White Paper

Medical Devices and Particulates

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This white paper includes a description and guideline to quantify and analyse the particulates associated with the use of medical devices.

Introduction

The FDA has asked intravenous and infusion medical device manufacturers to provide data regarding particulates to evaluate the potential effects the use of their device may have on patients. When a device is deployed or exposed to a patient, particles may be released and lodge in their vascular capillary system [1].

Manufacturers face many challenges when deciding how to test devices, including obtaining accurate particle counts and setting reasonable acceptance limits for particulates that reflect the potential effects of their size, quantity, and toxicity to patients [3].

Whether these particles are harmful to patients is determined by their size, shape, composition, and where and to what degree they cause an occlusion [1], [2]. The source of these particulates may be the manufacturing process, the environment, the product packaging or the device itself [3].

Several standards describe the requirements and specific parameters for testing particles [4]. When a medical device is not adequately covered by a standard (the most likely scenario), testing should be performed to closely mimic the clinical use of the device and all relevant accessories and supplies. The test method should be validated to determine that particulate recovery from a sample and, if used, model/supplies is accurate [3].

Background

Any particulates present on intravenous medical devices such as guidewires, catheters, and stent delivery systems potentially pose health risks to patients. When a device is deployed or exposed to a patient, particles may be released and become lodged in the vascular capillary system [1].

The concern for the FDA is what the total particulate load on a patient will be during the clinical use of a medical device. The agency is interested in knowing the number and size of

particles a device sheds and where on the device they originate. They may also want information about the size and number of particulates originating from other components used in the test system, such as the guide catheter or guidewire [3].

Why does FDA focus on particulates?

The size, shape, and composition of particles determine their potential toxicity and the adverse effects they may have on a patient's body [2].

Our concern should be device-specific and is highly dependent on the suspected route of exposure. Particles can induce immunological responses such as inflammation and allergy. Other side effects are blood clots and irritation. Particulate matter in the vascular system may cause an immunological response. Fibres are a general concern due to their shape and size if the material they are composed of is not biodegradable [5].

Consequently, acceptance limits need to be based on several factors, such as device category (i.e., the length of patient exposure to a device) and its clinical application, as well as particle sizes, their composition, and their potential toxicity [3].

Sources

Particulates can originate from the manufacturing processes, the surrounding environment, product packaging, or the device itself. The human body is the largest source of particulates found in a cleanroom, where both flecks of deodorant, skin cells, and clothing particles have been found. But, things like machining, lubricants, and building materials are also sources of particulates [3].

Surface-modified devices

Some stent delivery systems have drug coatings whose integrity can contribute to the total particulate load. The FDA has asked manufacturers of these types of devices to provide data regarding particulates to help evaluate the potential effects the use of their device may have on patients.

Whatever the case, any manufacturer must ensure that the final finished device is not shedding particles [3].

Analysis of particles in medical devices

- Clean workspaces

When evaluating a device in the laboratory, ensuring that particulates are not introduced into the test system is vital. Several guidelines recommend that all testing be performed using, at a minimum, a laboratory with an ISO Class N5 hood installed [3].

An area explicitly designed for particulate testing with positive air pressure and HEPA filtration adds an extra level of assurance for minimizing particulate contamination from the laboratory environment. Analysts should be well trained in aseptic techniques to further minimize contamination. These are the crucial factors to ensure accuracy and reproducibility and should be considered when evaluating laboratories [3].

- Filtration process

The extraction fluid is filtered through a membrane filter.

All glassware must be washed with a warm detergent solution and rinsed thoroughly with particle-free water before being used in the test system. Even though the filtration process consumes the entire sample, the filters are stored to allow for re-analysis using various microscopes [3], including single particle elemental analysis by Scanning Electron Microscopy coupled with Energy-Dispersive X-ray Detection (SEM/EDS) [6]–[9].

- Microscopes for analysing filters

Counting particulates on filter slides can be tedious, detail-oriented work. Conducting such work using manual processes can lead to significantly different counts between analysts; therefore, an automated method is used. More reliable and reproducible results are produced when the samples are analysed using an automated microscopy method, and the digital images are post-processed using a computational counting procedure [3].

- Inspection of device surface integrity using SEM

Surface imaging techniques are suitable for characterising surfaces; however, radiation interaction can exhibit signal from several µm down in a material, blurring layers of interest or even causing observers to miss the actual surface layer.

