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Parenteral Drug Association

Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products



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Executive Summary

Sterile injectable products are used extensively in health care. Patients, caregivers, manufacturers, and regulators have an inherent expectation for safe and effective injectable drug products. This expectation requires injectable pharmaceuticals to be produced to standards of quality, purity, and sterility that include being essentially free of extraneous matter such as particles. Despite guidance in producing product that is “essentially free” of particles, manufacturing such product is very challenging. In many instances, the observation of particles in pharmaceutical products has resulted in product recalls. While medical warnings have accompanied these recall notices, the specifics of these warnings have varied. The medical literature is sparse with respect to case reports and experimental studies providing data to support the safety risk of particles (intrinsic or extrinsic) in humans. A gap exists between the observation of small quantities of particles in injectable pharmaceutical products and patient-documented safety concerns resulting from the inadvertent administration of particles to patients. Thus, a need exists to create a framework to describe and assess the potential risk of administering particles to patients.

This paper provides a review of current compendial inspection requirements for visible particles along with a review of the medical literature associated with any observed harm from such particles. Guidance is provided on the assessment of risk in such circumstances including consideration of the following key attributes; patient factors, route of administration and use of filtration at the point of administration, the volume administered, particle size and their fate in body, particle type, source and amount, manufacturing process mitigation and the frequency of detection.

Globally, clinicians and patient populations are facing drug shortages in part due to inconsistent product release and recall decisions related to the presence of particles and a lack of understanding of the impact to patient risk. The decision to recall product from the market should be based on context of the manufacturing trend history, complaint rate trending, and medical risk assessment. Unless there are specific special circumstances, there should be no automatic requirement to recall a product lot for a single particle found in a single unit. Notwithstanding high risk clinical circumstances and acknowledging there are limitations to reporting clinical events to particle infusion, the existing data suggest the overall risk to patients is generally low and the benefit of these treatments is generally significant.

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Introduction

Sterile injectable products are used extensively in health care; in fact, more than 15 billion injectable doses are administered annually worldwide **(1)**. Patients, caregivers, manufacturers, and regulators have an inherent expectation for safe and effective injectable drug products. This expectation requires injectable pharmaceuticals to be produced to standards of quality, purity, and sterility that include being essentially free of extraneous matter such as particles. *(For the purposes of this paper, the meaning of the term particle includes particulate and particulate matter)* The standards of producing pharmaceutical products are described within the various pharmacopeias. Manufacturers strive to produce injectable products with the requisite quality outlined in these standards to ensure their safe and effective use.

Despite guidance in producing product that is “essentially free” of particles, manufacturing such product is very challenging **(2)**. For example, over the period of 2008–2012, particle-related issues led to 22% of product recalls for injectable products **(3)**. In 2007, the European Medicines Agency (EMA) performed an analysis of product quality defects reported in 2005 and noted that 6% of all product quality defects were attributed to particles **(4)**. Those particle defects that resulted in a recall would have been classified by EMA as either a class 2 (defects, which could cause illness or mistreatment, but are not Class 1, e.g., mislabeling such as incorrect text) or class 3 (defects, which may not pose a significant hazard to health but, where a recall has been initiated for other reasons e.g., faulty packaging) (EU recall) **(4,5)**. Between January 2013 and June 2014, the Medicines and Healthcare Products Regulatory Agency (MHRA) Drug Alert website issued forty-two drug alerts, with eleven alerts relating to particles **(6)**. Of these, alerts reported in 2014 were all class 2 and included metal particles, small white particles, fiber and glass particles, and silicone fragments **(7-11)**. Other agencies, such as FDA, have different class of recalls: Class I Recall - A situation in which there is a reasonable probability that use of, or exposure to, a violative product will cause serious adverse health consequences or death. (21 C.F.R. § 7.3(m)(1)); Class II Recall - A situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. (21 C.F.R. § 7.3(m)(2)); and Class III Recall - A situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences (21 C.F.R. § 7.3(m)(3)) **(12)**.

Parenteral solutions withdrawn from glass ampoules routinely expose patients to numerous glass particles of variable size. As an example, a 1972 study by Turco and Davis showed that opening a single 2 mL glass ampoule and withdrawing the medicine included 292 glass particles between 5 μm and 50 μm and 21 particles that were greater than 50 μm **(13)**. Vial presentations may contain particles from the rubber closure, a risk that is present with every injection **(14)**. These are known risks that may result from the packaging and use of the product and are not manufacturing related. The technology to produce, package, and store completely particle-free products on a large scale is not currently available. Additionally, Davis et al. identified 86 to 2,200 particles of >5 μm per liter following filtration from a wide variety of sterile infusion solutions in glass and plastic containers **(15)**. Based on the study by C.M. Backhouse et al., intensive care patients would likely often receive more than 10^7 foreign particles >2 μm per 24 hours with their intravenous therapy **(16)**.

