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Understanding and Applying the Updated FDA Guidance:

Inspection of Injectable Products for Visible Particulates

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Executive Summary

The growth of injectable products is driving efforts to tighten the control of particulate matter in pharmaceuticals. This white paper will discuss particulate risks, potential sources, and approaches to control particulates in injectables and review the draft regulatory guidance on the inspection of injectable products for visible particulates.

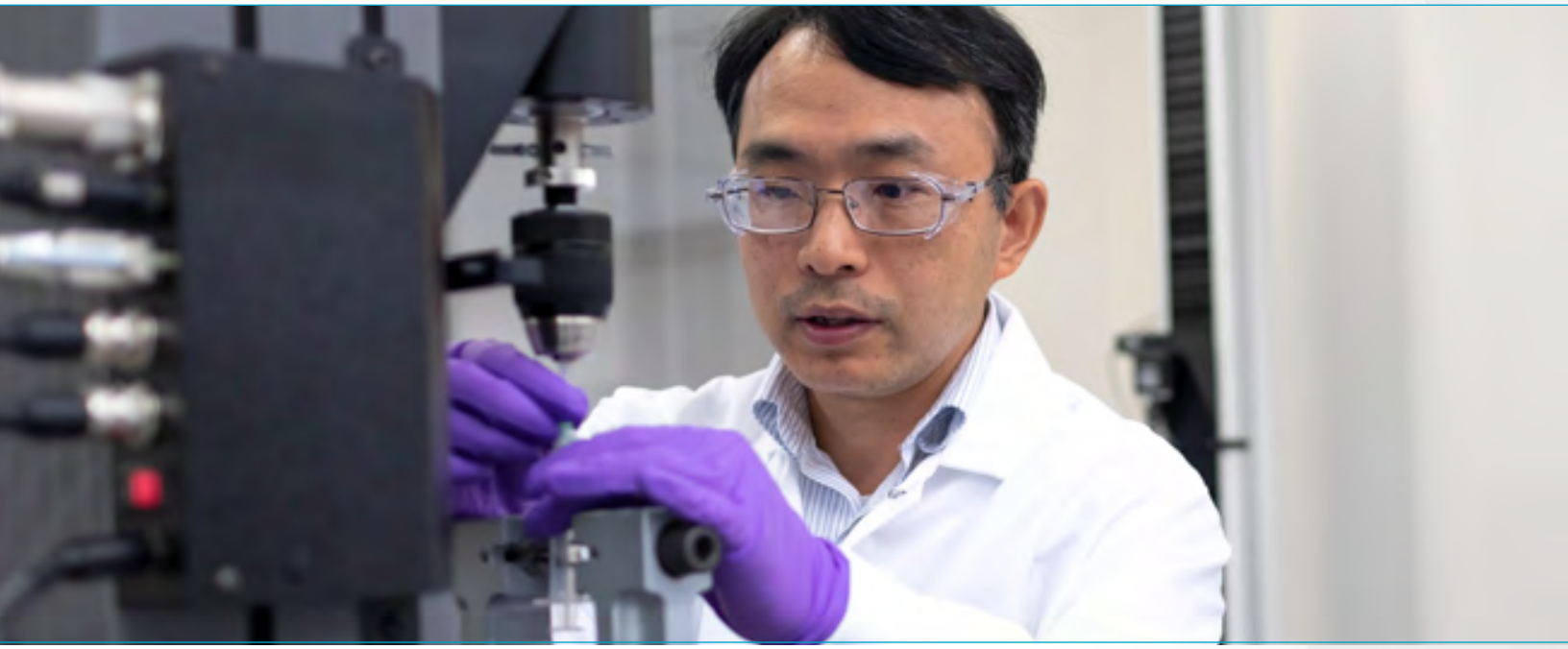
Understanding and Applying the Updated FDA Guidance:

Inspection of Injectable Products for Visible Particulates

Particulate control is essential for protecting both patient safety and a pharmaceutical company's reputation. The presence of visible or sub-visible particles is a common reason for recalls, which garner media attention and may be the public's first association with a drug. Analysis of 2022 FDA recall data shows that from 2018 through 2022, an average of 34% of recalls were due to particulate or lack of sterility attributable to container closure.[1,2]

In addition, trends in the current pharmaceutical market related to injectable products are driving the need for increased monitoring and control of particulate matter. For example, biologics and other specialized high-value treatments that must be injected are experiencing rapid growth, bringing an increased focus on patient safety and compliance and increasingly stringent regulations related to particulates. Furthermore, recommendations from the Food and Drug Administration (FDA) will focus on systems rather than components and will address the integrity of packaging and delivery systems used with injectables. These recommendations will further drive improvements in particulate control.

