



VOLUME 1/2005

# MICRO NEWS

## TERMINAL MEDICAL DEVICE STERILIZATION OPTIONS USING VAPORIZED H<sub>2</sub>O<sub>2</sub>

There are several commonly known methods for terminal sterilization, including ethylene oxide (EO), radiation (gamma and E-beam), dry heat, and steam. There are also newer sterilization options that utilize hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) vapor which are effective sterilization methods for highly resistant spore formers, non spore forming bacteria and other microorganisms. This article discusses the considerations and options for medical device terminal sterilization using vaporized H<sub>2</sub>O<sub>2</sub> with the STERIS VHP<sup>®</sup> MD series sterilization system.

### STERILIZATION CHOICES

The choice of terminal sterilization method can be difficult and depends on material compatibility, temperature and requirements for turnaround time. Typically, EO and gamma are better suited to be performed at a contract sterilization facility. Steam is a method used by hospitals, but only by a few device manufacturers because of its high temperature and incompatibility with many materials of construction.

In addition to these traditional sterilization processes, there are systems that utilize vaporized H<sub>2</sub>O<sub>2</sub>. For more than 15 years, vaporized H<sub>2</sub>O<sub>2</sub> has been used as an effective decontaminant in the pharmaceutical industry as it is highly sporicidal at low concentrations. During the past several years, vaporized H<sub>2</sub>O<sub>2</sub> applications for terminal sterilization of medical

devices have been introduced. These include Advanced Sterilization Product's STERRAD<sup>®</sup> system (ASP, a division of Johnson & Johnson, Inc.) and more recently STERIS Corporation's VHP<sup>®</sup> MD series (VHP<sup>®</sup>) sterilization system.

### VAPORIZED HYDROGEN PEROXIDE WITH STERIS VHP<sup>®</sup> MD

The STERIS VHP<sup>®</sup> MD system is an alternate sterilization process for medical device companies seeking a low temperature method combined with fast cycle times utilizing H<sub>2</sub>O<sub>2</sub> vapor. The VHP<sup>®</sup> system is designed to use H<sub>2</sub>O<sub>2</sub> vapor under vacuum conditions to penetrate a packaged medical device and to sterilize the finished device or kit. One of the key benefits of H<sub>2</sub>O<sub>2</sub> vapor is that it leaves no toxic residuals, resulting in excellent material compatibility and requiring no lengthy post-processing aeration. Additionally, the STERIS VHP<sup>®</sup> MD system is an excellent in-house sterilization option for JIT (just-in-time) at point of manufacture, thus improving overall turnaround time, and allowing a medical device manufacturer to process many loads of finished product per day. Furthermore, due to its fast cycle times, even small batches of custom devices can be sterilized rapidly, same day.

*"The STERIS VHP<sup>®</sup> MD sterilization system allows a medical device manufacturer to reduce finished goods inventory and improve*

*(cont. page 2)*

### IN THIS ISSUE

Medical Device Sterilization . . . . . pg. 1-3  
 Particulate Tests . . . . . pg. 3  
 Identity Crisis/Microbial ID . . . . . pg.4-5  
 Future Events/Seminars . . . . . pg. 6  
 2004 Nelson Golf Outing . . . . . pg. 6



6280 So. Redwood Road  
 Salt Lake City, Utah  
 84123-6600-80  
 800.826.2088

## TERMINAL MEDICAL DEVICE STERILIZATION

### OPTIONS USING VAPORIZED H<sub>2</sub>O<sub>2</sub>

(cont.)



*their overall manufacturing turnaround time because of the fast cycle times”, says Larry Lachowski of STERIS Corporation. “The VHP® MD system can be integrated with in-house manufacturing and packaging operations, thus providing greater control of the sterilization process.”*

Package design is also important. The primary package should either be a pouch or a lidded tray using a medical grade, breathable, sterile barrier package material, such as Tyvek®. Typical packaging that is suitable for EO will also work with VHP® except that cellulose (paper) packages are not compatible with VHP®. Another key parameter, sterilization cycle time, will vary depending on how complex the medical device is to sterilize. However, VHP® cycle times are generally rapid and usually faster than EO.

