Particulate Matter in Injectable Drug Products

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REVIEW

Particulate Matter in Injectable Drug Products

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ABSTRACT: Clinicians have had concerns about particulate matter contamination of injectable drug products since the development of the earliest intravenous therapeutics. All parenteral products contain particulate matter, and particulate matter contamination still has the potential to cause harm to patients. With tens of millions of doses of injectable drug products administered in the United States each year, it is critical to understand the types and sources of particulate matter that contaminate injectable drug products, the possible effects of injected particulate matter on patients, and the current state of regulations and standards related to particulate matter in injectable drug products. Today, the goal of manufacturers, regulators, and standards-setting organizations should be to continue to minimize the risk of particle-induced sequelae, especially in high-risk patients, without trading unnecessary manufacturing burden for minimal safety gains.

KEYWORDS: Injectable, Parenteral, Particulate matter, Pharmaceutical quality, Current good manufacturing practice (cGMP).

LAY ABSTRACT: All injectable drug products are contaminated with some level of solid particulate matter, including, for example, fibers, dust, rubber, and silicone. These materials enter drug products primarily during the manufacturing process. The possible effects on patients of injectable drug products containing particulate matter depend on a number of factors. However, given the large number of patients receiving injectable drug products each year in the United States and the potential for particulate matter to cause harm to patients, it is critical to continue to minimize particulate matter contamination in injectable drug products. Manufacturing standards and regulations have helped improve manufacturing quality. Nevertheless, manufacturers, regulators, and standards-setting organizations must continue to work toward improving manufacturing quality and minimizing the risk of harm from particle contamination, especially in high-risk patients.

Introduction

One of the basic tenets of pharmaceutical quality is the manufacture of drug products that are free of microbial, chemical, and physical contaminants. Although microbial contamination of injectable drug products is fairly well understood, defined, and measureable, it remains difficult to achieve injectable drug products that are free of chemical and particulate matter contamination. This is due, in part, to the nature of contaminants, the current state of pharmaceutical manufacturing, and the availability of extremely sensitive measuring techniques.

Concerns about the clinical use of injectable drugs containing particulate matter can be traced to the early intravenous fluid therapies employed in the 1830s. An Edinburgh physician named John Mackintosh, while developing methods of intravenous saline infusions to treat victims of a cholera outbreak, recommended that the solutions be strained twice through leather rather than cotton or linen, which could allow “minute portions of flakey threads” to be injected into the patient (1). Although processing and filtration technologies for intravenous injections have evolved exponentially in the years since, concerns about the potential effects of injected particulate matter on pa-
tients continue, especially given the equally exponential growth in the number of patients who could be affected.

According to the American Hospital Association, U.S. hospitals admitted 37,479,709 patients in 2009 (2). Assuming an average intravenous solution administration of 5 L per patient (3), nearly 190 million L of intravenous fluid are administered annually. Given these data, an accurate assessment is warranted of the factors causing particulate matter contamination of drug products, the patient risks associated with the administration of such contaminated drug products, and the current state of regulations and standards that provide the framework for achieving pharmaceutical quality.

This article describes some of the sources of particulate matter contamination in injectable drugs and the possible clinical effects that can result from such contamination. The article also reviews the development of standards and regulations to control contamination of injectable products and offers some preliminary next steps for manufacturers, regulators, and standards-setting organizations who are working together to ensure patient safety.

### Classification and Sources of Particulate Matter

Chapter <788> of the United States Pharmacopeia (USP), Particulate Matter in Injections (4), defines particulate matter as “mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions”. Groves (5) divided injectable drug particulate matter into two classes based on the source of the particulate matter: intrinsic particles, defined as those originally associated with the solution that were either not removed by filtration or precipitated out of the solution, and extrinsic particles, defined as those that enter the container or solution during manufacturing. USP Chapter <1788> Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions (6) provides similar, but more specific, definitions, classifying extrinsic particulate matter as “additive, foreign, unchanging, and not part of the formulation, package or assembly process”. It classifies intrinsic particulate matter as “associated with the package, formulation and/or assembly process and capable of change upon aging”. USP Chapter <1788> also notes that intrinsic particulate matter is not the same as inherent product characteristics such as the haze, coloration, or known populations of small particles common to certain high-concentration protein formulations. This inherent particle category also includes the normal particle size distribution of active pharmaceutical ingredients in suspensions and other common delivery forms (e.g., emulsions, lipids, etc.). Inherent particles or properties, when consistent and expected, may be completely acceptable.