Particulate matter in injectables can have multiple origins. This white paper will first examine the risks posed by particulates, the potential sources and types of particulates, and approaches to detect and measure visible particulates in injectables. It will then review the draft FDA guidance[3] on inspection of injectable products for visible particulates and discuss how to apply the recommendations.



PARTICULATES: WHAT THEY ARE AND WHY THEY MATTER

Particulates in injections and parenteral infusions, according to the FDA, consist of "mobile undissolved particles, other than gas bubbles, that are unintentionally present in an injectable product."[4]

Why Is It Important to Control Visible Particulate?

The central reason for controlling visible particulate is to protect patient safety. These measures are critical to minimize the risk of clinical effects at the injection site and systemic effects like infection and venous or arterial emboli.

The risk of an adverse event from particulate contamination is affected by many factors, including:

- Patient population
- Injectable route of administration
- Particulate type, size, shape, number
- Source of particulate: process-related, foreign, formulation-related, degradation product
- Volume of drug administered: potential risk is higher with larger volume and is also affected by time and frequency

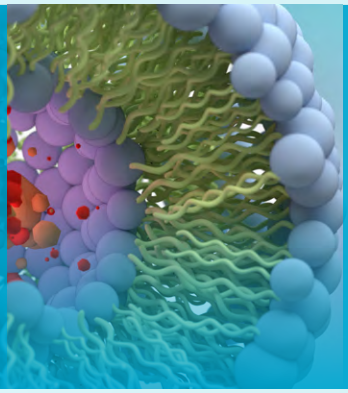
There is no single set of criteria to anticipate potential risk for the patient. Therefore, chapter <1790> of the United States Pharmacopeia (USP) recommends that safety considerations be assessed for each type of drug product being marketed.

Where Does Particulate Originate?

The three main types of particulates and their sources are as follows:

Inherent

These particulates are related to the biologic product, such as proteinaceous particles, liposomes, and agglomerates.



Intrinsic

Examples of intrinsic particulates are packaging material, such as glass, rubber, or silicone oil, which can be a necessary component of prefilled syringes (PFS) or other containers and precipitates of raw materials that result in interactions with packaging materials. Notably, these types of particulates can appear during storage of the drug product. That is, even if particulate is not present during manufacturing, it can be present later.

Extrinsic

Extrinsic particulates are those that are not part of the formulation, package, or assembly process. Examples include materials like cellulose, fibers from cleanroom/gowning garments, and particulates from personnel, such as hair or skin. These types of particulates represent the greatest risk to parenteral products.

How are Particulates Detected and Measured?

Particulates exist on a size continuum from submicron to subvisible to visible (Fig 1). 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 submicron particulates may agglomerate to form subvisible particulate, thereby decreasing the submicron particulate concentration and increasing the concentration of subvisible particulate.

Methods to detect subvisible and visible particulates vary depending on drug type, volume, and packaging. They include:

- Visual inspection
- Light obscuration
- Membrane microscopy
- Fluid imaging

USP <788> is used for testing subvisible particles ≥ 10 µm and ≤ 25 µm. There are separate specifications and sampling requirements for small-volume parenterals (containers with a nominal content ≤100mL) vs large-volume parenterals (containers with a nominal content >100mL), which can be found in the compendia. Light obscuration (LO) is the preferred analytical method, and membrane microscopy is only to be used if the former method does not meet given acceptance criteria or if light obscuration is not possible due to the nature of the product (for example, highly viscous or opaque).

