



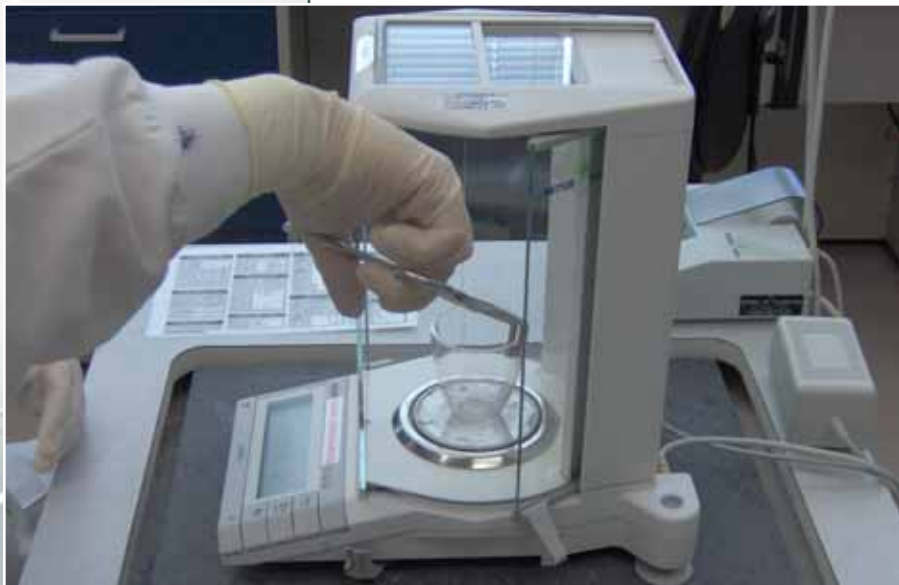
# MICRO NEWS

VOLUME 2/2006

## ANALYSIS OF RESIDUAL MANUFACTURING MATERIALS

ON NEWLY MANUFACTURED MEDICAL DEVICES

by Kierstan Baker, B.S., Chemistry Study Director



*Weighing a crucible for gravimetric analysis*

Nelson Laboratories, Inc. (NLI) provides several choices for cleaning validations, including various analytical, microbiological, and biocompatibility methods. This article addresses three analytical methods: Total Organic Carbon (TOC) analysis, gravimetric analysis, and detergent residual analysis by Ultraviolet/Visible (UV/VIS) Spectroscopy. This article does not address active pharmaceutical or excipient cleaning validations.

### CONSIDERATIONS

There are two factors which need to be considered when formulating a plan for cleaning validations.

1. The extraction procedure used must be specifically validated for each device and residue type.
2. There are no established limits for residual analysis.

Both of these factors may be addressed through the use of positive controls. Extraction techniques are usually validated by using spike recoveries and/or exhaustive extractions.

Spike recovery validations require that the positive controls contain a known level of contamination, therefore only a single extraction is needed to establish recovery efficiency. Normally, these positive controls are created at NLI using clean

*(cont. page 2)*

### INTRODUCTION

With the increased awareness of the potential dangers of residual manufacturing materials on medical devices, the Food and Drug Administration (FDA) often requests documentation of a thorough validation of the cleaning processes used to remove residual materials from newly manufactured devices. When determining a validation plan, a commonly asked question is “what methods exist which can validate a cleaning process?”

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devices which are spiked with a known amount of the target compound(s). Samples of the target compound(s) must be available to NLI for spiking purposes.

Exhaustive extractions require repetitive extractions, but they allow for the use of “real life” positive controls. These controls are created by exposing devices to the normal manufacturing processes, but then not subjecting them to the cleaning process being validated. This allows the manufacturer to establish the pre-cleaning levels of the target compound(s), which is the first step in establishing limits for residual analysis. Once the pre-cleaning levels are established, clean devices are tested to show a percent reduction or log reduction of residual manufacturing materials. Additional testing (such as microbiological or biocompatibility testing) can then be used to justify the acceptability of any residual levels on the clean devices.