In many instances, the observation of particles in pharmaceutical products has resulted in product recalls **(3)**. While medical warnings have accompanied these recall notices, the specifics of these warnings have varied **(17–22)**. Typically, these warnings are described as “potential” and are not accompanied by published reports of patient harm. The medical literature is sparse with respect to case reports and experimental studies providing data to support the safety risk of particles (intrinsic or extrinsic) in humans. Turco and others have demonstrated mechanisms for the inadvertent introduction of particles, sometimes in large quantities, to parenteral fluids prior to administration **(13)**. The in-line filter articles suggest a potential relationship of the reduction of particles and decrease in rate on infusion site phlebitis when filters are used **(16)**. The older literature on large volume infusion

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and parenteral nutrition and the literature on intravenous drugs addicts (IVDA), which have very limited general use for current medical practice show that mass, chronicity and unique characteristics of the particle may have a role in these special situations **(23,24)**. The paucity of current medical literature detailing harms from particulate, in pharmaceutical products might in part reflect the high standards of the current manufacturing processes.

A recently observed exception is the reaction of subvisible (<10 µm) protein aggregates to form anti-drug antibodies. Such antibodies have been observed in both preclinical and clinical studies with protein based drug products **(25-28)**. These particles are typically below the visual threshold, unless present in large quantity to be observed as a haze in the solution. With this exception, a gap exists between the observation of small quantities of particles in injectable pharmaceutical products and patient-documented safety concerns resulting from the administration of particles to patients. Thus, a need exists to create a framework to describe and assess the potential risk of administering particles to patients.

Current written expectations for limits on particles in injectable products can be found in the national or regional pharmacopeias. These requirements are more fully described in the section “Current Defined Rules” that follows. Historically, these expectations have required significant interpretation to translate into a usable numerical limit for product release and ongoing compliance considerations. This has led to a broad range of differing practices and decisions by individual pharmaceutical manufacturers and regulatory authorities. The evolving standards and a better understanding of patient risk will help to deliver consistent and safe products across the pharmaceutical industry.

With these considerations in mind, the medical officers and industry experts authoring this paper reached consensus on considerations to be used when assessing health hazards of particles in injectable solutions. The purpose of this paper, which purposely limits scope to focus on non-product particles (e.g., fibers, glass, rubber, metal), is to provide a scientific, medical risk-based approach for evaluating patient safety if a particle contained within injectable drug products is inadvertently administered to a patient. The paper is supplemented by a literature review of described harms to patients as well as a number of animal studies that have tried to evaluate the physiological effect; in general these studies have been highly experimental and used excessive quantities of particles **(29-31)**. Specific approaches to risk mitigation are not addressed in this paper.

To assess risk to health, consideration needs to include product sterility, patient factors as well as the variability in route of product administration and variability in particle type, size, and volume of any product within which the particle exists. The clinical impact can then be adequately assessed by understanding the likelihood and severity of the pathophysiological consequences if particles are administered to patients. By understanding the health risks, regulators and manufacturers will be better able to develop standards that support delivering high-quality drug products. These perspectives underlie the creation of a risk-based approach when assessing health hazards associated with particles.

Despite varying sources and types of inert particles, only four basic pathogenic mechanisms for potential harm exist: 1. Infection and inflammation due to local or systemic infections caused by the presence of micro-agents or endotoxins. 2. Physical presence of a particle may cause inflammatory response directly or through associated leachates that cause direct tissue injury. 3. Particles might also stimulate untoward immune responses such as allergic reactions or anaphylaxis. 4. Tissue damage can arise from the occlusion of the affected vasculature (thromboembolism). Symptoms and signs can manifest locally or systemically (e.g., temperature, feeling weak). As part of the base requirements for a quality system, the manufacturing environment is monitored for potential sources of microbial agents or endotoxin contamination. Product is routinely tested at final release to ensure product requirements (e.g., sterility) are met. Although microbial agents and endotoxins represent a potential

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concern, these risks are addressed through other commonly used compendial tests. However, this paper focuses on the concerns surrounding irritating inflammation or reaction, local tissue damage, and thromboembolism.

The routes of administration considered for the purpose of this paper are limited to drugs administered through direct injection or infusion. As defined in Table 1 later in this paper, the examples of the types of injections considered within scope include subcutaneous, intramuscular, intravenous, high-volume/pressure infusions, intrathecal, intraarticular, intraocular, intraarterial, and intraperitoneal. Examples of product types included are antibiotics, antitoxins, antivenoms, blood, blood derivatives, immune serums, immunologic diagnostic aids, therapeutic proteins, toxoids, IV solutions, and vaccines. Out of scope of this document are drug-release products that are implanted, even if implantation occurs through injection, as well as all routes of administration other than injection, including inhalation, topical, and ophthalmic. Furthermore, the paper does not include gross contamination, whereby particles may be included across a significant proportion of vials of a product lot or lots or a single vial with a large quantity of particles, and the product does not meet the expectation for “essentially free.”

Current Defined Rules

The current inspection methods and acceptance criteria for particle matter in injectable products may be found in the national or regional pharmacopeias. For the U.S. market, the U.S. Pharmacopeia (USP) General Chapter <788> Particulate Matter in Injections has been official for many years. It defines two methods for counting subvisible particles and sets limits of 6,000 and 600 particles per container for $\geq 10 \mu\text{m}$ and $\geq 25 \mu\text{m}$ particles, respectively. These limits apply to containers $\leq 100 \text{ mL}$. For containers larger than 100 mL, limits are set on a per milliliter basis. As this is a harmonized chapter, the same methods and limits are found in the European Pharmacopeia (EP) and the Japanese Pharmacopeia (JP).