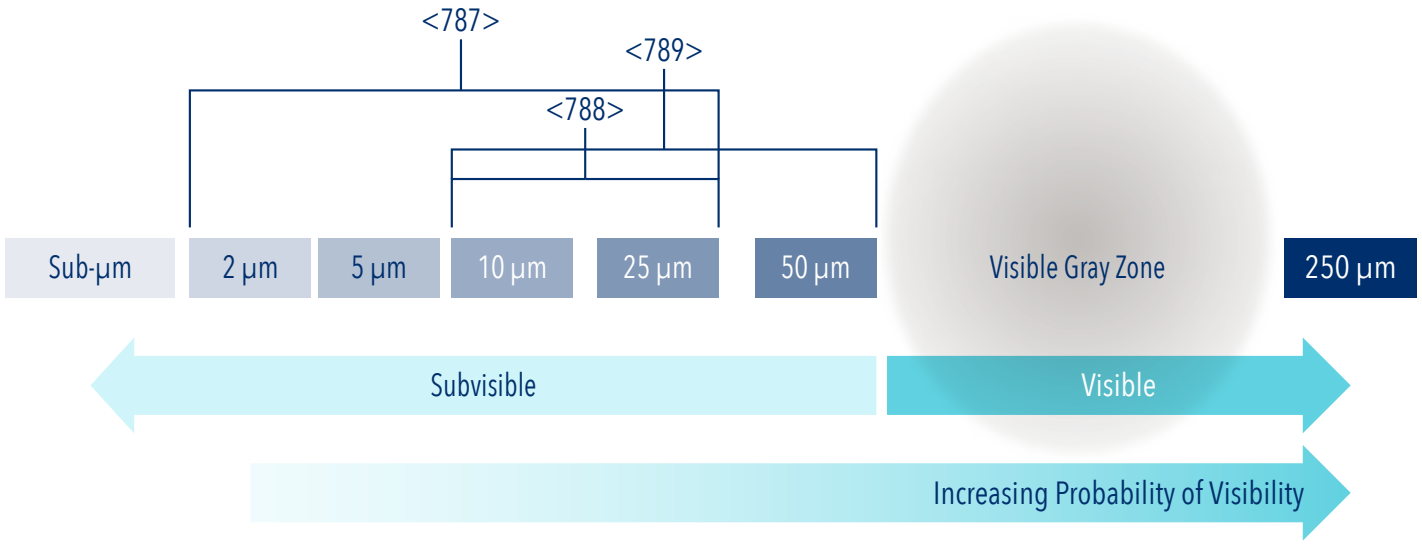
USP <787> is used for testing biologics and allows for smaller sampling volumes. Membrane microscopy is not recommended for USP <787> due to the difficulty of seeing proteinaceous (inherent) particles under standard brightfield illumination.

USP <789> is used for detection of subvisible particles in ophthalmics. This guidance overlaps USP <788>, covering particle sizes from 10 µm to 25 µm, but it includes testing particles up to 50 µm due to the risk associated with the presence of larger visible particles in an intravitreal injection. USP <789> has different acceptance criteria than USP <788>, which can be found in the compendia.

Although the compendia only have acceptance criteria for particles ≥ 10 µm, it is recommended in USP <1788> that particles ≥ 2 µm are monitored and controlled. It is also recommended that additional methodologies, such as fluid imaging, be used for testing of subvisible particles because imaging can characterize particles and differentiate between particle types (i.e., inherent, intrinsic, or extrinsic).

FIG 1

USP Guidance for Particulate Matter



OVERVIEW OF DRAFT FDA GUIDANCE "INSPECTION OF INJECTABLE PRODUCTS FOR VISIBLE PARTICULATES"

Draft FDA guidance, released in December 2021, "addresses 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."

The guidance also states that "meeting an applicable United States Pharmacopeia (USP) compendial standard alone is not generally sufficient for meeting the current good manufacturing practice (CGMP) requirements for the manufacture of injectable products."

The following principles are important in understanding and applying the draft guidelines and in implementing a holistic, risk-based approach:

Build In Quality

Considerations for quality and safety should be incorporated into the manufacturing process upstream and cannot be managed downstream through controls such as filtration. The presence of particulate can be compounded by many sources, including equipment and transfer bags, gowning, and engineering controls. Therefore, it's important to understand the equipment and the process and how they both can contribute to the visible particulate profile.

Component Evaluation and Selection Is Critical

It is important to choose components carefully to mitigate risk. Manufacturers can minimize risk and control intrinsic particulates before the manufacturing process through careful selection and quality control of components, containers and closures, packaging materials, and manufacturing equipment. In addition, studies can be conducted to determine whether the manufacturing processes generates particulate.

Following a risk-based approach during product development includes evaluating the risk level and sources of the visible particles observed so that they can be properly monitored and mitigated. Careful component selection is needed to control the impact of intrinsic particulates and ensure that the product is fit for its intended use. In addition to components, manufacturers should consider packaging materials and manufacturing equipment, as well as the potential impact of handling, washing and sterilization of that equipment.

Because intrinsic particles can form due to product-container interactions, process development studies may be necessary to evaluate the potential for this type of particle generation.

Visual Inspection Is Only Part of the Story

Although a well-established visual inspection program is an important aspect of the quality system for controlling visible particles, it's only part of the approach. As discussed above, it is necessary to take a holistic approach to quality. This means implementing a thorough inspection program that follows set procedures for inspection, statistical sampling plans (for Analytical Instrument Qualification, or AIQ, inspection), and acceptance/rejection criteria. These should all be established during development and reassessed during scale-up or transfer to another facility.

Manual, semi-automated, and automated inspection can all be part of a complete inspection program. Semi-automated inspection allows for automated handling (rotating or inverting) of the product with manual inspection of the product.