*Loading samples on total organic carbon analyzer. (TOC)*

Limits for the target compound(s) may be established based on the recovery level, reduction comparison, or limits of detection of the method when comparing clean devices and positive controls. Specific risk assessment and justifications should be prepared for the validation file to ensure regulatory reviewers can determine the rationale for a test plan and established limits for residual manufacturing materials.

### **TOTAL ORGANIC CARBON (TOC)**

TOC analysis is a relatively straightforward and inexpensive method for validating a cleaning process and for performing routine monitoring of residual levels once the validation is complete. TOC is also a very sensitive analytical

method with detection capabilities in the part per billion (ppb) range.

The TOC method used at NLI begins by acidifying the device extract in order to purge any inorganic carbon. Then, the organic carbon is oxidized with sodium persulfate at 100°C to form carbon dioxide. The resulting carbon dioxide is purged from the solution and detected by a non-dispersive infrared (NDIR) 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.

In order for TOC to be a suitable analysis technique, first it must be established that a significant amount of organic carbon is contained in the target compound(s). The carbon present must also be oxidizable under the TOC test conditions, and adequate water solubility of the target compound(s) must be demonstrated. Even some essentially insoluble organic target compounds may be removed by water extraction and analyzed by TOC.

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 (i.e. carbon from sources other than the target compounds) as much as possible. Any established limits for the target compounds must be corrected for background carbon.

One advantage of TOC is that a level has been established for purified water which represents a great target level for residual analysis. The United States Pharmacopeia (USP) and European Pharmacopeia (EP) both require purified water and water for injection (WFI) to contain approximately or lower than 500 ppb of TOC. This represents a defensible standard level because it would be hard for a regulatory agency to justify a cleaning level for a device lower than that required for purified water. By coupling TOC analysis with a conductivity/pH analysis (also required for purified water testing), device extracts may also be analyzed for any ionized species such as acids, bases, or salts.

### **GRAVIMETRIC ANALYSIS**

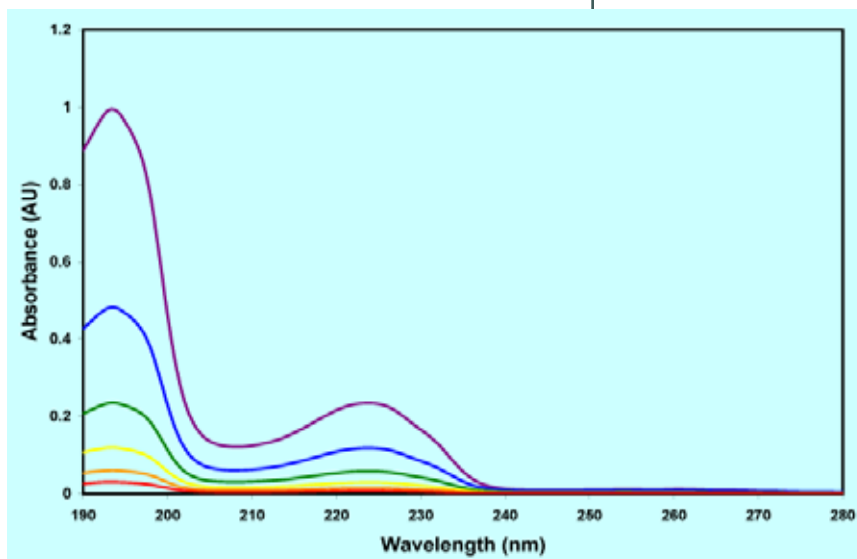
Another method used at NLI for cleaning vali-

dations is a gravimetric analysis based on the recently published document, ASTM F2459. NLI has been performing this type of gravimetric analysis for approximately four years. One advantage of this method is that extraction solvents other than purified water may be used, allowing for the detection of water-insoluble contaminants. If a significant residue is quantified, then the residue may also be identified (qualified) by infrared spectroscopy. A general analysis/interpretation of the sample spectrum can reveal the presence of certain types of compounds such as hydrocarbons and amines. This identification may also be accomplished by comparing the sample spectrum to the spectra of target compounds.