Environmental impact and safety issues should be considered when choosing a sterilization method. With most H<sub>2</sub>O<sub>2</sub> sterilization systems, including the STERIS VHP® system, the process breaks down the hydrogen peroxide sterilant to water vapor and oxygen after the sterilization process is complete. It is worker safe and environmentally friendly. For the STERIS VHP® system the vapor phase is safe for electronic components within a medical device. Devices that are sensitive to moisture, or that have high residual problems, may consider VHP® sterilization as an alternative sterilization method.

For those looking for a terminal sterilization process at point-of-manufacture, VHP® is a new option to consider:

- ✓ Low temperature process
- ✓ Rapid cycle times
- ✓ Non-toxic residuals
- ✓ No lengthy post-processing aeration
- ✓ Excellent material compatibility
- ✓ Fast turnaround time due to in-process design
- ✓ Safe environmental by-products
- ✓ Low operating costs

### VALIDATION GUIDELINES

Because there are currently no consensus standards for VHP® sterilization, guidelines are taken from ANSI/AAMI/ISO 14937 for general requirements of a sterilizing agent. In addition, concepts are taken from EO standards as both VHP® and EO are gaseous methods of sterilization. Validation and testing of the STERIS VHP® MD process is based in part on the following guidelines:

**ANSI/AAMI/ISO 14937: 2000** “Sterilization of Health Care Products – General Requirements for Characterization of a Sterilizing Agent and the Development, Validation and Routine Control of a Sterilization Process for Medical Devices”.

**ANSI/ AAMI/ISO 11135: 1994** “Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization”.

*Provided by Larry Lachowski, STERIS Corporation*

The VHP® MD 880 sterilizer installed at Nelson Labs is a double door unit that also permits sterile transfer of supplies into our cleanroom suites. This sterilizer provides the capability to process heat sensitive items such as respirators and goggles into the sterility test suites without residuals or exposure issues.

If you would like to learn more about alternative sterilization processes or for an independent assessment of VHP® or STERRAD® sterilization options for your device, please contact:

*Dan Floyd, Sterilization Section Leader  
Nelson Laboratories  
800-963-6280 ext. 9068  
dfloyd@nelsonlabs.com*

(cont. page 3)

*Nelson Laboratories is not affiliated with STERIS Corporation or Advanced Sterilization Products (a division of Johnson & Johnson, Inc.). All registered trademarks and copyrights are property of their respective owners.*



**P**articulate testing in the pharmaceutical industry has been a common practice for quite some time. Pharmaceutical products involve chemical or biological activity in the body, and often come in the form of a sterile injectable or liquid. Minimizing particulate contamination in these products is essential and typically is performed following USP <788>. In addition to pharmaceutical products, many medical device manufacturers are using a modified USP <788> (Particulate Matter Injections) test to verify device cleaning procedures and to prevent contamination.

According to Section 820.56 of the FDA GMP guidance, device manufacturers should have, “adequate cleaning procedures and schedules to meet manufacturing process specifications and prevent contamination.” In order to comply with these regulations, many medical device manufacturers have added particle counting to their quality control procedures. As there is currently no general standard for particulate contamination on medical devices, with the exceptions of EN 45502 for implantable medical devices, ISO 1134 for transfusion sets, and ISO 8536 for infusion equipment for medical use, many device manufacturers have adopted a modified USP <788> method to determine particulate contamination.

## PARTICULATE TESTS TO VERIFY DEVICE CLEANING PROCEDURES

Adopting a Modified USP <788> Method for Device Manufacturers

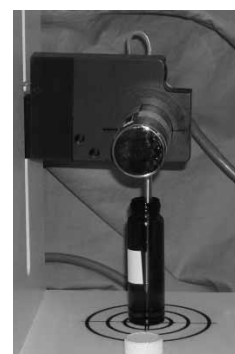
Bryan Wilson, B.S., RM(NRM)

For pharmaceuticals, USP <788> describes the light obscuration procedure as the first stage for testing particulate matter in injections. If the injection fails to meet the prescribed limits, it must be further tested using the microscopic procedure (stage 2) with its own set of test limits. Some pharmaceuticals cannot be tested by light obscuration for technical reasons. Examples of such products are emulsions, colloids, liposomal preparations, and products that produce air or gas bubbles when drawn into the sensor, such as bicarbonate-buffered formulations. For these products, microscopic testing must be used exclusively. Using a rinse or other appropriate extraction method, devices can also be evaluated for particulates following USP <788>.