Surfaces should be analysed for their physical, morphological, and topographical properties.

Therefore, when analysing a product for its surface characteristics and potential contribution to the total particle load, a combination of techniques will provide the most comprehensive answer [10].

Test for particulate contamination – the automated microscopy method

Extraction fluid is filtered through a membrane filter. Surfactants and colloids pass through the membrane during filtration, thereby not affecting the results. The filter is allowed to dry, and it is then examined microscopically with sequential images automatically obtained from the entire sample. The resultant digital images are analysed and the found particles are counted and sized using the circular equivalent diameter measurement. Samples and images can be revisited, and particulates can be identified by colour, shape, or other parameters. This process allows for fibres and particulates with uneven shapes to be easily distinguished. The characterisation of particles is helpful for evaluating the possible source of particulate contamination for remedial or preventive measures. The most important advantage of this test method is that, because it is automated, the results are reproducible and nonbiased.

Guidelines

Standards that set acceptable particulate count limits only exist for a few medical devices, including gravity-fed infusion sets (ISO 8536-4) [11], cardiac pacemakers (EN 45502) [12], and autologous transfusion devices (ANSI/AAMI AT6-2005) [13]. For the majority of medical device categories, such standards are not available. Most vascular medical device manufacturers turn to USP 788 or set their own acceptance limits. USP 788 should only be used as a general guide. Its use is generally acceptable as long as the small-volume criteria specified in the method are met. If the particulate counts of a device exceed these limits, an OEM may need to justify to the FDA how such counts are acceptable [3].

- USP 788 /International pharmacopeia: PARTICULATE MATTER IN INJECTIONS [4]
- Most vascular medical device manufacturers turn to USP 788 or set their own acceptance limits. USP 788 should be used only as a general guide. Its use is generally acceptable as long as the small-volume criteria specified in the method are met. If the particulate counts of a device exceed these limits, an OEM may need to justify to FDA how such counts are acceptable. USP 788 is applicable to all types of fluids.
- USP 787, Subvisible Particulate Matter in Therapeutic Protein Injections [14]
- Investigating the protein aggregation phenomenon is required to evaluate shelf life, stability, and efficacy, which is only a short list of examples of what should be investigated. USP Chapter 787 outlines testing for more sensitive therapeutic protein formulations and allows for a smaller sample volume testing framework to address proteinaceous particles in samples with small volume dosage forms. Protein injections are often only available in single millilitre dosages, so testing for them requires modified USP 788 testing procedures. USP 789 is specific to eye solutions.

However, other guidelines might wholly or partly require the same setup:

EN 45502 is specific to active implantable medical devices [12], ISO 8536-4 (1135-4) is specific to infusion appliances [11], ISO 10079 covers medical suction equipment [15].

Most devices do not have a specific guideline. In these cases, testing should be performed to closely mimic clinical use, include all accessories and supplies used clinically, and validate the test method to determine particulate recovery from the sample and model/supplies if used. USP 788 is not designed for medical device testing, but its use to cover a device has been historically acceptable and may be rationalised [3].

Other Useful documents:

- AAMI TIR 42: AAMI TIR 42 describes how to evaluate particulates associated with vascular medical devices. This document contains extensive guidance for particulate testing. It also focuses on best practices to help manufacturers minimize particulates on their devices through the design, development, and manufacturing processes. It also addresses possible sources of particulates from raw materials, the manufacturing process or the manufacturing environment and provides guidelines for minimizing and controlling contamination.

  It is equally important for manufacturers to find guidance for setting their own acceptance limits based on such factors as the category of the device (i.e., the length

of patient exposure to the device) and its clinical application, as well as appropriate particle sizes and their potential toxicity. Specifications may be tied to the category of the device [16].

- FDA guidance: Class II special controls guidance document for certain percutaneous transluminal coronary angioplasty (PTCA) catheters [17].

Conclusion

Particles are everywhere and always have been.

Among the many challenges manufacturers face are deciding how to test their devices to obtain accurate particulate counts and setting reasonable acceptance limits for these particulates. Acceptance limits for particulates need to reflect the effects of particulate size, quantity, and potential toxicity to the patient due to the chemical composition of the particles. Some manufacturers set their own acceptance limits.

This article evaluated the test methods used to analyse medical devices for particulates, the documentation the FDA may request from medical device manufacturers, and the guidelines under development to help manufacturers establish acceptance criteria for their devices.