There are five general sources of particulate matter in injectable drug products: the environment, packaging materials, solution and formulation components, product packaging interactions, and process-generated particles. Proper product development and appropriate manufacturing and packaging process design can successfully exclude particulate matter sourced from four of the five categories. The fifth category, particulate matter sourced from the environment, can be excluded only by use of highly controlled filling areas, rather than by an intimate understanding of the product, process, and container closure system. A list of potential particle contaminants, their sources, and intrinsic/extrinsic natures as defined by USP Chapter <1788> is presented in Table I.

Note that certain types of particulate matter, including metal and glass, may be either intrinsic or extrinsic depending on the point at which they enter the container. For example, glass particles can enter the manufacturing process from the outside (extrinsic, e.g., through the use of broken or poorly washed incoming vials) or come from inside the container through degradative change during product storage or from process-related glass breakage events (intrinsic, e.g., lamellae, tunnel/oven, or during filling). Likewise, metal particles can come from the containers, the manufacturing environment (extrinsic, e.g., building materials), or the manufacturing process (intrinsic, e.g., blending equipment). Even particle levels that meet compendial or company target limits can be of concern. For example, so-called point-source contamination, which is the predominance of one particle type (7), may indicate the presence of process contribution or package instability that requires investigation and remediation. An overall understanding of the product and processes and the establishment of methods that can control particulate matter contamination during development, manufacture, and packaging are essential to be able to design systems capable of preventing particulate matter contamination problems before they start (8, 9).
Clinical Effects of Injected Particulate Matter

Many clinical effects have been documented in subjects who have received injections containing particulate matter contamination. Examples include phlebitis (3, 10–13), pulmonary emboli (14–16), pulmonary granulomas (3, 11, 17), immune system dysfunction (3, 18), pulmonary dysfunction (13, 15), infarction (15, 19), and death (14, 20–22). The patient risk associated with the injection of drugs containing particulate matter depends on a number of factors, including the route of administration used, the particle size and shape, the number of particles injected, the particle composition, and the patient population.

### Route of Administration

The route of pharmaceutical product administration can influence the deposition of the injected particles, the total particle load administered to the patient, and the overall risk to the patient. Immunologically inert particles, such as glass or cellulosic fibers, delivered via intramuscular and subcutaneous routes have received little attention with regard to their potential for causing adverse events due to the fact that the delivered volumes (and the overall particle load) are relatively small, the risk of a systemic reaction is low, and the ability of these particles to migrate far from the injection site is negligible (23). However, vascular
injections make possible the delivery of greater volumes of fluids and the broader dissemination and deposition of particulate matter throughout the body.

Because the size of veins increases in the direction of blood flow, most particles injected intravenously will travel through the venous system to the heart on their way to the lungs via the pulmonary artery. The diameter of capillaries is approximately 6–8 μm. As a result, most particles larger than 6–8 μm will remain in the pulmonary capillaries, with smaller particles passing through the lungs and depositing in organs such as the liver and spleen, where they are processed by phagocytic cells of the reticuloendothelial system (16). Phagocytic overload of the reticuloendothelial system by large numbers of particles has the potential to block the system and lead to secondary infections in a debilitated host (3). There is little information in the literature regarding the ability of the immune system to clear relatively large (>10 μm) inorganic particles (e.g., rubber, glass, and metal) lodged in organs such as the lung or what effect, if any, the accumulation of such particles in vital organs may have over time.

Because arteries decrease in size with the direction of blood flow, the inadvertent administration of intrarterially injected particles that are too large to pass through arterioles and capillaries may cause occlusions that could affect blood flow to tissues downstream of the injection site. The physiological effects of any such occlusion will depend upon the size of the particle and the collateral circulation available to the affected area (23). Ironically, smaller particles capable of blocking terminal arterial vessels—and causing infarctions—may be more detrimental than larger particles capable of arteriole occlusion due to the reduced collateral blood supply available to the affected tissue (24). The inadvertent intravascular injection of corticosteroid formulations containing particles has been linked to adverse central nervous system sequelae in humans not observed with non-particulate steroid formulations containing FreAmine III as an amino acid source (14, 20). Analysis of the precipitate isolated from the admixtures administered to each patient revealed the posing intravenous administration of total nutrient admixtures containing FreAmine III as an amino acid source has caused a number of serious clinical events (21). In 1994, two young female patients undergoing treatment for pelvic infections died of pulmonary emboli following inadvertent administration of total nutrient admixtures containing FreAmine III as an amino acid source (14, 20).

