliness after manufacturing. A little homework helps pick the right one.

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Due to increased awareness of the potential dangers of residual manufacturing materials on medical devices, the FDA often requests documentation of a thorough validation of how residual materials were cleaned from newly manufactured devices. An essential part of this validation includes quantification or counting contaminants which may remain on the devices following the cleaning procedure.

There are several ways to analyze devices and possible contaminants as part of a cleaning validation. They include analytical, microbiological, and biocompatibility methods. This article examines total organic carbon (TOC) analysis, gravimetric analysis (ASTM 2459), and detergent residual analysis by ultraviolet/visible (UV/VIS) spectroscopy.

Start with a few questions

When formulating a plan for cleaning validations, start by answering questions, such as:

1. What is the purpose or goal of the cleaning?
2. How many devices must be tested to establish that the cleaning is reproducible?
3. To what types of contaminants are the devices exposed?
4. How can limits be established for the residual materials?

The obvious goal of a cleaning may be simply to produce a clean device, but it may also include

manufacturing a biocompatible device, or reducing bioburden or endotoxin levels, or both. Understanding the purpose of the process brings the validation plan into clearer focus.

Demonstrating reproducibility in a cleaning validation is also an important step. Reproducibility should be two-fold: uniformity in a cleaning run and consistency from run to run. If there are variables in the cleaning operation which can significantly impact the cleanliness of the devices, it is advisable to test worst-case as well as nominal conditions.

A single device may be exposed to many contaminants during manufacturing and cleaning. How a team validates a cleaning operation is affected by the number and type of contaminants. Residues may be analyzed by direct surface analysis or measured after extraction. Extraction analysis is most common so the methods discussed here are all extraction-based.

Contaminants usually fall into one of three categories: water soluble and nonwater-soluble residue, and nonsoluble debris. Water-soluble residues are usually ionic compounds such as detergents and salts. Nonwater-soluble residues, such as oils, greases, and other hydrocarbons, are soluble in solvents other than water. Non-soluble debris includes residues such as metals, organic and inorganic solids, and ceramics.

There are no established regulatory limits for residual analysis, so it is important to justify an

acceptable level. A few practical techniques for setting limits include comparing clean and unclean devices, evaluating a new process versus an old one, and assessing residue amounts based on the detection limit of the method. Residue limits are usually specified in micrograms or milligrams per device. When comparing devices with different surface areas, it is advisable to define limits based on surface area, such as $\mu\text{g}/\text{cm}^2$ or mg/cm^2 .

Additional testing (such as for endotoxin, bioburden, or biocompatibility) may be required to justify established limits, demonstrate the effectiveness of the cleaning, or evaluate the risk of the detected residual levels on the clean devices. Specific risk assessment and justifications should be prepared for the validation file so regulatory reviewers can determine the rationale for a test plan and established limits for residual manufacturing materials.

Validating the extraction

In most instances, the team must validate the extraction procedure for each device and contaminant. In some cases, devices or contaminants may be grouped into “families” which have similar characteristics. Appropriate justification for these groupings must be included in the validation file. Then the extraction validation is performed on each family.

Extraction techniques are validated with spike recoveries, or exhaustive extractions, or both. Spike recovery uses positive controls with a known level of contamination. These controls are created by spiking clean devices with a known amount of target contaminant. Only one extraction is needed to establish recovery efficiency. Spike recovery shows the removal efficiency of each contaminant tested, but it can get complicated as the number of contaminants on a device increases.

The exhaustive extraction technique uses positive controls which contain an unknown level of contamination. These “real-life” positive controls are created by exposing devices to the regular manufacturing operations but not the cleaning process being validated. Positive controls for exhaustive extractions require repetitive extractions to establish recovery efficiency. The method provides “real-life” data but may not demonstrate adequate removal of every possible contaminant.

The exhaustive-extraction method lets manufacturers establish precleaning levels of the target compounds, an important step in establishing limits for residual analysis. After establishing the precleaning levels, clean devices are tested to show a percent reduction of residual manufacturing materials. This percent reduction is an indication of the effectiveness of a cleaning process.

Total organic carbon analysis

TOC analysis is a relatively straightforward process for validating a cleaning method and

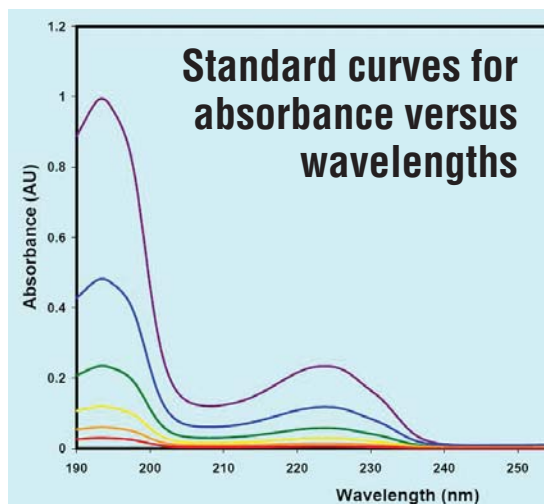
performing routine monitoring of residual levels once the validation is complete. TOC is also a sensitive analytical method with detection capabilities in the parts-per-billion (ppb) range. Residuals are extracted from the devices in a known amount of purified water, and the extract is analyzed on a TOC instrument. The extraction ratio must be controlled for accurate analytical results. If too much water is used, the residue may not be detectable even though it is present. If too little water is used, the residue may not be adequately removed from the device.