To perform the gravimetric procedure, first the devices are immersed in the appropriate extraction solvent. Devices may be pooled for the analysis in order to increase the sensitivity of the method, though there is a risk of added particulates created through friction between devices during the extraction procedure. The devices are sonicated for a pre-determined time and at a specified temperature. These extraction times and temperatures must be validated with each study based on the target residues. After extraction, the devices are removed and the extract is reduced. The concentrated extract is then transferred to a pre-weighed crucible where it is evaporated to dryness. The crucible is re-weighed, and the resulting weight difference represents the amount of soluble and insoluble residue on the device.

## DETERGENT RESIDUAL ANALYSIS

A third method for cleaning validations focuses on compounds which readily absorb ultraviolet light. Detergents are the most common residue detected using this technique. Samples of the pure detergent must be available to NLI for validation purposes. Devices are extracted in a known volume of purified water and the extracts are analyzed using a UV/VIS spectrophotometer. The concentration of the target compound is then calculated using linear regression and a standard curve. Because each compound responds differently to this test, each analyte must be validated for accuracy, precision, ruggedness, limit of detection, and



limit of quantitation.

This method is also quantitative but not qualitative. If there are several contaminants present which absorb ultraviolet light, there is no way to distinguish one compound from another. The concentrations are calculated as worst-case, assuming that all of the resulting absorbance is due to a single contaminant. NLI has been performing this procedure for more than ten years, and many common detergents have already been validated for method suitability. The “real life” positive controls for this method are devices which have been cleaned using the target compound but have not been rinsed. These devices must be previously cleaned in order to reduce any background interferences.

## SUMMARY

TOC analysis will not detect inorganic contaminants; some compounds are unsuitable for analysis using UV because they do not absorb; gravimetric procedures will exclude any residue more volatile than the extraction solvent. It is important to have a knowledge of and a thorough assessment of the materials used in manufacturing and cleaning.

Nelson Laboratories has been performing cleaning validations for a number of years. The experience gained is invaluable in consulting with clients as to which method is most suitable for their product or process. For more information regarding analysis of residual manufacturing materials, please contact us at [sales@nelsonlabs.com](mailto:sales@nelsonlabs.com).

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# DISINFECTION VALIDATION OF MEDICAL DEVICES

*By Emily Mitzel, B.S., M.S., Hospital Reprocessing Section Leader*



**M**any medical devices are designed and manufactured to be used for multiple patients. The cleaning and disinfection/sterilization of these devices is becoming an increasingly critical infection control issue. Residues which can be harmful to both patients and medical staff must be removed. The medical device must first be cleaned to remove all traces of residue, using a detergent that digests protein, fat, carbohydrates, and starches. When the cleaning procedure is complete, a disinfection or sterilization process can effectively be performed.

Nelson Laboratories, Inc. has performed this type of testing for many years. We are also knowledgeable about the standards associated with this testing and maintain membership on the standard writing societies.

Many devices are heat sensitive and cannot be exposed to steam. They may also be incompatible with other sterilization methods; therefore, a disinfection process may be the only option. These processes are categorized as low level, intermediate level, or high level disinfection.

The process used is based upon the criticality of the device, i.e., how it is used on the patient.

The following definitions apply.

**CRITICAL DEVICES** – medical devices that are introduced into or have contact with the bloodstream or normally sterile areas of the body. Examples include, but are not limited to, implants and surgical instruments.

**SEMICRITICAL DEVICES** – medical devices that contact intact mucous membranes or non-intact skin, but do not ordinarily penetrate the blood barrier or otherwise enter normally sterile areas of the body. Examples include, but are not limited to, gastrointestinal endoscopes and respiratory therapy equipment.

**NONCRITICAL DEVICES** – medical devices that only contact intact patient skin. Examples include bedpans, reusable anesthesia masks, and blood pressure cuffs.

**LOW LEVEL DISINFECTION** – process that kills most vegetative bacteria, some viruses, and some fungi, but not mycobacteria or bacterial spores.