Requirements for visible particles are found in USP General Chapter <1> Injections. The requirement set in this chapter is that every final container is inspected for particles to the extent possible, and any showing the presence of observable foreign and particulate matter are rejected. It further requires that “the inspection process shall be designed and qualified to ensure that every lot of parenteral preparations is essentially free from visible particulates” **(32)**. General Chapter <790> Visible Particulates in Injections was published in the first supplement to USP 37 and became official August 1, 2014 **(2)**. This chapter establishes reference inspection conditions and provides quantitative limits based on acceptance sampling to meet the expectation for every lot to be essentially free from visible particles. The inspection conditions are harmonized with those found in the EP **(33)**.

Additional requirements for products marketed in Europe can be found in the Finishing of Sterile Products section of the European Medicines Agency Annex 1. This section sets the requirement that “filled containers of parenteral products should be inspected individually for extraneous contamination or other defects.” It also sets an expectation that inspectors pass regular vision tests and that frequent breaks be given to avoid fatigue. The EP, in Parenteral Preparations-Injections (0520), specifies “solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles.” It follows with an inspection method described in 2.9.20 Particulate Contamination: Visible Particles. This section specifies illumination intensity, background, and pace for the conditions suitable for inspection. The EP monograph Monoclonal Antibodies for Human Use (2013) aligns with the EP monograph Parenteral Preparations for Injections, allowing for an appearance specification of “practically free from particles.” The specification must be “justified and authorized” **(34)**.

The requirements for product marketed in Japan are contained within the JP. It specifies inspection with the unaided eye with light coming from an incandescent source with intensity below that stated in the EP and USP.

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The acceptance criterion for this inspection is “injections or vehicles must be clear and free from readily detectable foreign insoluble matters” **(35)**.

All of the pharmacopeias establish the need to perform 100% inspection of units in a batch or lot of product under controlled condition, but they recognize the probabilistic nature of the inspection process in the acceptance criteria.

Evolving Stances and Drivers

Particles represent an ongoing challenge in drug product manufacturing. The use of clear and colorless injectable liquids and containers permits continuous, nondestructive inspection throughout the drug product life cycle for most products. Where product formulation (e.g., powders, suspensions and strongly colored solutions) and/or the container (e.g., amber glass or translucent plastic) limit visual inspection, supplemental destructive testing of a small sample is recommended to further assess the risk of particles in the batch **(2)**. Points of failure, based on particle presence, include in-process waste (rejects) and customer complaints. As seen in a recent benchmarking study, the most common cause for rejections was the presence of particles **(28)**. Sources of particles include the manufacturing environment, primary packaging components, processing equipment, and the drug product itself. Together with cosmetic and other appearance defects, particles continue to impact product quality and availability.

The presence of visible particles in injectable drug products has been a matter of intense discussion, both from a regulatory and a compliance perspective, within global regulatory agencies as well as industry over recent years **(35)**. There is an expectation to not only reduce particles but also control them, including those in the subvisible range. To better understand the particles’ source, and thus aid in their reduction, particle detection and identification are important parts of regulatory compliance and product quality assurance. Lot release acceptance criteria such as “free from,” “without,” or “no visible particles” risk the rejection of entire batches of drug product should a single particle be detected in a single container of product. Further, current inspection methods and technologies, including human manual inspection and fully automated inspection systems, cannot provide this level of absolute assurance. Visual inspection is a probabilistic process **(36,37)**, with detection probabilities less than 100%, especially for particles less than 200 μm in diameter **(27,28,38)**. This 100% inspection is supported by acceptance sampling methodology (“AQL inspection”), which again does not support absolute assurance of the absence of all particles. These practical limitations should be considered when establishing any visual inspection limit.

Industry has been working with regulatory agencies worldwide to update guidelines and monographs to reflect these pharmaceutical developments and to gain improvements in control and methods for identification of visible particles. Industry has begun to advocate for regulatory distinction between particles introduced into a product as an intrinsic or extrinsic contaminant versus the formation of inherent particles from the drug product, recognizing that Inherent particles should have been fully characterized by the application holder during product development and described in the product application.

Despite these efforts, the published guidance from regulatory bodies has limited specificity on allowable particle size, numbers, and types of visible particles **(2,29,32,34,40)**, or on visible particle investigations **(41)**. There is no published guidance on the potential impact of small numbers of visible particles to patient safety. In a general sense, this is the most common issue facing manufacturers. While the published literature contains a number of anecdotal reports describing exposure to large numbers of particles, none of these reports reflect the potential hazards of more typical particle administration via large- or small-volume parenteral pharmaceutical

administration to patients. There continues to be emotional stances lacking data around the subject; a clear understanding of the facts to benefit all is required.

Particle Matter Consideration

The European, Japanese, and US Pharmacopeias share the following harmonized definition for particulate matter in injectable products:

Particulate matter in injections and parenteral infusions consists of extraneous mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.

Identification of the composition of the particulate matter is the first step in characterizing particulate matter risk. Based on this information, particles can be further classified into one of three subcategories: extrinsic, intrinsic, and inherent. Both extrinsic and intrinsic particles are considered within the scope of this paper, while inherent particles are not. The following discussion provides definitions and examples of extrinsic, intrinsic, and inherent particles.