**Size and Shape**

The size and shape of an injected particle can affect both its deposition within the body and its clinical effects on the subject. Rabbits injected with radiolabeled polystyrene particles of different sizes showed rapid deposition of 15.8 μm particles in the lungs while 1.27 μm particles were deposited mainly in the liver (16). Similar results were obtained when dogs were injected intravenously with radiolabeled microspheres of 3, 5, 7, and 12 μm in diameter. The 7 and 12 μm particles were deposited primarily in the lungs, while the 3 and 5 μm particles migrated mainly to the spleen and liver. As expected, clearance from the bloodstream was size-dependent, with the larger particles clearing first (27). Rabbits injected with 5 μm diethylaminoethyl (DEAE) cellulose fibers demonstrated deposition primarily in the lungs, but also in the liver and kidneys (16). Rabbits injected intravenously with 30 μm DEAE cellulose fibers died within 4 minutes of administration due to an acute toxic response (tachycardia, dyspnoea, dystaxia) caused by pulmonary emboli (16). In contrast, 40 to 60 μm DEAE cellulose microspheres, although entrapped by the lung, caused no adverse reactions and each of the rabbits injected survived until the completion of the study (16). These studies suggest that the shape of a particle may be just as important as its size when determining its potential for harm. Certainly the total particle load must be considered as well.

Due to the obvious challenges associated with controlled clinical studies to investigate the effects of injected particles in humans, little is known about the risk to diverse patient populations posed by particles of various sizes, shapes, and composition injected via different routes of administration. Adverse event reports and autopsy results are the only sources of information about the effects of larger particles on patient populations. Visible particulate matter composed of calcium salt precipitates in drug admixtures has caused a number of serious clinical events (21). In 1994, two young female patients undergoing treatment for pelvic infections died of pulmonary emboli following inadvertent administration of total nutrient admixtures containing FreAmine III as an amino acid source (14, 20). Analysis of the precipitate isolated from the admixtures administered to each patient revealed the
presence of calcium and phosphorous salts matching those found in the pulmonary microvasculature of the autopsy specimens. Co-administration of the antibiotic ceftriaxone and calcium-containing intravenous solutions to neonates resulted in eight adverse event reports and seven deaths. One patient experienced cardiopulmonary arrest after a white precipitate in the patient’s intravenous tubing was pushed into the infant in an effort to clear the tubing (28). Pulmonary emboli were reported in multiple cases, and autopsies revealed the presence of white crystalline precipitates in the lungs, heart, kidney, and liver (21, 28). Both the ceftriaxone and FreAmine III incidents resulted in the issuance of U.S. Food and Drug Administration (FDA) drug safety warnings regarding the potential for calcium precipitation in these drug products (28, 29). Cant et al. (22) reported the case of a premature neonate who was treated with an umbilical artery catheter shortly after birth. Injections were made into the catheter using polypropylene syringes. The catheter was removed on day 4, but the patient soon developed abdominal distension and died at 52 days of age. An autopsy revealed acute infarction of the small bowel and the presence of polypropylene fragments of 50 to 200 um in size. Although this may be the only documented case of a fatality resulting from the injection of material derived from a pharmaceutical container closure system, the case underscores the vulnerability of neonates to sequelae resulting from the infusion of particles and suggests that the intra-arterial route of administration may carry additional risks.

Number

Estimates are that patients in intensive care receive more than a million injected particles >2 microns in size daily (18, 30, 31). One method for controlling the particle load administered to critically ill patients has been through the use of final filters. A controlled clinical study of 88 infants receiving either filtered or unfiltered infusions via a central line revealed significant reductions in the incidence of complications such as thrombi and necrotizing enterocolitis (32). Studies on adult patients using 0.22 and 0.45 um intravenous in-line filters seem to indicate that the use of in-line filters reduced the incidence and time of onset of particle-induced phlebitis (3). In vitro studies also showed that human macrophages and epithelial cells displayed decreased cytokine production following exposure to silicone particles mimicking those obtained from intravenous line filters obtained from pediatric intensive care units (18). However, the use of final filters may present other problems, such as the possibility of drug product reaction with or absorption by the filter material or impaired fluid flow through the filter. Opinions vary regarding the economic benefit of in-line filtration to remove microorganisms and particulate matter during drug product infusion (32–36). Nevertheless, a review of clinical case reports involving calcium phosphate precipitation in intravenous admixtures revealed that the use of in-line filtration made the difference between non-fatal and fatal cases (37). Thus, the use of in-line filtration for extemporaneously prepared, multi-component intravenous admixtures may be prudent.

