



## ALSO IN THIS ISSUE

Antimicrobial  
Agents on  
Personal Protective  
Equipment

New Sample  
Submission  
Form Benefits  
Sponsors!

VOLUME 2/2008

# MICRO NEWS

## THE "PARTICULARS" OF CONTROLLING VASCULAR PARTICULATE CONTAMINATION

— By Morris L. Jessop —

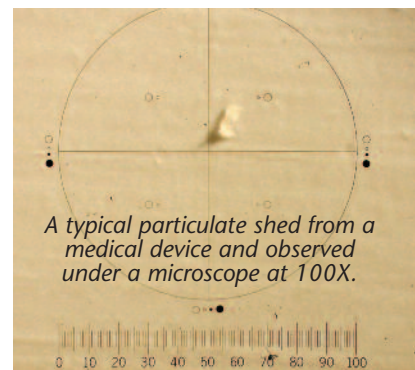
**D**islodged from a medical device or infused with an injection, a single particulate enters the vascular system. Drifting up the systematic venous system towards the heart, the particulate casually passes into the right atrium, surges through the tricuspid valve, and gushes through the right ventricle. Like a floating tree branch in a turbulent mountain stream, the particulate catches the pulmonary artery's swift current and lodges in the narrow branches of the alveolar capillary bed.

Over time, the particle is joined by others. Unable to be completely dissolved or phagocytosed by alveolar macrophages, these particles (and others throughout the body) may become detrimental to a patient's health. Numerous studies<sup>11, 12</sup> have shown or suggested that too much particulate contamination introduced into the vascular system may interfere with wound healing, cause inflammation, thrombosis, granuloma formation, or even death. Thus minimizing the levels of particulate contamination during the manufacturing of a medical device or parental injection is important.



Ryan Lunceford and the HIAC Royco liquid particle counter.

As a study director for particulate testing at Nelson Laboratories, my clients frequently request guidance on the appropriate limits of particulate contamination in their injections or in/on their medical devices. For injections, the limits are well defined by commonly used standards in the pharmaceutical industry such as United States Pharmacopeia <788>, European Pharmacopeia 2.9.19, and the Japanese Pharmacopeia. These



A typical particulate shed from a medical device and observed under a microscope at 100X.

(continued on page 2)

1. Barber, Thomas A. The Control of Particulate Matter Contamination in Healthcare Manufacturing. CRC Press – Taylor & Francis Group, copyright 2000.

2. United States Pharmacopeia 31 & National Formulary 26. 2008. <788> Particulate Matter in Injections. United States Pharmacopeial Convention, Inc., Rockville, MD.

3. European Pharmacopoeia 6th Edition. 2006. 2.9.19. Particulate Contamination: Subvisible Particles. Council of Europe, Strasbourg, France.

4. British Pharmacopoeia 2007. Vol. 4, Appendix XIII A. Particulate Contamination: Sub-visible Particles. The Stationary Office, London, England.

5. BS EN 45502-1:1998. Active implantable medical devices. General requirements for safety, marking and information to be provided by the manufacturer. European Committee of Standardization, Brussels, Belgium.

6. prEN 45502-2-2:1998. Active implantable medical devices - Part 2-2: Particular requirements for active implantable medical devices intended to treat tachyarrhythmia (includes implantable defibrillators). European Committee of Standardization, Brussels, Belgium.

7. BS EN 45502-2-1: 2003. Active implantable medical devices. Part 2-1: Particular requirements for active implantable medical devices intended to treat bradyarrhythmia (cardiac pacemakers). European Committee of Standardization, Brussels, Belgium.

8. ISO 8536-4 British Standard. 2004. Infusion Equipment for Medical Use – Part 4: Infusion Sets for Single Use, Gravity Feed. International Organization for Standardization, Geneva, Switzerland.