Extrinsic particles are defined as those that are not part of the formulation, package, or assembly process, but rather are foreign and unexpected. Examples of extrinsic particles include fibers (e.g., cellulous), clothing fragments, hair, rubber, metal, plastic, and paint. Materials such as rubber, metal, and plastic are defined as extrinsic in cases where the specific material identified is not a product-contact material and therefore not considered part of the formulation, package, or assembly process. Extrinsic particles present a greater risk to sterility assurance, especially for aseptically filled products, as their bioburden is unknown and uncontrolled.

Intrinsic particles are defined as those that arise from sources related to the formulation, packaging, or assembly processes. Examples of intrinsic particle materials include glass, stainless steel, rubber from stoppers, and gasket material. In each of these cases, the particle material should be a known product-contact material to be considered intrinsic. Such materials are chosen because they are inert and unreactive to the drug product. Intrinsic particles can also be related to changes in the product over time or due to physical and chemical reactions between the product and the components (e.g., oxidation, incompatibility between admixture drug and the carrier solution). Such reactions may form a visible precipitate or glass lamellae. While these are formed in part from the drug formulation, they are not considered inherent particles, as discussed below, because they are indicative of an unexpected reaction and a lack of product stability.

Inherent particles are defined as materials that are expected from the drug formulation, and thus represent a generally accepted characteristic of the product. Examples of inherent matter include the following: adjuvant material in suspension products, certain excipients such as human serum albumin, proteinaceous aggregates in therapeutic proteins, and mannitol crystallization (38). Inherent particles, although anticipated, should be handled as a particle defect when found to exceed expected levels. Because inherent particle by its nature is product specific, assessing its safety is considered out of the scope of this document. Importantly, products with inherent particles should be characterized fully and both the product quality and the patient safety impacts should be analyzed with similar risk assessment considerations as laid out in this document.

Particle Size

While particles of varying size have been observed in injectable drug products, they are generally classified into one of two categories; visible and subvisible. Visible particles are defined as those that can be detected under controlled conditions by the unaided human eye (i.e., without supplemental magnification) (2,33,35). As a reference, studies have demonstrated that under idealized conditions, trained inspectors performing the

pharmacopeia inspection method will begin to have reliable detection of near 70% efficiency when particle sizes reach 150 μm (38). The 150 μm threshold should be considered a best-case threshold for human visual identification of particle in injectable drug products given that it represents idealized inspection conditions. Any changes in product, container, or particle material from those idealized conditions will cause the visible detection threshold to shift above 150 μm . There are specific nonzero limits in the pharmacopeias for subvisible particles ≥ 10 μm and ≥ 25 μm . The subvisible particle category covers materials ranging in size from submicron up to the visible threshold. The limits are harmonized in the USP, EP, and JP and are 6,000 and 600 per container, respectively, for containers ≤ 100 mL.

Pathophysiological Considerations and Clinical Implications

The effects of particles in injectable drug products have been discussed in the medical literature for decades (42-47), and are based on in vitro studies, some animal data, human case reports, and small observational studies. Human data is limited because it is ethically impossible to prospectively test the impact of particles in injections. Further, even if particulate matter is administered to patient, the clinical impact to a patient can be hard to assess or even may be unnoticed or asymptomatic. Potential clinical sequella could, in some circumstances, be indistinguishable from an underlying disease or other treatment impact. The literature often contains the most extreme examples from intravenous drug abuse and hyperalimentation. Given these limitations, it's best to understand potential harm to patients based on an understanding of the pathophysiology of particle infusion.

The type and degree of clinical impact is dependent on multiple factors, including the route of administration, the size and amount of the particle(s) injected, and patient factors such as underlying health status. Although there are limited data on human exposure to infused particles, it is estimated that "patients in intensive care units may receive more than a million injected particles >2 μm daily" (48). As such, particles could theoretically have meaningful clinical impact if highly experimental animal studies are considered appropriate surrogates (49,50,51). As an example, ICU patients are at greater risk of consequences of particle infusion, due to their need for continuous infusion of parenteral solution, including that for hyperalimentation.

Many injectable drugs are administered intramuscularly and subcutaneously. Intramuscularly and subcutaneously administered drugs containing particles generally have minimal impact on patient health. Complications from subcutaneous and intramuscular medications generally arise from the irritating properties of the drug product and are often drug-specific (52). For particles that are primarily mechanical obstructions and inert (e.g., cellulose, metal, or glass), the composition of a particle is not critical to clinical impact except for impact on sterility, which is discussed below. Subcutaneous administration of small, inert, sterile particles would not be expected to induce a clinically significant reaction beyond minor irritation or perhaps a small granuloma (53). Likewise for intramuscular injections, Greenblatt and Allen looked at 26,294 hospitalized medical patients, 46% of whom received at least one intramuscular injection, finding that clinically apparent local complications are uncommonly (less than 0.4%) associated with IM injections (54). In consideration of glass particles in particular, glass fragments from tubular and molded glass can generally be considered inert, and in small quantities they are not likely to cause significant injuries. However, the special case of glass lamellae which can be either visible or subvisible can be present in large numbers and can increase in number with time, can have a higher clinical impact if administered in large volumes.