Composition

Barber (23) provides an excellent review of several pre-1980 animal studies involving different types of particulate matter (filter paper, glass, rubber, hair, polystyrene, plastic, and insoluble drug residues) in various animal models (rabbits, dogs, rats, mice, guinea pigs, and hedgehogs). The clinical effects seen in these studies range from relatively minor tissue damage associated with the administration of silicone and polystyrene particles to rabbits and dogs, to more serious reactions such as local inflammation, the formation of pulmonary granulomas, and death in rabbits, dogs, and rats injected with plastics, ground filter paper, or large numbers of polystyrene particles >40 um in size.

One of the most common contaminants of injectable drug products is glass derived from the manufacturing process, reaction of the drug with the container closure system, or that produced by opening glass ampoules (36, 38, 39, 40). Recent glass delamination issues involving multiple drug products have increased concern about the risk posed by glass particles and interest in developing methods to control the formation of glass lamellae over the product shelf life (40, 41). Sequelea attributed directly to glass particles include phlebitis (3), pulmonary granulomas (31), systemic inflammatory response syndrome (18), and adult respiratory distress syndrome (34). Studies have also suggested that glass particle–induced sequelae may require considerable time to develop and, as a consequence, may often be overlooked (38, 39, 42).

Another common pharmaceutical contaminant is metal particles (43, 44). Although the most common source of metal particles is processing equipment, they have also been found to contaminate the raw materials used
in drug product formulation (43). Lead and chromium are considered among the most dangerous metal contaminants, but serious adverse events related to aluminum ingestion have also been well documented (43–46). Aluminum toxicity in premature infants has been linked to total parenteral nutrition admixtures (45, 46) and contributed to the issuance of FDA regulations regarding the aluminum content of drug products used for total parenteral nutrition (47). By far, the most common and expected type of metal particles found in liquid injectables is stainless steel (44). Recent drug product recalls due to the presence of stainless steel particles in lipid emulsions requiring high shear force manufacturing processes have necessitated the development of modified manufacturing processes and visual inspection methods to detect potentially harmful levels of metallic particles (48).

In the class of inherent particles, proteinaceous particulate matter poses a unique risk to the patient because of the unintended host immune responses it may elicit (49). Host responses resulting in antibody-mediated neutralization of the protein’s active site or the production of drug-induced antibodies to the therapeutic version of an endogenous protein have the potential to cause catastrophic cross-reaction and neutralization of the endogenous protein (49, 50). Although the precise characteristics of proteinaceous particles associated with immune response elicitation are not well understood (50, 51), it is believed that protein aggregation and the formation of repetitive arrays of antigens are contributing factors in the elicitation of an immune response (49).

The causative factors of protein aggregation are also poorly understood. However, the complex manufacturing and purification methods used in the processing and handling of therapeutic proteins can influence a number of different product characteristics, including particle size (49, 50, 52). One potential cause of protein aggregation is the presence of extrinsic particulate matter that may serve as nucleation sites for the formation of larger particles (52). The overall net charge of the protein solution has also been shown to influence the degree of protein aggregation and the type of protein aggregates formed in a given solution. Studies have shown that solubilized proteins held under conditions near their isoelectric point may be prone to aggregation into spherical particles due to exposure of hydrophobic residues to the solvent caused by the solution’s low net charge (52, 53). Alternatively, proteins held under conditions of high net charge tend to organize into amyloid fibrils due to electrostatic repulsion and slow aggregation (53). The potential for aggregation and the monitoring of sub-visible protein particles in the 0.1 to 10 um size range should be considered during biologic product development and surveillance programs (49).