**INTERMEDIATE LEVEL DISINFECTION** – process that kills most vegetative bacteria, some viruses, and some fungi, but not mycobacteria or bacterial spores.

**HIGH LEVEL DISINFECTION** – process that kills all microbial organisms but not necessarily large numbers of bacterial spores.

The type of disinfection necessary for the criticality of the device is not uniform in every standard or guidance document. Medical devices that are determined to be noncritical may either be processed by cleaning alone or by a low level disinfection procedure. Medical devices that are determined to be semicritical may either be processed through a low, intermediate, or high level disinfection process, depending upon the

type of device and how it is used. Medical devices that are determined to be critical must be processed with a high level disinfection procedure.

After being cleaned, an item is typically immersed in the disinfectant for a defined period of time at a specified temperature. These parameters are determined by the manufacturer or by preliminary lab tests and indicated in the product labeling.

The efficacy of a low level disinfection procedure is evaluated by contaminating the devices with a minimum of  $1.0 \times 10^6$  CFU/device vegetative organisms. The low level disinfection test criterion requires a minimum of a  $6 \log_{10}$  reduction of the specific organisms tested.

The efficacy of the high level disinfection evaluation procedure is evaluated by contaminating devices with a minimum of  $1.0 \times 10^6$  CFU/device of *Mycobacterium* species. The high level disinfection of the devices must demonstrate a minimum  $6 \log_{10}$  reduction after processing.

Disinfection can be performed using either thermal or liquid chemical processes. The advantage of thermal disinfection is that heat can penetrate barriers such as biofilms, tissue, and blood to ensure organism kill. Items to be considered when utilizing liquid chemicals are the viscosity of the disinfectant and the post-processing envi-

ronment of the device, which includes rinsing with sterile water. All devices processed with the disinfectant should be thoroughly rinsed with sterile water to maintain sterile integrity and to reduce chemical residues.

Evaluation of toxicity may include skin irritation, skin sensitization, cytotoxicity, acute dermal toxicity, hemocompatibility/hemolysis, and sub-chronic dermal toxicity testing. Acute oral toxicity, primary eye irritation, acute inhalation toxicity, genotoxicity, chronic toxicity, and reproductive and developmental toxicity testing are often also indicated.

Prior to the disinfection validation, a neutralization test should be performed to demonstrate the recovery of the test organism(s). The neutralizer chosen for a particular disinfectant must demonstrate its ability to neutralize the disinfectant without adversely affecting the viability of the test organism.

Nelson Laboratories, Inc. staff is knowledgeable with the standards and disinfection validations of medical devices. We can help determine the necessary testing for specific medical device applications.

Please contact Emily Mitzel or Alpa Patel for additional information. For a quote, contact [sales@nelsonlabs.com](mailto:sales@nelsonlabs.com).

*Nelson  
Laboratories,  
Inc.  
staff is  
knowledgeable  
with the  
standards  
and  
disinfection  
validations of  
medical devices.*

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# sterile filtration validations

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**N**elson Laboratories, Inc. (NLI) specializes in sterile filtration validations and has performed them for 20 years. NLI is ISO certified and is routinely audited by FDA and other regulatory agencies.

We have a 62,000 square foot laboratory with a dedicated laboratory for filtration studies. The filtration laboratory features a HEPA-filtered positive pressure (Class 1000) environment with filtered air, nitrogen, and vacuum utilities and purified water (USP) plumbed in. We have validated in-line steam sterilization, ethylene oxide or steam autoclave facilities, and a complete supply of pumps, pressure vessels, filter housings and sanitary (type) plumbing fittings for simulating most processes.

## FILTRATION VALIDATION

The FDA defines validation as:

*“Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product, meeting its pre-determined specifications and quality attributes.”*

The U.S. Food and Drug Administration published *A Guideline on Sterile Drug Products Produced by Aseptic Processing*. In this guideline, the FDA recommends that whenever filtration is used as the aseptic step in the production process, validation procedures will include microbial retention testing of the filters. These tests must be conducted using simulated pharmaceutical processing procedures which define “worst case” production conditions. Parameters to be considered in these “worst



case” conditions include: organism size, number of organisms, flow rate, temperature, pH, viscosity, pressure, etc.