Whenever a drug is injected into a contained space, for example, intraocular or intrathecal use, there may be more risk for inflammation from particles or a particle may serve as a nidus for infection, causing harm (55). There are limited data, but the presence of particles in solutions for intrathecal use has been reported from use of drugs within glass ampoules (56). The average number of particles was 17 (7–38) with a range in size from 15 μm to 80 μm . At the time of the study, the incidence of central nervous system complication following subarachnoid

anesthesia was low. The authors note that a foreign body reaction may have resulted and may account for the reported events of chemical meningitis.

Intravenous infusion of particles might result in phlebitis due to particles causing direct traumatic damage to the vein, or chemical damage from undissolved particles, or infection if the particle is non sterile. Non-dissolvable particle matter will become trapped in small vessels or capillary beds, when the introduced particle is larger than the vessel. The diameter of the smallest capillary or blood vessel is about 7 μm in an adult (57) and the diameter of a pulmonary capillary, which is approximately 10-15 μm , just larger than the size of red blood cells which are responsible for oxygenation of blood as they travel through the pulmonary vasculature. Therefore any intravenously administered particles greater than 7 μm but less than 10 μm may occlude some capillaries. If pulmonary capillaries are compromised in the presence of microemboli (pulmonary embolism), the clinical consequence is impaired oxygen transfer and compromised respiratory function (58). Smaller particles (<7 μm) will generally be phagocytosed by macrophages and ultimately deposited in spleen or liver. Massive amounts of subvisible particles might not be phagocytosed and might then be deposited in other organs, especially the kidney. In general the clinical consequences are negligible because most organ systems have significant reserve capacity (30,31).

The clinical impact from an occluded vessel is dependent on many variables, including the size of the vessel affected as well as the number of vessels supplying a particular organ. In many instances, there may be no clinical impact as some tissues or organs have extensive blood vasculature so that numerous vessels may be feeding the same tissue. Therefore, one or numerous occluded small vessels may have no clinical significance or patient symptoms. In fact, solid particle microemboli are a recognized complication of extracorporeal circulation in open-heart surgery (59-62). Microsphere infusion during bypass in laboratory animals showed pulmonary ultrastructure damage was proportionally related to particles increasing in size from 20 μm to 75 μm . After simple perfusion of the extracorporeal circuit, Liu reported that the 15 to 80 μm particle count reached 199 ± 69 per mL (63). Despite these risks, the clinical benefits outweigh the risks, justifying why extracorporeal circulation has continued to be used in open-heart surgery. This highlights that risk alone is but one consideration when assessing the use of products and should not be the only consideration when assessing impact.

Numerous animal studies have been conducted to determine the fate of intravenous particles of differing size and composition (29,51,64,65). Most studies have focused on subvisible particles, with a diameter of less than 50 μm . In these studies, the infusion of massive quantities of particles has been accompanied by histologic evidence of injury to pulmonary capillary endothelial cells (63), microscopic thrombi in the pulmonary capillaries (66), microscopic pulmonary granulomata (67), and hepatic inflammatory effects (68). In a hamster model using antibiotics with subvisible and visible particles, capillary perfusion was jeopardized in posthypoxic tissue but not in normally perfused tissue (24). While useful in understanding the pathophysiologic response to intravenous particle exposures, the large mass of particles employed in these animal studies provides little guidance on the risk of small numbers of macroscopic particles to human patients.

There are limited data on human exposure to infused particles. Clinically detectable patient harms from particle injection are difficult to detect even if suspected, suggesting minimal short-term impact. Garvin and Gunner were among the first to report a concern about the effects of particles in human patients, finding postmortem pulmonary vasculature granulomas (cellulose fiber) in the lungs of patients who had received large volumes of IV fluids (69,70). For obvious ethical reasons, there is a lack of controlled human studies on the effect of particles in human patients. However, clinical events from total parenteral nutrition (TPN) complications, intravenous drug use, and cardiopulmonary bypass provide relevant information on the effects of high (and prolonged) particle exposure (these are specific and not necessarily generalizable circumstances).

The American Society of Parenteral and Enteral Nutrition (ASPEN) Guidelines note particles of 5 to 20 μm and larger are capable of obstructing blood flow through the pulmonary capillaries, which could lead to complications such as pulmonary embolism (42). A review of the literature reveals a case report of a dyspneic patient receiving TPN who had diffuse <1 mm micronodules on computerized tomography examination, elevated pulmonary artery pressures, and, on postmortem, amorphous material microemboli in the pulmonary vasculature (71). This finding highlights that particles may have a clinical impact when administered over an extended period of time with multiple exposures (72). Hyperalimentation associated with inherent particles (calcium and phosphate) administered to pigs has been shown to cause respiratory distress and sudden death with amorphous calcium-phosphate precipitant debris (71).