Finally, it is important to distinguish between hard and soft particles. A hard particle is a rigid structure that often has a non-spherical, irregular shape. Such particles are inflexible and, if large enough (>5 μm), are more likely to produce mechanical obstruction and vascular emboli. All of the particles described above would be considered hard particles capable of inducing embolic phenomena upon intravascular (i.e., intravenous, arterial) infusion. In contrast, a soft particle is a flexible, or deformable, structure that is spherical, such as an emulsified oil droplet. As with hard particles, soft particles may also produce embolic phenomena upon intravascular infusion, but due to their deformable characteristics, the embolism is incomplete, that is, when large hard particles flow towards a vessel with a smaller diameter, the occlusion cannot be overcome by compensatory increases in venous and/or arterial pressures. When the same-sized soft particles flow towards the same small vessel, the occlusion can be overcome due to the malleability of the lipid droplet. As the occlusion clears, however, the large-diameter droplets can accumulate in downstream vital organs, such as the liver, producing a systemic inflammatory response (54, 55).

**Patient Population**

The patient populations that may be most at risk for particulate matter–related sequelae include patients with existing tissue damage, critically ill patients, and neonates (3, 15, 18, 31, 38, 55). Two recent animal studies investigated the effects of injected particles in the presence of pre-existing tissue damage. Schaefer et al. (15) demonstrated that the injection of particles from two generic antibiotics containing particulate matter levels 4 to 50 times higher than those found in the innovator drug resulted in a nearly 50% loss of damaged capillary networks in the ischemic muscle tissue of hamsters as compared to muscle treated with the innovator drug product. Passing the generic formulations through a 0.2 um filter prior to administration eliminated the damaging effect of the generic antibiotics (15). Lehr et al. (56) conducted a similar study comparing the clinical effects of particles from the innovator and generic manufacturers of cefotaxime. Although the capillary perfusion of healthy muscle was not affected by the intrave-
nous injection of the concentrated antibiotic particles, post-ischemic muscle tissue demonstrated reduced capillary perfusion following intravenous treatment with the concentrated particle solutions. Histological sections revealed that particulate matter caused mechanical disruption of the circulation to striated muscle. These findings suggest that injected particles could be more detrimental to patients with existing tissue damage, such as in the case of trauma, surgery, or sepsis (13).

The heavy particle loads incurred by critical care patients due to the sheer volume of administered intravenous solutions have been linked to adult respiratory distress syndrome (SIRS) (34), systemic inflammatory response syndrome (SIRS) (57), and immune system dysfunction (3). Walpot et al. (34) used energy-dispersive x-ray analysis to show that critical care patients may be more susceptible to particulate matter deposition in pulmonary tissue than healthy subjects. Additional studies have suggested that in-line filtration may benefit critically ill infants by offering protection against SIRS and other glass particle–induced adverse events (38, 57).

The potential effect of heavy particle loads on neonates was also reported by Puntis et al. (31), who compared the necropsy results of 32 infants who died of sudden infant death syndrome with those of 41 infants who died following total parenteral nutrition therapy. Two of the 41 parenterally fed patients showed widespread pulmonary granulomas containing material such as glass fragments and cotton fibers. No such granulomas were identified in the patients who expired due to sudden infant death syndrome. Although the capillary diameter of neonates is the same as those of adults, the overall number of blood vessels and the diameter of the major blood vessels are smaller in children as compared to adults, a factor that could accentuate the effects of injected particles relative to the effects seen in adult patients.

Relevant Regulations and Standards

Over the years, a number of statutes and regulations have been enacted and implemented intended to control particulate matter contamination of injectable drug products. Nevertheless, federal regulations pertaining to current good manufacturing practice (cGMP) do not specifically address the subject of particulate matter, but do contain several passages applicable to particulate matter contamination. With regard to the effect that the container closure system might have on particulate matter in a product, regulations at 21 CFR 211.94(a) state that “drug product containers and closures shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements”. Regulations at 21 CFR 211.165(a) and (f) state that “for each batch of drug product there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product” and “drug products failing to meet established standards or specifications . . . shall be rejected”. These regulations apply to the visible and sub-visible particulate matter specifications cited in drug product applications (see Table II).

Section 501 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) states that a drug or device will be considered adulterated (1) “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health”; (2) “if . . . the facilities or controls used for its manufacture, processing, packaging, or holding do not conform or are not operated or administered in conformity with current good manufacturing practice to assure that the drug . . . meets the quality and purity characteristics, which it purports or is represented to possess”; or (3) “if it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium”. Although a manufacturer’s level of compliance with Section 501 of the FD&C Act may be subject to interpretation, the emphasis on cGMP and compendial standards is clear.

