Quality-Control Analytical Methods: Particulate Matter in Injections: What is It and What are the Concerns?

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Abstract

The presence of particulate matter in intravenous injections, especially in large numbers, represents a potentially life-threatening health hazard. The United States Pharmacopeia has established procedures and standards to ensure the quality of intravenous injections, including particulate counts. Compounding pharmacists can reduce the incidence of adverse events in patients by assuring the quality of their preparations through filtration of intravenous preparations and analytical testing procedures.

Professionalism requires that pharmacists consider the issue of particulate matter when compounding injections, including admixtures and high-risk preparations. The objective of this article is to provide compounding pharmacists with information they need to reduce the risk to patients associated with exposure to particulates, as follows:

- Understand the importance of particulate matter and its potentially harmful effects
- Identify the sources of particulate matter and how it gets into a preparation
- Determine which preparations need particulate matter testing and the limits placed by the *United States Pharmacopeia (USP)* on these preparations

Definitions and Sources of Particulates

Particulate matter consists of randomly sourced, extraneous substances (other than gas bubbles) that cannot be quantitated by chemical analysis owing to the small amount of material that it represents and its heterogeneous composition.[1] Particulate matter can consist of many different things (e.g., including dust, glass, precipitate from drug incompatibility, rubber, cotton fibers, latex, other insoluble materials).[2]

Dr. Michael Akers has observed, "Anything that directly or indirectly comes in contact with a parenteral solution, including the solvent and solutes composing the solution itself, represents a potential source of particulate contamination."[3] In a sterile product or compounded preparation, particulate contamination may originate from any of the following:[4]

- The solution itself and its ingredients
- The production process and its variables (e.g., environment, equipment, personnel)
- The product's packaging
- The preparation of the product for administration (e.g., manipulating the product, the environment in which it is prepared)

Reports have been published on the formation of precipated particulates from physical and chemical incompatibilities,[5-7] and on the generation of particulates from various containers, including plastic syringes.[8]

Problems with Particulates

Particulate matter in injections can be harmful when introduced into the bloodstream. The contamination of parenteral fluids and drugs by particulate matter has been recognized as a potential health hazard. Adverse reactions may include vein irritation and phlebitis,[9,10] clinically occult pulmonary granulomas detected at routine autopsy examination, local tissue infarction, severe pulmonary dysfunction, occlusion of capillaries and arteries, anaphylactic shock, and death.[11,12] Clearly the presence of particulate matter in intravenous injections, especially in large amounts, represents a potentially life-threatening health hazard.[4] In 1994, the US Food and Drug Administration received a report that described two deaths relating to calcium phosphate precipitation. The precipitation was in a three-in-one total parenteral nutrition admixture that was given to patients. Autopsies revealed that the patients had diffuse microvascular pulmonary emboli that contained calcium phosphate.[13] This demonstrates the fatal effects that particulate matter can have on patients. Patients receiving parenteral nutrition require specific attention, because as a group they tend to receive more parenteral therapy and for longer periods than other patients.[14] Compounding pharmacists are not the only

ones facing this issue—even drug manufacturers have struggled with particulate matter contamination problems. Too frequently, particulate matter contamination has exceeded the legal limits.[12] Between 1996 and 1999, 28 recalls (Class II and Class III) of commercial sterile products were initiated because of the presence of foreign substances, particulate matter, or precipitate.[4] Compounding pharmacists can reduce the incidence of adverse events in patients by assuring the quality of their preparations through filtration of preparations and analytical testing procedures.

The size of particulate matter is an important factor when considering the potential risk to patients. Particles as small as 2 µm in diameter have been associated with microthrombi formation in patients, according to Walpot et al.[12] Akers et al noted that the smallest capillary blood vessels are considered to have a diameter of approximately 7 µm.[3] Therefore, all particles having a size equal to or greater than 7 µm can conceivably become entrapped in and occlude capillaries, increasing the potential for adverse effects. Simple visual inspection, which is required for compounded injections,[1] may be adequate for large particles but is inadequate for smaller particles. The lower limit of visibility of the naked human eye is approximately 40 µm.[15] Specialized testing methods are therefore necessary to adequately assess the total particulate burden of injections.[1]

Standards for Particulates

The United States Pharmacopeia (USP) has established fixed parameters for particulate matter in preparations intended for intravenous use. Particulate matter testing is an official test of the *USP* and is performed to ensure that unintended and nontherapeutic particulates in solution dosage forms do not exceed established limits.[1] Determination of sizes of nonsoluble drug particles should not be confused with testing for extraneous particulate matter. Particle size is often determined for nonsolution particulate therapeutic entities (e.g., emulsions, liposomes) in which the particle size distribution is important.