9. The Association for Advancement in Medical Instrumentation. Information on Committees. Medical Device Particulates Committee  
<http://www.aami.org/committees/central/Committee/ShowCommitteeDetail.cfm?ComID=0DP0000>

10. ANSI/AAMI AT6-2005. Autologous Transfusion Devices. Arlington, VA.

11. Russell, J. H. 1970. Pharmaceutical Applications of Filtration. J. Hosp. Pharm. 28:125-126

12. Pesko, L. J. 1996. Physiological Consequences of Injected Particles. In Liquid and Surface Borne Particle Measurement Handbook, edited by J. Z. Knapp, T. A. Barber, and A. W. Lieberman. New York: Marcel Dekker.

## LIGHT OBSCURATION

Volume	≥ 10 µm	≥ 25 µm
Small	≤ 6,000 Particles/Container	≤ 600 Particles/Container
Large	≤ 25 Particles/mL	≤ 3 Particles/mL

## MICROSCOPIC

Small	≤ 3,000 Particles/Container	≤ 300 Particles/Container
Large	≤ 12 Particles/mL	≤ 2 Particles/mL

*Standard limits in USP <788> for particulate matter in parental injections via light obscuration and microscopic measurement.*

standards define test methods and set the limits for both small and large volume injections.

For small volume injections (≤ 100 mL), testing is performed to these standards by combining ten or more individual samples. Aliquots are removed from the pooled solution and tested with a liquid particle counter or counted manually under a microscope. Large volume injections (> 100 mL) are usually tested in the same manner, but do not necessarily require pooling samples.

Unlike liquid injections, the particulate specifications and testing methods for medical devices are not as well defined. Although standards dictating appropriate limits for certain medical devices such as infusion sets<sup>8</sup>, cardiac pacemakers<sup>5, 6, 7</sup>, and autologous transfusion devices<sup>10</sup> exist, standards dictating particle requirements for most categories of medical devices are yet to be published. This lack of guidance partially stems from the diversity of devices and from the unknown affects from the size, quantity, and chemical composition of the particulates<sup>1</sup>.

Many medical device manufacturers establish their own controls or limits for particulate contamination. Devices are often evaluated by conventional laboratory techniques (such as flushing or rinsing with particle-free water) to remove particulates from the surface of their devices and suspend them in solution. Once suspended, the particulate matter may then be analyzed as a solution under standards such as USP <788> and EP 2.9.19. However, these compendial standards are designed for parental injections and fail to address key issues unique to devices such as testing methods, application, and proper limits for particulate matter.

Despite the lack of knowledge about the affects of particulate contamination, this area is and has been an active subject of research. Healthcare providers, scientists, and the medical

device industry understand the need for controlling particulate matter in and on medical devices. Some organizations, such as the Association for Advancement in Medical Instrumentation (AAMI), are stepping up to provide guidance to medical device manufacturers<sup>9</sup>. Currently, a technical information report (TIR) is being developed by AAMI that will address the limits on acceptable size and quantity of particulate matter in/on vascular implants. This document will also describe the manufacturing environment for these devices, methods for detecting and identifying particulate contamination, and summarize biological responses to particulate matter.

While the AAMI TIR will provide guidance or vascular implantable medical devices, guidance for other devices will most likely follow. These standards are often adopted by a national medical, compendial, or regulatory body so that it has the same status as compendial requirements. Thus it's important for device manufacturers to not only keep track of these standards, but also be actively involved in their development.

Nelson Laboratories provides particulate testing services, resources, expertise, and are actively involved in the development of standards affecting the pharmaceutical and medical device industries. For more information about particulate testing, please contact us at [sales@nelsonlabs.com](mailto:sales@nelsonlabs.com). Our scientists, customer service department, and sales department are ready to help you.



# ANTIMICROBIAL AGENTS ON PERSONAL PROTECTIVE EQUIPMENT

— by Karl Perkes, B.S., SM (NRM) —

**O**n a worldwide basis, antimicrobial agents have been added to a diverse array of products, including medical devices. With the recent rise in diseases such as SARS and avian flu, many companies have begun marketing personal protective equipment (PPE) incorporated with antimicrobial agents.

In May 2007, the FDA convened an advisory committee to discuss recommendations on the review process for incorporating antimicrobial agents into PPE. Three types of PPE were discussed:

- surgical masks and respirators
- surgical and isolation gowns
- surgical and examination gloves

Prior to this advisory meeting, the FDA had cleared medical devices containing antimicrobials; however, had not yet done so for surgical masks, respirators, medical gloves, or isolation gowns. Several important differences exist between previously cleared medical devices and PPE with antimicrobial agents, and these differences are important to consider prior to the FDA review process.