Particulate tests for devices may

be performed to ensure acceptable particulate limits are defined during the device design phase. Possible sources of contamination include raw materials, components, manufacturing practices, personnel, or other environmental conditions. In most particulate test procedures a device is either rinsed, flushed, or immersed in an extraction fluid (e.g., particle free USP water) to remove particulates. The extraction fluid is collected into a particle-free container and then analyzed using a laser particle counter. Standard test sizes for USP <788> are  $\geq 10\mu\text{m}$  and  $\geq 25\mu\text{m}$ . Each device manufacturer should establish their own specifications for acceptable limits and sizes of particulate contamination.

Once a cleaning procedure has been established for a device production process, particulate monitoring should be repeated periodically to confirm the on-going effectiveness of the cleaning operation. Some companies find quarterly tests to be indicative of particulate counts over time, however, others have moved to lot-release testing to ensure protection from particulate-related emboli with certain devices. In either case, particulate count determinations using a modified USP <788> procedure have become an inexpensive but effective way for device manufacturers to verify their cleaning procedures and quality of device products.



United States Pharmacopeia  
28 National Formulary 22.  
2004. <788>  
*Particulate Matter  
in Injections*  
USPC, Inc. Rockville, MD.

EN45502-1:1998.  
Active Implantable  
Medical Devices - Part 1:  
General Requirements for  
Safety, Marking and  
Information To  
Be Provided by the  
Manufacturer.

PREN 45502-2-1: 1998.  
Active Implantable  
Medical Devices Part 2-1:  
Particulate Requirements  
for Active Implantable  
Medical Devices Intended  
to Treat Bradyarrhythmia  
(Cardiac Pacemakers).

PREN 45502-2-2: 1998.  
Active Implantable  
Medical Devices Part 2-2:  
Particulate Requirements  
for Active Implantable  
Medical Devices Intended  
to Treat Tachyarrhythmia  
(Includes Implantable  
Defibrillators).

European Pharmacopeia.  
5<sup>th</sup> Edition. 2005.  
Method 2.9.19.  
Council of Europe,  
Strasbourg, France.

ISO 8536-4 International  
Standard. 2004. Infusion  
equipment for medical use  
- Part 4: Infusion sets for  
single use, gravity feed.  
Annex F. International  
Organization for  
Standardization, Geneva,  
Switzerland.

### TERMINAL MEDICAL DEVICE STERILIZATION OPTIONS USING VAPORIZED $\text{H}_2\text{O}_2$ (cont.)

To conduct an initial feasibility evaluation of your device or for more information about purchasing a STERIS VHP® MD sterilization system, contact:

Larry Lachowski  
STERIS Corporation  
949-495-7974  
larry\_lachowski@steris.com

Both the STERIS VHP® MD and STERRAD® systems are available to medical device manufacturers considering alternative sterilization processes. Both systems are unique, viable alternatives for low temperature sterilization of medical devices. Nelson Laboratories offers medical device manufacturers an independent evaluation of product sterilization validations for these sterilization options and can assist clients considering an in-process sterilization solution.

# IDENTITY CRISIS?

by April Wanstrom,  
B.S., RM(NRM)  
and  
Brandon Tillman,  
B.S., RM(NRM)



## IDENTITY CRISIS?

Determining the source of contamination is critical during product sterility failure investigations and microbial contamination issues in the manufacturing environment. Proactively identifying or characterizing product bioburden and environmental isolates can help you with root cause analysis in these situations. This article discusses characterization and identification methods and considerations for proactively understanding your product bioburden and environmental isolates to avoid a contamination identity crisis.

## DEFINITIONS:

**Characterization** involves knowing colony morphology, microscopic morphology (rods, cocci, coccobacilli, or yeast) and gram reaction. Some take characterization a step further by testing for key enzyme activities, but overall characterization is a generalization of the organism type or classification.

**Identification** results in a genus and species name for the organism. There are several methods used to determine organism identification. At Nelson Laboratories for example, isolates are generally gram stained first to help indicate which organism type is present so that the appropriate organism identification system and database can be searched.