The first compendial standard for visible particles in drugs for use in the United States came in 1936 when the National Formulary VI stated that injectable solutions were to be “substantially free from precipitate, cloudiness or turbidity, specs or flecks, fibers or cotton hairs, or any undissolved material” (58). In 1942, the USP and the American Pharmaceutical Association (publisher of the National Formulary at that time) stated that aqueous injections were to be “essentially free” of particles discernable with the naked eye. This definition eventually evolved into those currently used by the three major pharmacopeia stating that injectable drug products should be “essentially free” (USP), “practically free” (European Pharmacopeia) or free of “readily detectable” (Japanese Pharmacopeia) visible particles (58).
<table>
<thead>
<tr>
<th>Submission Date</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
<th>Container Type</th>
<th>Container Volume</th>
<th>Subvisible Particle Limit (µm)</th>
<th>Visible Particle Specification</th>
<th>Visible Particle Results (Stability Batches)</th>
<th>Method</th>
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<tbody>
<tr>
<td>9/28/2010</td>
<td>Liposomes</td>
<td>Intraperitoneal injection</td>
<td>Glass vials</td>
<td>10 mL and 20 mL</td>
<td>&lt;788&gt; per container</td>
<td>All lots “Free of Foreign Matter”</td>
<td>Free from visible particles</td>
<td>&lt;788&gt;</td>
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<td>9/29/2010</td>
<td>Solution</td>
<td>Intramuscular or subcutaneous</td>
<td>Glass cartridge</td>
<td>0.15 or 0.3 mL</td>
<td>1 mg</td>
<td>17 ± 1.2</td>
<td>Free of precipitates</td>
<td>788.0</td>
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<td>10/5/2010</td>
<td>Lyophilized powder</td>
<td>Intravenous, intramuscular or subcutaneous</td>
<td>Polypropylene vial</td>
<td>1 mg</td>
<td>3000/300 per container</td>
<td>&lt;788&gt; per container</td>
<td>Essentially free from particles that can be observed on visual inspection</td>
<td>&quot;Essentially Free from visible particles&quot;</td>
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<td>Intravenous</td>
<td>Glass vial</td>
<td>20 mg or 100 mg</td>
<td>6000/600 per container</td>
<td>66.6 ± 15.4</td>
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<tr>
<td>1/13/2011</td>
<td>Solution</td>
<td>Intravenous, intramuscular or subcutaneous</td>
<td>Pre-filled plastic syringe</td>
<td>1–10 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt; per container</td>
<td>No specification</td>
<td>N/A</td>
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<tr>
<td>1/14/2011</td>
<td>Solution</td>
<td>Intravenous, intramuscular or subcutaneous</td>
<td>Pre-filled glass syringe</td>
<td>3 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt; per container</td>
<td>No specification</td>
<td>N/A</td>
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<tr>
<td>2/25/2011</td>
<td>Solution</td>
<td>Subcutaneous</td>
<td>Pre-filled glass syringe</td>
<td>3 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt; per container</td>
<td>No specification</td>
<td>N/A</td>
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<tr>
<td>Submission Date</td>
<td>Dosage Form</td>
<td>Route of Administration</td>
<td>Container Type</td>
<td>Container Volume</td>
<td>Subvisible Particle Limit</td>
<td>≥ 10 um Particle Count Average ± SD</td>
<td>≥ 25 um Particle Count Average ± SD</td>
<td>Visible Particle Specification</td>
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<td>4/7/2011</td>
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<td>Intravenous, intramuscular or sub-cutaneous</td>
<td>Glass vials</td>
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<td>Glass vial</td>
<td>1 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt;, 2.9.29</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
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<td>Polypropylene vials</td>
<td>1 mL–20 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt;</td>
<td>32.1 ± 42.5</td>
<td>14.1 ± 24.5</td>
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<td>5/23/11</td>
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<td>Intravenous or subcutaneous</td>
<td>Glass pre-filled syringe or glass vials</td>
<td>0.5–2 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt;</td>
<td>234.3 ± 268.9</td>
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<td>Subcutaneous</td>
<td>Pre-filled glass syringe</td>
<td>1 mL</td>
<td>6000/600 or 3000/300 if LO method fails</td>
<td>USP &lt;788&gt;</td>
<td>694.3 ± 342.5</td>
<td>3 ± 1.3</td>
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<td>Glass vial</td>
<td>2.5 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt;, (Ph.Eur. 2.9.19)</td>
<td>47 ± 33.1</td>
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<td>Intravenous</td>
<td>Glass vial</td>
<td>5 mL</td>
<td>6000/600 per container</td>
<td>&lt;788&gt;</td>
<td>59 ± 26.2</td>
<td>1 ± 0</td>
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</table>