Additional anecdotal information for human patient risk may be obtained from the examination of case reports involving intravenous drug abusers (68,73,74). In these cases, a powder or pulverized tablet is suspended in a vehicle, then variably filtered through cotton (75). These patients may develop dyspnea and show reduced pulmonary function testing (72). Cutting agents or excipients such as microcrystalline cellulose, talc, and starch have been identified in pulmonary, foreign-body emboli and granulomas in these individuals (75-77). In one instance, the particles lodged in the pulmonary arteriole, causing inflammation and thrombosis, subsequently eroding through the arteriolar wall and becoming a giant cell granuloma (77). Talc granulomas in organs other than the lungs were found to be of negligible clinical significance (78). Niden and Aviado (1956) found that experimental intravenous injection of a given mass of glass beads produced greater pulmonary dysfunction with smaller particle sizes suggesting systemic effects might be related to surface area rather than size of particles (58). Importantly, the meaningful clinical risks to human patients are difficult to infer from these observations of extreme cases of particle infusion that result in chronic exposure, extremes in mass, number, and diversity of foreign particles, as well as the uncontrolled conditions in which they were administered.

In another paper where embolization events resulted in a less extreme case in regards to number of events, Baydur et al. demonstrated that prolonged indwelling central venous catheter use may degrade and lead to embolization of catheter material (79). This occurred in a patient where the catheter particles entered the pulmonary circulation. This patient required a central venous catheter for more than five years, and numerous catheters were utilized in this time period. The patient was clinically asymptomatic throughout that time and four years later developed symptoms of sarcoidosis that included granuloma formation of the skin. The patient required further evaluation, including an open-lung biopsy, which revealed pulmonary granulomas of two distinct types, that from sarcoidosis and the other of catheter material. The author reports the two granulomatous processes were unrelated. This paper and case reports of IV drug abusers highlight that a localized pulmonary inflammatory response may be more likely to result from particles than pulmonary embolism or clinically symptomatic tissue damage.

Perhaps more relevant are clinical results of arterial embolization procedures performed using materials such as polyvinyl alcohol embolic agents (80), collagen-coated acrylic microspheres, and gelatin spheres (81). These procedures provide us some insight on the potential human pathophysiologic outcomes due to non-target embolization within intravenous infusions (82). These procedural reported cases involved massive, 300–500 μm particle loads moving from the arterial injection site into the venous circulation. While these embolization procedures did result in the intended thromboembolic event, they have not resulted in significant long-term consequences from material that would be considered extrinsic particles for most, if not all, drug products (27,83-87).

In the presence of an abnormal communication between the venous and arterial systems, intravenously administered particles can bypass the lung and its vasculature. Aberrant anatomy might be known, for example fistulae for renal dialysis, or unknown for example, up to 30% of the adult population has a patent foramen ovale that allows for a right to left shift of the blood circulation within the heart and bypasses the lungs (38). This allows for the possibility of particles to enter directly into the central vascular system, with potential complications to include ischemic stroke and myocardial ischemia, or into the peripheral vascular system, where peripheral vascular ischemia may result. In addition, end organ damage can occur through deposition or embolism of particle into the organ vasculature. Further, even with an intact normal vascular anatomy, particles less than 10 μm may pass through the lung's circulation, into the peripheral circulation, and deposit in other organs, such as the liver, kidney, and spleen. Patients with existing end-organ disease and small-vessel disease may be considered at greater risk.

In summary, particle administration has a low probability of clinically significant injury on the vascular system, and current hypothetical assessments are overestimated. Clearly some impact can exist, but cases are infrequent and often associated with extreme risk situations. Data suggest administration of a large volume of particles over time, the use of hyperalimentation and large volumes of small size particles may cause clinical damage. Small amounts of inert particles are unlikely to cause clinically meaningful patient harm. In addition, intramuscular and subcutaneous injections of sterile inert particles are very unlikely to cause meaningful patient injury. Further consideration should however be given to patients with end-organ disease, immune-compromised, or neonates and infants, as well as when particles are injected into closed spaces (e.g., intrathecal, intraocular, intraarticular) as these situations may have a greater potential for harm.

Risk Assessment

To assess the potential impact of the particle to the patient, a risk assessment should be performed in accordance with recognized guidance documents and standards (88). In the International Conference on Harmonisation *Quality Guideline Q9: Quality Risk Management*, "risk is defined as the combination of the probability of occurrence of harm and the severity of that harm" (89). In relation to particles, when assessing the risk to the patient population, the assessment can be reduced into the likelihood for the hazard to occur and the severity of the harm or clinically significant outcome that might occur to the patient due to the hazard. The risk is derived after assessing the likelihood of the harm against the severity of the harm under specific circumstances. Differentiation should be made between the likely general population and a subset of patients who might be most at risk.

Noting that post-hoc process controls should not be used as a safety-net for poor manufacturing methods, the risk assessment needs to consider the possible types of clinical impact the patient might experience and assess whether the harm would be likely to occur given the specific circumstances. Some products are known to have a risk for precipitant, and labeling and standard use reflect this understanding and the importance for product inspection prior to use within the pharmacy as well as at patient bedside. The assessment should account for standard clinical practice to reflect real-world use.