For phenotypic identification, if it is a bacteria the isolate is run on the MIDI® fatty acid system using one of two database libraries (environmental or clinical). If it is a yeast the isolate is run on a BIOLOG® system that searches a specific yeast database to find a relevant match. For fungi (mold), microscopic observation for fungal taxonomy is still a viable method that can be used to achieve identification to a genus level. By using a BIOLOG® FF system, genus and species names for most molds can be determined. New DNA/RNA sequencing systems and technologies, such as the MicroSeq® system from Applied Biosystems, use organism genetic libraries for genus and species organism identification.

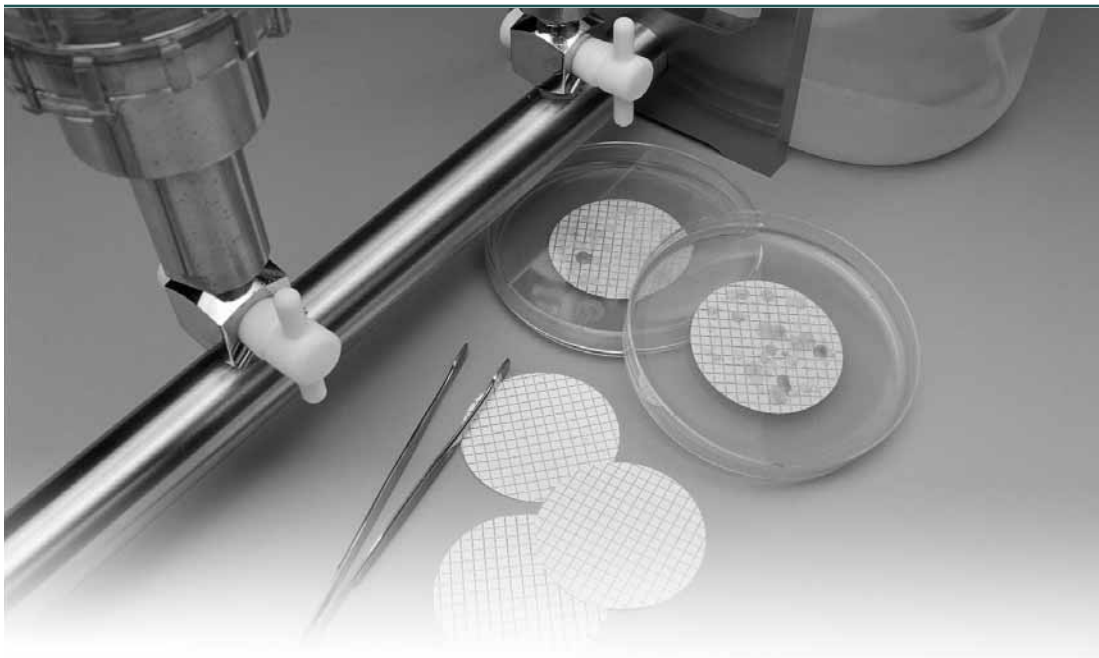
## AREAS FOR CONSIDERATION:

**Environmental monitoring** is a necessary part of your product manufacturing process. Microbial identification or characterization will give meaning to the flora count found in your monitoring process and assist in root cause analyses in the event of contamination or sterility test failures. For example, Staphylococous organisms on product typically come from people, whereas Bacillus organisms found on product typically indicate an environmental (air or surface) contaminant.

**Water systems monitoring** is important to your end product bioburden. Do you know what organisms are present in your water system(s) and how that population changes over time? Microbial identification gives you this information and preliminary indications of water system problems. For example, Pseudomonas organisms found on product typically indicate water system contamination issues as a starting point for root cause analysis.

**Product microflora** or the natural bioburden present on your product can be a key indicator of your manufacturing environment and systems. Understanding your product bioburden can be an advantage for sterilization considerations and preventing sterility test and system failures. Product bioburden characterization and identification can also help you detect a change in the microorganisms that inhabit your manufacturing environment or staff. ISO/DIS 11737-1 specifically mentions the importance of an estimation of the microorganisms on the product.