USP guidelines state that all large-volume injections for single-dose infusion, and small-volume injections for which the monographs specify such requirements, are subject to the particulate matter limits set by the *USP*.[1] Large-volume intravenous solutions are injections labeled as containing more than 100 mL, unless otherwise specified in the individual monograph, and small-volume injections are injections labeled as containing 100 mL or less. Excluded from the requirements of *USP* Chapter <788> Particulate Matter in Injections are injections intended solely for intramuscular or subcutaneous administration.

The *USP* guidelines also state that, prior to dispensing, all containers of parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter in their contents. Every container whose contents show evidence of visible particulates shall be rejected. Preparations compounded as intravenous injections according to *USP* monographs require particulate matter testing if labeled as *USP*.[1]

USP Chapter <788> sets forth two test procedures for the determination of particulate matter. These two tests are (1) the light obscuration particle count test and (2) the microscopic particle count test. The two procedures test for particulate matter in preparations and count the particles that are larger than 10 and 25 µm. Currently, the predominant method of testing for particulate matter is the light obscuration particle count test. The microscopic test is used when a sample fails the light obscuration test or when the sample material (such as emulsions, colloids, and liposomal preparations) may produce erroneous data when analyzed by the light obscuration test.[1]

The light obscuration particle count test uses an electronic, liquid-borne particle counting system utilizing a laser light obscuration sensor to detect particulate matter. The apparatus works by passing a sample fluid past a window through which light from a laser beam is detected by a photomultiplier tube. As the particles pass through the laser light, the intensity of the light beam is reduced and the amplitude of the resulting signal is proportional to the projected area of the particle. This provides the operator with the amount and size of the particles in a sample.[2] The *USP* limits for the light obscuration test are shown in Table 1.[1]

Table 1. Particle Count Limits, Light Obscuration Test.

	≥10 µm	*≥25 µm*
Small-volume injections	6000	600 per container
Large-volume injections	25	3 per milliliter

Note: This table shows the limits for small-volume and large-volume injections detected by using the light obscuration test. Columns present the limits for all particles larger than or equal to 10 µm and 25 µm. Preparations that exceed any of the relevant counts should be discarded and not dispensed to patients.

The microscopic particle count test involves filtering the sample through a microporous membrane filter and counting the particles collected on the membrane under a compound binocular microscope. The operator uses a circular diameter graticule to compare the sizes of the particles with the references and then count the particles larger than 10 and 25 µm.[2] The *USP* limits for the microscopic particle count test are shown in Table 2.[1]

Table 2. Particle Count Limits, Microscopic Method.

	≥10 µm	*≥25 µm*
Small-volume injections	3000	300 per container
Large-volume injections	12	2 per milliliter

Note: This table shows the limits for particle counts in small-volume and large-volume injections as detected by using the microscopic test. Columns present the limits for all particles larger than or equal to 10 µm and 25 µm. Preparations that exceed any of the relevant counts should be discarded and not dispensed to patients.

Conclusion

It has been demonstrated that particulate matter can be a potential health hazard in preparations intended for intravenous use. The *USP* has established guidelines to limit the amount of particulate matter introduced into these preparations and thus into the patient. The testing methodologies provided by the *USP* can assure compounding pharmacists of the quality of their preparations and the quantification of subvisible particles. Pharmacists can use these tools to enhance the safety of their patients.

The *United States Pharmacopeia (USP)* states the following concerning particulate matter in compounded injections:

- Prior to dispensing, all containers of parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter in its contents.
- Every container whose contents show evidence of visible particulates shall be rejected.
- Sterile filtration is designed to remove all particles greater than 0.22 µm in size.
- If a drug is dry-heat sterilized, it should be passed through at least a 5-µm filter prior to dry-heat sterilizing in the final container.
- Injections for intramuscular or subcutaneous administration are excluded from the requirements of *USP* Chapter <788>.

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