SD = standard deviation.
USP standards for subvisible particles (those measuring \(\geq 10\) \(\mu\)m and \(\geq 25\) \(\mu\)m in size) were first established in 1975 for large-volume parenteral products. Particulate matter standards for small-volume parenterals became official in 1986 as part of USP General Chapter \(<788>\) Particulate Matter in Injections. Chapter \(<788>\) was revised in 1995 to include the current limits for large and small volume parenterals. In 2007, Chapter \(<788>\) was harmonized with Japanese Pharmacopeia Chapter 6.07 Insoluble Particulate Matter Test for Injections and European Pharmacopeia Chapter 2.9.19 Particulate Contamination: Subvisible Particles. The test methodologies (light obscuration and microscopic particle count test) and acceptance criteria for \(\geq 10\) \(\mu\)m and \(\geq 25\) \(\mu\)m particles in this harmonized chapter are the most commonly cited particulate matter tests listed in FDA drug product application specifications (see Table II).

Less consistent are the specifications for visible particles in injectable drug products. As noted by Thomas Barber in his 1999 book *Control of Particulate Matter Contamination in Healthcare Manufacturing* (8), the “freedom of a product from particles that can be readily observed by an end user, given that relatively low light intensity, short inspection times, and untrained inspectors are involved, would seem to be highly desirable”. More important, the presence of visible particulate matter is an important indicator of manufacturing process control worthy of a rigorous compendial standard. As shown in Table II, the specifications and acceptance criteria for visible particles in new drug applications submitted to FDA are inconsistent or non-existent. The opposite is true for specifications for subvisible particles, which nearly always follow the harmonized compendial recommendations.

USP Chapter \(<1>\) Injections states that “each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter in its contents”. USP Chapter \(<1>\) also states that “every container whose contents show evidence of visible particulates shall be rejected” and “the inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates”. Absent from USP Chapter \(<1>\) are a definition for “essentially free” or a standardized method for visible particle inspection. USP Chapter \(<790>\) Visible Particles in Injections, published in the March-April 2012 edition of *Pharmaceutical Forum* (59), proposes a test method and acceptance criteria allowing a lot of drug product to be considered “essentially free” of visible particulate matter. The test procedure is based on European Pharmacopeia Chapter 2.9.20, which calls for the observation of swirled units in front of black and white backgrounds for a defined period of time under specific lighting conditions. The test is to be conducted on a subset of units from each lot that has already been subjected to 100% visual inspection. An acceptable quality level of 0.65, using American National Standards Institute–American Society of Quality (ANSI/ASQ) Z1.4 General Inspection Level II single sampling plans, is considered acceptable for batch release purposes. Chapter \(<790>\) also states that other procedures having equal or better sensitivity may be employed and that injectable products containing inherent particulate matter should be tested according to the procedures established in the product monograph or approved regulatory submission.

Another compendial weakness with regard to particle standards is the discrepancy in Chapter \(<788>\) between the particulate matter limits in large-volume injectables (LVI, those containing >100 mL) and small-volume injectables (SVI, those containing \(\leq 100\) mL). The current limits for particles \(\geq 10\) \(\mu\)m and \(\geq 25\) \(\mu\)m in SVI using the light obscuration method are 6000 and 600 particles per container, respectively. The limits for LVI using the light obscuration method are 25 per milliliter for particles \(\geq 10\) \(\mu\)m in size and 3 per milliliter for particles \(\geq 25\) \(\mu\)m. Thus a 1 L LVI can have greater than four times the number of particles \(\geq 10\) \(\mu\)m and 5 times the number of \(\geq 25\) \(\mu\)m particles per container as compared to a SVI. This discrepancy in the particle limits for SVI and LVI is relevant due to the sheer volume of parenteral solutions administered to critical care patients and the potential impact of high particle loads on these patients (15, 18, 30, 56). As documented by Nath et al. (60) and corroborated by the data, albeit limited, presented in Table II, most injectable product particle level counts fall far below those allowed in USP Chapter \(<788>\). Given the clinical risks associated with the administration of large amounts of particulate matter to critically ill patients and the fact that improved cGMPs allow for better control of particle loads, tighter sub-visible particle standards for large-volume parenterals should be considered.