A common TOC method begins by acidifying the device extract to purge inorganic carbon. The organic carbon is oxidized with sodium persulfate at 100C to form carbon dioxide. The resulting carbon dioxide is purged from the solution and quantified using a non-dispersive infrared detector. The resulting mass of carbon dioxide is proportional to the mass of TOC in the sample which is interpreted and reported as the total organic carbon extracted from the device.

For TOC to be a suitable analytical technique, users must first establish that the target compounds contain a significant amount of organic carbon. Also, it must be possible to oxidize the carbon present under the test conditions, and the target compounds must be water soluble. Even some essentially insoluble organic target compounds may be removed by water extraction and analyzed by TOC. The analysis will not detect inorganic contamination.

A TOC analysis is quantitative but not qualitative. In other words, TOC does not identify or distinguish among different compounds containing oxidizable carbon. Therefore, a manufacturer should limit the amount of background carbon (carbon from sources other than the target compounds) as much as possible. Established limits for target compounds must be corrected for background carbon.

An advantage of TOC is that a level has been established for purified water which represents a good target level for residual analysis. The United States and European Pharmacopoeias require purified water and water for injection.



The standard curves plot absorbance units (AUs) versus wavelengths. Detergent residual analysis looks for compounds which readily absorb ultraviolet and visible light, most often detergents. Devices are extracted in a known volume of purified water and analyzed with a UV/VIS spectrophotometer.

tion (WFI) to contain no more than 500 ppb of TOC. This represents a defensible standard level because it would be difficult for a regulatory agency to justify a cleaning level for a device which is lower than that required for purified water. By coupling TOC analysis with a conductivity and pH analysis, also required for purified water and WFI testing, device extracts may also be analyzed for ionized compounds such as acids, bases, or salts.

Gravimetric analysis

Another method used to validate cleaning procedures is a gravimetric analysis based on ASTM F2459. The procedure extracts and quantifies residual manufacturing materials on medical devices. One advantage of the method is that extraction solvents other than purified water may be used, allowing for detection of nonwater-soluble contaminants. However, this gravimetric method excludes residues more volatile than the extraction solvent.

The extraction solvent is chosen based on the solubility of the target residues and characteristics of the device materials. Several solvents may be required if more than one type of residue

is present on the devices. Devices may be pooled for the analysis to increase the method's sensitivity, but there is an increased risk of adding non-soluble debris created through friction between devices during the extraction.

The devices are sonically agitated for a specified time and temperature. The extraction times and temperatures must be validated with each study based on the target residues. To meet criteria specified in ASTM F2459, extraction parameters must be adjusted for an extraction efficiency greater than 75%. After extraction, devices are rinsed and removed, and the extract reduced. The concentrated extract is then transferred to a crucible of known weight where it is evaporated. The crucible is reweighed. The weight difference represents the amount of extractable soluble and insoluble residue from the device.

If the test quantifies a significant extractable residue,

it may also be identified by infrared spectroscopy. A general analysis or interpretation of the sample spectrum can reveal the presence of certain compounds such as hydrocarbons and amines. This identification may also be made by comparing the sample spectrum to the spectra of target compounds.

Another option with this method is to separate the extractable residue into soluble and insoluble portions. The residue is dissolved in the appropriate extraction solvent and the solution filtered. The soluble and insoluble residues are then calculated based on the weight change of the filter. This information is invaluable if non-soluble debris is a primary concern.


Detergent residual analysis

A third method to validate cleaning operations focuses on compounds that absorb ultraviolet and visible light. It is most often used to detect detergents. Residuals are extracted from the devices in a known volume of purified water and the extracts are analyzed using a UV/VIS spectrophotometer. As with TOC, the extraction ratio must be controlled for accurate analytical results. If too much water is used, the residue may not be detectable even though present. If too little water is used, the residue may not be adequately removed from the device.

Linear regression and a standard curve are used to calculate the concentration of the target compound. Because each compound responds differently, each analyte must be validated for accuracy, precision, ruggedness, limit of detection, and limit of quantitation. A sample of the pure detergent must be available to perform the validation. Of course, some compounds are unsuitable for analysis using this method due to insufficient response to ultraviolet/visible light.

The method is also quantitative but not qualitative. If several extracted contaminants absorb ultraviolet/visible light, there is no way to distinguish one from another. Concentrations are calculated as worst-cases, assuming all resulting absorbance is due to a single contaminant. This method does not identify the absorbing substances in the extract.

The procedure has been used over 10 years, and many common detergents have been validated as suitable for the method. The "real life" positive controls for this method are devices which have been cleaned using the target compound but not rinsed. These devices must be cleaned beforehand to reduce background interferences.

Quantifying the residuals from manufacturing is crucial when validating a cleaning procedure for newly manufactured medical devices. The TOC, gravimetric, and detergent analyses are all practical techniques that may be used during the validation process. 

For further reading

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