If microbial identification is performed, you will gain a historical database of the organisms present in your manufacturing systems and environment. This gives you excellent information for root cause analysis if contaminants are found in a media fill, if product bioburden counts are escalating, or if there is a product sterility failure (USP <71> Sterility Tests).



## REFERENCES

Sutton, Scott V.W. and Cundell, Anthony M. Microbial Identification in the Pharmaceutical Industry. Pharmacopeial Forum. Vol. 30(5). pp.1884-1891. USPC, Inc., Rockville, MD.

United States Pharmacopeial Convention, Inc. 2005. <1227> Validation of Alternative Microbiological Methods. USPC, Inc., Rockville, MD.

United States Pharmacopeial Convention, Inc. 2005. <71> Sterility Tests. USPC, Inc., Rockville, MD.

ANSI/AAMI/ISO 11737-1 1995. Sterilization of Medical Devices-Microbiological Methods Part 1; Estimation of Population of Microorganisms in Products.

## WHEN TO CHARACTERIZE OR FULLY IDENTIFY

The decision to characterize and/or fully identify the microorganisms should be based on regulatory and compendial requirements. You should also take into account what others in the industry are doing, and perform risk assessment in terms of the criticality of the isolates to your process, product, or end user. As an example, criticality would be high for a sterility test positive, but may be low for an isolate recovered in a non-controlled room during environmental monitoring.

Consider whether the identification or characterization is part of a validation or routine monitoring. Additionally you may ask: Are the organism levels above or below my alert and/or action levels? Has this level of growth occurred once or is it occurring frequently? If your answers to these questions tend to the more serious condition, then you should consider full identification of your microorganisms.

Characterization should be considered for routine monitoring with environmental isolates that are below your alert limits, during pre-sterilization bioburden estimates, and for contaminants not normally encountered in the pre-sterilization process. ANSI/AAMI/ISO 11737-1 supports characterization of this kind.

Full microbial identification should be done when resistance to sterilization is a concern, BI or sterility tests are positive, alert or action levels have been exceeded, and when validating processes. The decision to use characterization or full identification should be made by the manufacturer as part of the manufacturers risk assessment strategy. Most effective risk assessments tend to escalate the importance of microbial identification.

## CONCLUSION

Microbial identification and characterization of environmental isolates in the manufacturing facility and product bioburden will assist you in fully complying with regulatory and compendial requirements while providing helpful environmental and product monitoring data. This data can be useful in the event of an identity crisis during sterility test failure investigations and compliance audits.

Contact [sales@nelsonlabs.com](mailto:sales@nelsonlabs.com) to learn more about our quarterly dose audit bioburden characterization program or to discuss your environmental or product bioburden characterization and microbial identification needs.



FUTURE EVENTS BY NELSON LABORATORIES

## RADIATION STERILIZATION VALIDATION WORKSHOP

This workshop is a follow-up to "The Science of Sterilization Validation Seminar". Discussions will include a more in-depth look at requirements necessary for the validation process.

**Location:** Nelson Laboratories, Salt Lake City, Utah

**Date:** April 7-8, 2005 • 8:00-5:00 PM

**Price:** Before March 16, 2005 \$500.00,  
after \$550.00

**Contact:** Jared Forsyth, [jforsyth@nelsonlabs.com](mailto:jforsyth@nelsonlabs.com)  
800-963-6280, ext. 9051

**For more info:**  
[www.nelsonlabs.com/seminars](http://www.nelsonlabs.com/seminars)

LIMITED SEATING

## 2004 GOLF OUTING

A beautiful golf course, great weather, and excellent food describes the Nelson Laboratories 2004 Golf Tournament. The tournament was held Saturday, September 11<sup>th</sup> at Mountain Dell Golf Course in Parley's Canyon. The field was complete with forty teams competing in two divisions, with competitions for longest drive and closest to the hole. During lunch the prize drawing was a hit where golf bags, clubs, and other equipment were given out.

Nelson Labs would like to thank all employees, clients, and sponsors that helped make the 2004 tournament a great time and success.

We hope to see you there next year.



6280 So. Redwood Road  
Salt Lake City, UT 84123-6600-80

PRSR 1<sup>ST</sup> CLASS  
US Postage  
**PAID**  
SLC, UT 841  
Permit No. 7259



*Celebrating 20 Years of  
Test Service Excellence*