The accepted industry standard for “sterilizing grade” 0.2µm rated filters is the complete retention of *Brevundimonas (formerly Pseudomonas) diminuta* ATCC #19146 at a concentration of at least  $1.0 \times 10^7$  organisms per square centimeter of effective filtration area at a differential pressure of 30 PSIG and a flow rate of at least 3.86 L/min/0.1 m<sup>2</sup>.

The mechanism of retention in membrane filters is not only a sieving function; the chemical and physical properties of the product can also have a significant influence on the effectiveness of the filter. It is therefore essential that the product’s effect on the retention function is evaluated before traditional challenge testing is performed. Filter compatibility studies may be required, and the chemical and physical properties of the product must be evaluated prior to or concurrent with the design of the validation protocol. Other applicable tests that may be required are extractables testing using a model solvent to identify leachables that may be entering the product stream during filtration, and product wetted integrity test validation if actual product is used to wet the filter for an integrity test. Please contact [sales@nelsonlabs.com](mailto:sales@nelsonlabs.com) for a price quote for your next filtration validation.

Salt Lake City, UT — On March 7, 2006, Nelson Laboratories, Inc. announced the naming of Jeffery Nelson as the President/CEO of the company. “The purpose of this change is to establish an exciting new direction for the company. We also feel that this will allow the company to grow and inovate, while continuing the long standing tradition of service and quality,” says Lynda Nelson, newly appointed Chairwoman.

Dr. Jerry Nelson will continue in his role as Laboratory Director and Chief Science Office (CSO) but will focus more on imparting his microbiological and regulatory expertise to staff, customers, and industry partners. “We are delighted to have Jeffery serve as our President/CEO,” says Dr. Nelson. “He has served at every level of the company and knows our operation very well. He has definitely earned our trust and we are confident that his leadership will ensure the company’s long term success.”

Nelson has served in various positions throughout the company during his 19 years of service including: Glassware Technician, Laboratory Technician, Associate Study Director, Study Director, Complaint Coordinator, Client Service Manager, VP Client Services and Business Development, and Vice President of Operations. “Nelson Laboratories is a great company with a long history of doing things right. I am excited to serve as President of a company with such a rich history and such great upside potential,” says Nelson. Nelson also emphasized his plan to incorporate a dynamic strategic planning process closely linked to reporting and accountability. “My goal is to get everyone in the company aligned with our mission, strategy, and goals.”

Nelson Laboratories, Inc. recently celebrated its twentieth anniversary in October 2005. Nelson Laboratories serves the medical device, pharmaceutical, and nutraceutical industries by providing the highest standard in microbiological laboratory testing.



**Jeffery R. Nelson**

*named new President/CEO of Nelson Laboratories, Inc.*

## Future Events By Nelson Laboratories

### THE SCIENCE OF STERILIZATION VALIDATION WORKSHOP

Join us for this two day workshop offering an opportunity to understand Radiation and EO Sterilization methods, microbiological basics and how to validate your sterilization and manufacturing process.

**TOPICS TO INCLUDE:**

Sterilization Basics  
Microbiology Basics  
Radiation Sterilization  
EO Sterilization  
Bicompatibility  
Packaging/Shelf Life

**LOCATION:** Hilton Salt Lake City Center,  
Salt Lake City, Utah  
**DATE:** October 2-3 • 8:00-5:00  
**PRICE:** Before September 18 \$650.00,  
after \$750.00  
Seating is limited to the  
first 50 registrants.  
**CONTACT:** Clarence Baker  
or Jared Forsyth at  
Seminars@nelsonlabs.com  
800-963-6280, ext. 9189 or 9051

**FOR MORE INFO:**

[www.nelsonlabs.com/seminars.jsp](http://www.nelsonlabs.com/seminars.jsp)

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