The severity of harm is determined based on the potential clinical impact that the patient will experience due to administering product from the affected lot. Severity can be rated as temporary discomfort all the way to patient death. Potential harms, as discussed in the Pathophysiology section, may include phlebitis, granuloma, and occlusion or thromboembolic events, each with differing severity levels of harm. For example, an otherwise healthy individual receiving a subcutaneous or intramuscular injection containing sterile extraneous inert particle would likely experience no adverse effect or at worst develop a small granuloma. The severity of the harm may be considered minor with no need for medical intervention. By comparison, a critically ill premature infant receiving

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a particle-laden infusion directly through an umbilical catheter might suffer permanent or life-threatening injury (47,90). This outcome may be considered critical, as a life-threatening situation arose. In some situations, permanent injury may result and should be considered in determining the degree of severity of the harm.

The scope of this paper does not allow the creation of a specific template to consider risk; however, the factors presented in **Table 1** should be taken into consideration in such an assessment.

Table 1: Factors to be considered in particle risk assessment

Parameter	Potential Risk Factor
Patient factors	Age, gender, weight, disease being treated, underlying illness, immune status, other treatments, physical activity
Route of administration and use of filtration at point of administration	Subcutaneous, intramuscular, intravenous, high-volume infusions, intrathecal, intraarticular, intraocular, intraarterial, other; use of filter (and type) at point of use
Volume of administration	Number of particles likely present per volume of administration
Size	If visible particles are present, determine the likelihood of additional subvisible particles present and the likely size. Determine if the subvisible particles are within acceptable limits
Fate in body	Remains at site of administration (e.g., subcutaneous or closed cavity), peripheral versus central venous administration, intrinsic reactivity (immunogenicity, pro-inflammatory, nonreactive/inert)
Particle type	<i>Inherent</i> : intact therapeutic protein, denatured therapeutic protein, degree of degradation, other protein component(s) <i>Intrinsic</i> : silicone, glass, rubber, stainless steel, fibers (cellulose, polyester), etc. <i>Extrinsic/process related</i> : autoclave tape, gowning materials, Tyvek wrap, etc. <i>Extrinsic/foreign</i> : hair, insect parts, clothing fragments, metal, paint, etc.
Characterization	Symmetrical, asymmetrical/irregular, rigid, thick, thin, fragile, flexible, malleable, charged, chemical composition, metallic components, surface characteristics, bioreactivity, leachability, infectivity, sterility, infection risk
Source	Process related, foreign to process
Amount	Number per container, number of containers per lot
Manufacturing process mitigation	Point of filtration, particle reduction mitigation, sterilization procedures (terminally sterilized/aseptic processing), potential for

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	detection [100% visual inspection, acceptable quality level (AQL), alert/action limits based on trend and statistical analysis]
Frequency of Detection	Inspection process and product and package attributes

A key consideration is to assess the source of the particle and to assess the risk to the sterility of the drug product in this regard. The impact might be modified by additional manufacturing variables, such as terminal sterilization (as compared to aseptic filling) for determination of possible microbial contamination. Thus, understanding the manufacturing process and where the particles were introduced into the product is important in understanding the overall risk to the sterility assurance of the product. Microbial contamination and/or endotoxin introduction into the product should be considered in addition to pathophysiological considerations for particles in order for health care professionals to have a comprehensive understanding of potential impact to the patient.

As previously stated, the overall risk is determined by assessing the likelihood of harm, which may be determined qualitatively or quantitatively, occurring against the severity of the harm. Based on the assessment, a determination can be made as to the actions required for a particle (e.g., limit use to specific patient population, recall the lot). For particles, it might be possible to establish predefined acceptable risk to which manufacturers can refer; this should in no way prevent manufacturers from continual improvement of systems with a goal to eliminate all particles. For example, in-line filters for intravenous administration of parenteral solutions at the point of use would reduce risk for larger particles but not all subvisible particles. Allcutt et al. (1983) showed that in-line filtration delayed the onset of infusion phlebitis which is the only well-documented clinical complication of particle drug contaminants (91). When the risk to patients exceeds these established parameters, field action should be considered. When new types of failures or particles are discovered, a new risk assessment should be completed for the product to determine appropriate actions. These can include internal manufacturer actions as well as external field actions. Patient populations should be defined as part of the intended use of the product. A determination of appropriate actions should be based on label indications for product use rather than speculation on off-label potential uses.

In addition to the risk assessment, the risk of having limited product available to the public must be considered when assessing the true impact of product containing particles. This risk-benefit analysis provides a broader perspective with an understanding of the market conditions, including availability of an alternate product as well as potential drug shortages.

During a presentation to the U.S. Senate Committee on Health, Education, Labor and Pensions on December 15, 2011, Dr. Sandra Kweder, the deputy director of the Office of New Drug Development, FDA, stated that between January 2010 and September 2011, there were 127 episodes of drug shortages. Of these, 120 of the product shortages involved sterile injectable drugs (92). Further, 54% of these had product quality issues (particles, microbiologic contaminants, impurities, and stability). The availability of injectable drug products to patients due to potential risk from a single vial containing a particle creates an additional concern for patient safety. An outcome of a serious adverse event may be the exception and not the rule for injectable drug products with limited numbers of particles present in product released as “essentially free” of particles.

Quality Risk Management

The frequency or rate at which the particle is likely to occur should be determined and based on objective data. The presence of particles, for example, can occur as a single particle or as multiple particles contained within a single unit. One must consider the distribution of these particles, that is, whether the particle is an isolated event

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or its detection may implicate other units or batches. Further consideration should also be given to other products manufactured on the same production line.