**Continuing Efforts**

Manufacturers, regulators, and standards-setting organizations are collaborating on several particulate matter-related projects designed to improve manufacturing stan-
dards and patient safety. One such collaboration relates to the establishment of a standardized test method and minimum acceptance criteria for visible particles in injectable drug products. Members of the USP Dosage Forms Expert Committee, the FDA Standards Working Group, industry consultants, and USP officials have met several times to discuss challenges faced by the pharmaceutical industry regarding the USP Chapter 1787. Injections definition of “essentially free” as it pertains to the presence of visible particles in each lot of injectable drug product. The pharmaceutical industry expressed a desire for a clearer definition of the term “essentially free” and explained that although the goal of visual inspection is to manufacture product that contains zero visible particles, achieving this goal is nearly impossible given the current process capability and inspection technology. The FDA was able to convey its concerns about the administration of visible particulate matter to “at–risk” patient populations and emphasized the need for product-specific particulate matter limits and minimum acceptable visible particle standards. The result was the development of USP Chapter 1790 Visible Particulates in Injection. Chapter 1790-, the sister Chapter to 1790-, is in development and will provide additional information on potential sources of visible particles, the characterization of visible particles, and a holistic approach to minimizing the presence of visible particles in injectable drug products.

A second collaborative effort to address issues related to subvisible particulate matter standards and test methods for the growing number of protein therapeutics resulted in USP Chapter 1787 Subvisible Particulate Matter in Therapeutic Protein Injections (61). Chapter 1787 addresses the unique properties of protein therapeutics, such as protein aggregation, sample viscosity, and limited sample volume that can make test procedures recommended in USP Chapter 1788 untenable. An informational chapter, Chapter 1787, is under development and will provide additional information about the choice of test methods for protein particle characterization—especially for protein particle populations of 1–100 micrometers, which have the potential to affect the safety and efficacy of the product throughout its shelf life.

Finally, representatives from the FDA’s Center for Drug Evaluation and Research actively participate as panelists and presenters at conferences sponsored by organizations such as the Parenteral Drug Association, the European Compliance Academy, and the USP. These conferences serve as a forum to discuss topics such as drug product recalls related to particulate matter contamination, inspection methods for visible and subvisible particles, and the use of compendial standards for the establishment of suitable drug product specifications. The goal of these presentations is to promote dialog between the FDA and industry with regard to the establishment and enforcement of consistent particulate matter standards and the challenges faced by both industry and regulators regarding the control of particulate matter in injectable products.

Conclusion

Given the large number of patients receiving injectable drug products each year and the potential for particulate matter to cause harm to patients, it is critical to monitor the presence of and reduce through all reasonable means the presence particulate matter in injectable drug products. Moreover, the level of particulate matter present in a drug product is a key indicator of pharmaceutical quality (62). The development of compendial standards over the past several decades has helped to assimilate the test methods’ minimum acceptance criteria for pharmaceuticals in the global market. Likewise, improved cGMPs have helped to lower subvisible particle levels in injectables far below the compendial limits. Today, the goal of manufacturers, regulators, and standards-setting organizations should be to minimize the risk of particle-induced sequelae, especially in high-risk patients, without trading unnecessary manufacturing burden for minimal safety gains. The many challenges associated with estimating the risk imparted by particles of various sizes, shapes, and consistencies administered to multiple patient populations in varying amounts by numerous routes of administration make a one-size-fits-all approach to particle limits for all injectable products untenable. Nevertheless, continued collaboration among regulatory authorities, regulated industry, standards-setting organizations, and other relevant stakeholders will be crucial for the development and/or modernization of risk-based, particulate matter–related standards, regulations, and guidance designed to ensure the availability of high-quality pharmaceutical products.

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Conflict of interest Declaration

The author declares that he has no competing interests.

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