How can we help you?

Contact SAXOCON A/S to request a tailor-made solution for your device and application. Check out our analytical services here. Our experts can also assess the toxicity of particles and materials in your products.

ISO Classes of air cleanliness by particle concentration (ISO 14644-1:2015) [18]

Maximum allowable concentrations (particles/m3) for particles equal to and greater than the considered sizes

ISO Class number (N)	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm
2	100	24	10	-	-
3	1000	237	102	35	-
4	10000	2370	1020	352	-
5	100000	23700	10200	3520	83

SAXOCON conducts all processes, including filtration and microscopy in clean workspaces. Our workbenches live up to ISO Class N2, which is a higher standard than the minimum required Class N5.

References

[1] L. J. Pesko, "Physiological Consequences of Injected Particulates," in *Liquid- and Surface-Borne Particle Measurement Handbook*, J. Z. Knapp, T. A. Barber, and A. Lieberman, Eds. New York: Marcel Dekker, 1996, p. 661.685.

[2] M. Riediker *et al.*, *Particle toxicology and health - Where are we?*, vol. 16, no. 1. Particle and Fibre Toxicology, 2019.

[3] S. Reynolds and R. Lunceford, "Analyzing Particulate Matter on Medical Devices," 2009. https://www.mddionline.com/news/analyzing-particulate-matter-medical-devices.

[4] USP 788, "Particulate Matter in Injections," in *The United States Pharmacopeial Convention*, 2012, pp. 1–3.

[5] T. C. Kupiec, L. A. Trissel, and T. Tran, "Particulate Matter in Injections: What is It and What are the Concerns?," *Int. J. Pharm. Compd.*, vol. 10, no. 3, pp. 202–204, 2006.

[6] A. Laskin and J. P. Cowin, "Automated Single-Particle SEM/EDX Analysis of Submicrometer Particles down to 0.1 µm," *Anal. Chem.*, vol. 73, no. 5, pp. 1023–1029, 2001.

[7] A. Brostrøm, K. I. Kling, K. S. Hougaard, and K. Mølhave, "Analysis of Electron Transparent Beam-Sensitive Samples Using Scanning Electron Microscopy Coupled With Energy-Dispersive X-ray Spectroscopy," *Microsc. Microanal.*, vol. 26, no. 3, pp. 373–386, Jun. 2020.

[8] K. Kandler *et al.*, "Electron microscopy of particles collected at Praia, Cape Verde, during the Saharan Mineral Dust Experiment: Particle chemistry, shape, mixing state and complex refractive index," *Tellus, Ser. B Chem. Phys. Meteorol.*, vol. 63, no. 4, pp. 475–496, 2011.

[9] D. Moro, G. Ulian, and G. Valdré, "SEM-EDS nanoanalysis of mineral composite materials: A Monte Carlo approach," *Compos. Struct.*, vol. 259, 2021.

[10] M. Farré and D. Barceló, "Chapter 1 - Introduction to the Analysis and Risk of Nanomaterials in Environmental and Food Samples," *Compr. Anal. Chem.*, vol. 59, pp. 1–32, 2012.

[11] International Organization for Standardization, "Infusion equipment for medical use — Part 4: Infusion sets for single use, gravity feed (Standard No. 8536-4)," 2010. https://www.iso.org/standard/55799.html.

[12] BS European Standards, "Implants for surgery. Active implantable medical devices General requirements for safety, marking and for information to be provided by the manufacturer (Standard No. 45502-1)," 2015. https://www.en-standard.eu/bs-en-45502-1-2015/.

[13] The American National Standards Institute, "Autologous Transfusion Devices (Standard No. AT6)," 2005. https://webstore.ansi.org/standards/aami/ansiaamiat62005.

[14] Beckman Coulter, "USP 787," 2014. https://www.beckman.com/resources/industry-standards/usp-787.

[15] International Organization for Standardization, "Medical suction equipment — Part 4: General requirements (Standard No. 10079-4)," 2021. https://www.iso.org/standard/77571.html.

[16] AAMI TIR Draft, "Particulates Associated with Vascular Medical Devices," *Arlington, VA Assoc. Adv. Med. Instrum.*

[17] U.S. Food and Drug Administration, "Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters - Class II Special Controls Guidance for Industry and FDA," 2010.

[18] International Organization for Standardization, "Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration (Standard No. 14644:1)," 2015. https://www.iso.org/standard/53394.html