The addition of an antimicrobial agent into a PPE can raise important scientific and clinical issues related to these types of products. Questions that may need to be addressed include: Can the antimicrobial truly enhance the protective barrier function of the PPE, and what are the risks associated with the addition of the antimicrobial agent?

It should be noted that some PPE are classified as Class I or Class II surgical apparel. Class I has traditionally been exempt from premarket notification requirements, but Class II products require FDA approval. Under the new requirements, if the PPE falls within the exempt Class I category but has an incorporated antimicrobial agent, the device may exceed the limitations of the exemption and require a 510 (k) premarket notification approval by the FDA.



*Collection of antimicrobial particles using simulated inhalation setup.*

The current FDA review approach for medical devices with an antimicrobial agent consists of four parts. The following is an outline of those parts, and is provided as a general guide for submission review of PPE which incorporate an antimicrobial agent:

1. Provide information on the antimicrobial agent alone
  - a) Has the antimicrobial been previously approved?
  - b) What are the approved indications?
  - c) What is the effective concentration?
2. Provide information on the antimicrobial agent associated with the PPE
  - a) What is the method and location of its application?
  - b) What are the characteristics of the antimicrobial on the product?
    - 1) Elution properties
    - 2) Mode of attachment
  - c) Is the antimicrobial agent safe?
    - 1) What is the historical experience with the antimicrobial agent on other product?

- 2) Can it cause potential biocompatibility concerns?
3. Can it cause potential interaction with the PPE material?
4. What are the overall associated risks from adding the antimicrobial agent to the PPE?
5. Can the antimicrobial come off the device, such as leach off (physically detach) or gas off?
6. What is the intended use/indication for use?
  - a) There are four general indication claims (efficacy data must be included when substantiating a category):
    - 1) Does it prevent contamination?
    - 2) Does it prevent colonization?
    - 3) Does it prevent or reduce infection?
    - 4) Is it a preservative?
7. Evaluation of efficacy of the antimicrobial agent
  - a) Is there performance testing to support the indication claim?
  - b) Does the test evaluate special characteristics of the PPE with the agent?
  - c) Does the test reflect the conditions in which the PPE is used?
    - 1) Uses clinically relevant organisms
    - 2) Uses relevant inoculum concentrations
8. Evaluates the finished product

Currently there are no FDA recognized standard test methods available to evaluate antimicrobial efficacy because each antimicrobial has different characteristics. In general, methods should be selected that apply universally, that use accepted scientific technique, and that provide quantifiable data to support the indication for use.

Meeting FDA's expectations for a submission is a complex process. This article is intended to guide and assist manufacturers in navigating through some of the new performance and safety requirements that may be requested by the FDA. We recommend that manufacturers contact their FDA reviewer prior to submission in order to establish an exact testing plan. For more details on the FDA advisory meeting about adding antimicrobial agents to PPE see <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=681>.

## NEW SAMPLE SUBMISSION FORM BENEFITS SPONSORS!

**N**elson Laboratories has published a new and improved **Sample Submission Form**. After gathering much feedback from our sponsors and our laboratory staff, we have designed a form that we feel will greatly improve the clarity and efficiency of submitting samples.

### Improved features on this form include:

- Increased room for sponsor comments
- Increased room for sample ID's
- Space for billing information in addition to sponsor information
- Dedicated area for protocol/sample detail sheet (PDS/SDS) number
- Options for designating samples to be tested individually or pooled

- Increased options for sample storage, sterilization, shipping, and return
- Cleaner, more usable design
- Information about fast, eco-friendly electronic download of final reports

As always, it is our mission to provide ever-increasing quality to our sponsors and staff. We feel that this improved Sample Submission Form will enhance our ability to serve you.

If you have any questions or comments about the new **Sample Submission Form**, please feel free to contact one of our client services representatives, at **(801) 290-7503**, or e-mail: [clientservices@nelsonlabs.com](mailto:clientservices@nelsonlabs.com).