Mitigating Particulate Risk in Injectables

What are the sources of such particulates in injectables and how should manufacturers apply the latest regulations to ensure best practice when producing sterile drug products?

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The rising prevalence of chronic diseases has driven the global injectable market up from $148bn to $581bn (2018-2022), mainly brought about by sterile injectable biologic drug products.[1] Illnesses driving this growth are predominantly cancer, diabetes, cardiovascular and other auto-immune conditions.[1] Commercial treatments are delivered to patients primarily in a sealed vial, pre-filled syringe with/without an auto-injector, or pre-filled cartridge in a device.

Drug manufacturers face increased pressure to minimize patient risk, which requires a robust, holistic control plan, and a continuous improvement mindset, to achieve the highest quality and safety. One important aspect is the control of visible particulates in injectable drug products. Having visible particulates in a parenteral product can cause patient harm. However, removing them can be challenging. FDA draft guidance, titled 'Inspection of Injectable Products for Visible Particulates', which is undergoing industry review, along with the latest European Good Manufacturing Practice (EU GMP) Annex I revisions, must be taken into account here.[2]

Particulate Types – Sources

Particulates can be introduced to the product throughout the manufacturing process and can originate from extrinsic, intrinsic, or inherent sources.

Visible particulate matter refers to visible particles in injectable drug products, which can range in size from a few microns to several millimeters. They are classified into three major types:

- **Inherent.** These particulates are related to biologic products, such as proteinaceous particles, liposomes and agglomerates
- **Intrinsic.** Examples are packaging materials, such as glass, rubber, or silicone oil. These can appear during storage; even if particulate matter is not present during manufacturing, it can be present later
- **Extrinsic.** These particulates are not part of the formulation, package, or assembly process, such as cellulose or fibres, and they represent the greatest risk to parenteral products.

Requirements and New FDA Guidance

Injection of particulate matter can result in clinical effects at the site of injection, such as phlebitis and pulmonary granulomas. It can also have systemic effects, such as infection and arterial emboli. The risk is related to numerous factors (Figure 1). There is no single set of criteria to anticipate potential patient risk. Therefore, the US Pharmacopeia (USP) Chapter <1790> Visual Inspection of Injections recommends that safety risk is assessed for each type of drug product being marketed. Regulatory agencies are providing further guidelines on this topic.

FIGURE 1 Factors Impacting Risk[3]

Patient Population	Injectable route of administration	Particle Type	Source of Particle	Volume Administered
Age	Subcutaneous	Subcutaneous	Process related	Time
Weight	Intramuscular	Intramuscular	Foreign	Frequency
Disease/Illness	Intravenous	Intravenous	Formulation related	
Immune status	Intraocular		Degradation product	
	Intrathecal			
	Etc.			

The FDA references USP Chapter <790> Visible Particulates in Injections, where injectables should be 'essentially free' of particulates. It adds that chapter compliance alone is not sufficient to achieve GMP compliance. It first defined the requirement 'essentially free from particulates' via an acceptance quality limit (AQL) of <= 0.65. Additionally, the US, EU and Japanese Pharmacopoeia provide information in several chapters (USP <790>, <1790>, as well as EP 2.9.20, 5.17.2 and JP 6.08) regarding the testing requirements.
The FDA's new guide on parenteral visual inspection, 'Inspection of Injectable Products for Visible Particulates', was released in December 2021 and is intended to address multiple areas that drug manufacturers must consider, including:

- The development and implementation of a holistic, risk-based approach to visible particulate control that incorporates product development, manufacturing controls, visual inspection techniques, particulate identification, investigation and corrective actions designed to assess, correct and prevent the risk of visible particulate contamination
- Clarify that meeting an applicable USP compendial standard alone is not generally sufficient for meeting the current GMP (cGMP) requirements for the manufacture of injectable products

While there is more covered in the FDA guidance, three pivotal areas of improvement are investigated below. Each has associated implementation approaches and highlights that high quality, elastomer components are foundational to minimizing risk.[2]

1. Intrinsic particulates: Manufacturers should control such particulates in advance of commencing manufacturing through careful selection and quality control of components, containers and closures, packaging materials and manufacturing equipment. Manufacturers should also evaluate trends in reject data at designated manufacturing facilities and use a life cycle management approach. Studies should be conducted to determine whether the manufacturing processes generate more particulates (Box A).
2. Manufacturers should not rely on downstream adjustments during manufacturing to justify a poorly designed product or process. Instead, quality should be built in to the manufacturing process, starting with early development phases and continuing during scale-up, process qualification studies and commercial manufacturing (Box B).
3. Process performance and product quality monitoring systems should provide information to ensure process control throughout a product's life cycle. Process performance measurements provide information on the state of control during manufacturing (Box C).

BOX A

4-Step Approach: Product design should include a suitable container closure system, so particle contribution can be studied during development

1. Formulation Optimization and container closure screening can be performed to mitigate risk of product-related intrinsic particles, like precipitate
2. Careful component selection, along with appropriate controls for receipt of components, to control risk of particulate
3. Process development studies utilizing selected components to understand impact of handling and equipment
4. Components with scalability should be considered during development.