A determination needs to be made as to how often the hazard, particles in this case, is likely to occur within a lot of product or across product lots. This assessment needs to take into account how widespread the particle hazard might be (e.g., one particle in one vial of one batch of product or ten particles in two hundred vials within twenty batches of product). To make this determination, a manufacturing site needs to conservatively assess the potential causes of the hazard and determine how long these potential causes have been occurring. Ultimately, even if the product is within the specified AQL, it is incumbent on the manufacturer to understand leading and lagging trends over time.

Manufacturers are encouraged to take a life-cycle approach to understand where particles may be generated, detected, and removed in a production process. Characterization of defects at the time of manufacture can provide valuable insights into the overall understanding of particle generation and subsequent mitigation to reduce the level of particles in products. Examples of items to review to determine a failure rate include, but are not limited to, the following: complaint data (trends or spikes), exception report/CAPA records, manufacturing batch records, supplier incoming reports/data, and inspection results of inventory as well as of retained samples. From this analysis, the manufacturing site can estimate at a base level the likelihood of occurrence for particles within the affected lot or lots of product.

Conclusion: Overall Medical Risk

Advances in process capability to reduce the particle burden, and continued vigilance for particles, have resulted in reported injuries being rare and most appear limited to the case reports associated with the infusion of significant quantities of precipitated admixtures. Additionally, macroscopic particles are more likely to be discovered prior to administration or can be too large to pass through the lumen of a needle. Further, even when larger particles are used purposefully to occlude AVMs (and they have been shown to cross into the venous circulation), there is rarely significant sequelae observed for these patients who are under close observation. However, clinical data suggests that product conforming to compendial particle limits can contain subvisible particles, which, can result in patients being exposed to low levels of particles as part of the practice of routine health care. The intravenous infusion of rigid particles greater than the 10-12 μm diameter of a pulmonary capillary will be occlusive. Once infused or injected an aggregate number of subvisible particles might impart a similar pathophysiological effect as a macroscopic particle, but more importantly, it is increasingly recognized that subvisible aggregates might induce an untoward immune response **(27)**. Thus, the often prevailing assumption, that larger particles pose a greater risk to patients rather than smaller particles, maybe a misconception.

An estimated 15 billion injectable doses of medicines are administered worldwide each year **(1)**. The evidence in this paper suggests that true patient harm associated with injections is extremely limited at the current the level of particle matter contained therein. While manufacturing processes, recall procedures, and clinical practices all contribute to this current state, current processes and procedures seem adequate. Small amounts of inert particles are unlikely to cause clinically meaningful patient harm. In addition, intramuscular and subcutaneous injections of sterile inert particles are very unlikely to cause meaningful patient injury. Further consideration should however be given to patients with end-organ disease, immune-compromised, or neonates and infants, as well as when particles are injected into closed spaces (e.g., intrathecal, intraocular, intraarticular) as these situations may have a greater potential for harm. There is insufficient evidence to conclude that intravenous injection of inert visible particles results in harm to patients **(47,71,93)**.

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As there is limited direct evidence of patient risk due to sterile, inert particles, it is reasonable to conclude zero tolerance should not be the requirement, but instead considered as the goal in manufacturing injectable drug products (**72,90,93**). Despite manufacturing process improvements and an increased surveillance with improved detection methodology, the manufacture of particle-free injectable product is not technically feasible, but continuous process improvement is an expectation.

A pragmatic approach ensuring high-quality drugs are available to patients is provided by USP <790> and <1790>. These chapters require a robust quality management system with a 100% inspection process, particle identification process, and a good investigation and monitoring process to ensure the occurrence and composition of particulates are understood. The composition of the particulate matter is very important when considering the medical significance when performing a risk assessment. To understand the composition, a firm would need a system to identify the particulate matter found in the drug product. USP <790> and <1790>, together with a medical risk-based approach, offer a practical strategy to ensure manufacturers meet expectations for visible particles. This standard was written considering both current manufacturing capability and patient risk. Following the recommendations in USP <790> and <1790> will provide the minimum expectations for manufacturing standards. For low-risk routes of administration, such as intramuscular and subcutaneous injections, the acceptance criterion of an AQL of 0.65% based on USP <790>, ensures the adequate safety of the product. There may be clinical circumstances where tighter AQL values (limits) may be appropriate for high-risk patients and for other routes of administration based on an evaluation of patient risk.

Globally, clinicians and patient populations are facing drug shortages, in part due to inconsistent product release and recall decisions related to the presence of particles and a lack of understanding of the impact to patient risk. Safety considerations related to particles in injectable drug products must be assessed on the basis of the factors identified in this paper, which include the intended patient population and method of administration. The decision to recall product from the market should be based on the context of the manufacturing trend history, complaint rate trending, and medical assessment of patient risk. Unless there are specific special circumstances, there should be no automatic requirement to recall a product lot for a single particle found in a single unit. While manufacturers strive to remove particles from injectable products, this paper has outlined considerations important to assessing the risk-benefit ratio of administering product to a patient. In general, notwithstanding high risk clinical circumstances and acknowledging there are limitations to reporting clinical events to particle infusion, the existing data suggest the overall risk to patients is generally low and the benefit of these treatments is generally significant.

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