BOX B

3-Step Approach: Quality by Design is a key part of drug development but is not often considered in packaging decisions

1. Manufacturers need to implement a holistic approach to quality
2. Quality should be embedded into every step and aspect of drug development and manufacturing
3. A risk assessment approach can be used when establishing an inspection programme.

BOX C

3-Step Approach: Process performance and product quality indicators can be used to evaluate effectiveness of visible particle control strategies

1. An effective visual inspection programme may result in an increase of visible particulates rejected due to quality issues, such as uncontrolled changes to the manufacturing process or inadequate practices by personnel
2. In contrast, a known process or product issue that does not result in an increased detection of particulates during visual inspection may indicate a lack of effectiveness
3. The choice of high-quality components in container closure systems helps build quality into the process. Vendors should be selected based on their willingness to work with clients to select fit-for- use components.

Requirements of Latest Revision of EU GMP Annex 1: Manufacture of Sterile Medicinal Products

In August 2022, the European Commission published the final, revised version of EU GMP Annex 1 relating to the Manufacture of Sterile Medicinal Products for human and veterinary use. The updated Annex 1 is scheduled to come into force on 25 August 2023 (with the specific exception of Chapter 8.123).[4] The review process was a collaborative effort with the WHO and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

The new version of EU GMP Annex 1 focuses on the need for a holistic contamination control strategy, with an expectation for a formal document that reflects the site-wide strategy for minimizing contamination, such as particulates, microbes and pyrogens, throughout the whole sterile manufacturing process. Another focus is guidance for the use of new technologies, such as restricted access barrier systems (RABSs) and isolators. In addition, greater attention has been given to an in-depth understanding of container closure integrity (CCI) and container closure integrity testing (CCIT).

Finally, the current revision embraces the philosophy of a holistic risk management system – the expected benefit being that there will be fewer deviations in manufacturing and improved supply chain integrity, which aims to help address the fact that 34% of FDA recalls for approved injectable products were attributed to issues with foreign particulates or a lack of sterility attributable to the container closure being suboptimal.[5,6]

Elastomeric Closure and Testing Methodology

Leading manufacturers of elastomeric components, such as stoppers, plungers and cartridges, have been instrumental in offering products with tightly controlled particulate specifications. Proven components should be used in drug development strategies and applied to commercial drug manufacturing. Selection criteria should anchor around a best-in-class elastomer with a barrier film; such components should be designed and manufactured using Quality by Design principles to mitigate risk.

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The selected components must include the tightest specifications for both sub-visible and visible particulates, which are managed through a control strategy and by manufacturers who analyse data trends from production to identify areas for continuous improvement.

Sub-visible particulates are just as important, though, as particulates exist on a size continuum from sub-micron to sub-visible through to visible. Generally, the smaller the particulate size, the higher the concentration. The particulate profile of a parenteral product can change over time. For example, during storage, smaller sub-micron particulates may agglomerate to form sub-visible or even visible particulate.

Specifications, testing and standards of elastomer components can vary between manufacturers. One approach for testing is applying ISO 8871-3:2003 Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 3: *Determination of Released- Particulate Count*. ISO 8871-3:2003 specifies methods for calculating the number of visible and sub-visible particulates, respectively, detached from elastomeric parts by rinsing. It does not specify particulate contamination limits. These are set by the manufacturer and end user.

METHOD APPROACH A: Apparatus for Method Approach A

Use of membrane filtration and manual microscopic analysis as a means of counting particulate matter ≥ 25.0 µm that are loosely adhered to elastomeric closures (Photo 1).

METHOD APPROACH B: Apparatus for Method Approach B

An automated vision system overcomes challenges of historic methods; Light Microscopy Image Analysis (LM/IA) software uses a proprietary software algorithm for detecting particles on membranes (Photo 2).

Although Method Approach A (as defined by ISO-8871-3:2003) requires the use of 100cm^2 surface area (SA) to perform the extraction of loose surface particulate, Method Approach B was developed to more accurately quantify sample sets of very low particulate level, by requiring an SA of 400cm^2 for the particulate extraction process.

Conclusion

All potential sources of particulates must be addressed to derive an effective contamination control strategy. Understanding particulate risk will enable a proactive approach to minimize downstream risk to patients; this ethos is being driven wholeheartedly by regulatory agencies. Addressing the impact of visible particulates must be from a holistic, risk-based standpoint, rather than testing quality at the end. Choosing high quality, elastomeric components is an essential part of an effective contamination control strategy and elastomer manufacturers are leading the industry's efforts to develop innovative solutions for addressing particulate testing needs with new products. These solutions support the need to meet tighter, evolving regulatory guidance on visible particulates.

Understanding particulate risk will enable a proactive approach to minimize downstream risk to patients; this ethos is being driven wholeheartedly by regulatory agencies

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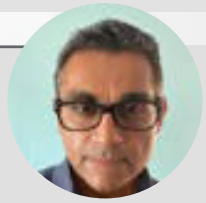

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