Following the 100% visual inspection, whereby defect product is removed (and subsequently investigated), Acceptable Quality Limit (AQL) testing is performed. This inspection must be performed manually. Although not expressly mentioned in the FDA guidance, USP <790> also notes that it is important to know the unacceptable quality limit (UQL) for the sampling plan used.

Use Certified Inspectors and Qualified Equipment for Product Inspection

Personnel conducting inspections must be adequately trained. A complete visual inspection program should include training materials, Standard Operating

Procedure, and testing. These tools should be continually reassessed to make sure they are appropriate during events like scale-up or transfers.

Equipment used for inspection programs should be calibrated, and qualified and automated inspection systems should be validated. Automated systems should meet or exceed human capabilities. Operators should be trained using defect photographs and defect units that contain visible particles that simulate production defects and simulate particles that would occur in the manufacturing process. After training is completed, operators can be qualified using a test kit containing 10-20% defect units.

Implement Systems to Measure Process Performance and Product Quality Throughout a Product's Life Cycle

Process performance measurements, such as deviations, in-process defect results, product control reports and investigations into equipment or facility issues, provide insight into the control of the manufacturing process.

Product quality indicators, like stability study results, complaints, and returned product, can help to determine if particulate matter in the product is related to an event. In this way, the presence of particle contamination can be used as an indicator for broader quality issues, such as inadequate process controls, or flawed personnel practices, such as inadequate gowning.

Using a life-cycle approach, event outputs can be used to improve the product or process controls and improve product quality overall.

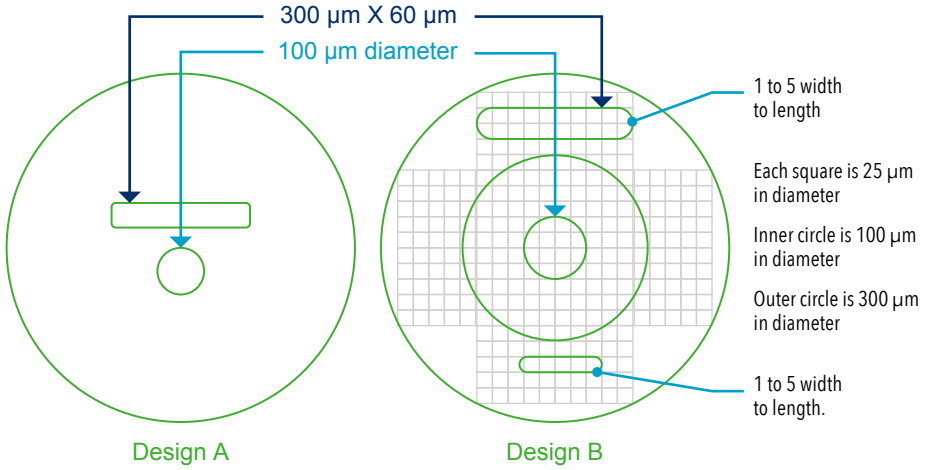
DEVELOPING THE PARENTERAL DRUG ASSOCIATION (PDA) TEST METHOD

The PDA Test Method, developed by an expert task force, addresses the historical lack of standard test methods for particle detection and serves to provide quantitative results for suppliers and pharmaceutical companies to discuss and compare particle data in a fair and meaningful manner.

The task force authored Technical Report 85: Enhanced Test Methods for Visible Particle Detection and Enumeration on Elastomeric Closures and Glass Containers, that was published by the PDA, to present details on the process used to develop and evaluate different particle inspection methods. Initial development studies compared different reticle designs, (Fig 2) operator training methods, and protocols to determine which method had the most reliable and repeatable results for particle detection. The multi-lab method qualification yielded results that demonstrated quantifiably the robustness of the particulate differentiation and counting process. The outcomes will be used to inform industry standard-setting organizations and to develop an elastomer particle enumeration method and training program. The findings point to the importance of protocol design and proper operator training and can be applied in the qualification process.

FIG 2

Two New Reticle Designs to Compare



HOW NOVAPURE® PRODUCTS HELP CUSTOMERS OVERCOME THE CHALLENGES OF PARTICULATES

Biotechnology companies that manufacture injectable drug products depend on high-quality components to help them meet the highest standards for safety and exceed regulatory guidelines. West's advanced solutions help customers mitigate particulate risks, with layers of controls built in. For example, NovaPure® components are built to deliver the highest possible particulate control, risk mitigation, drug-closure compatibility, excellent design, and yield maximization (see Fig 3).

FIG 3

NovaPure® Components Address a Range of Industry Challenges

Particulate Control	Tightest particulate specifications available for West elastomers Particulate Task Force focused on identifying and implementing further improvements
Risk Mitigation	Annual Quality and Operations product reviews Continuous improvement program Scalable transition from the West Ready Pack® system to full production NovaPure® components
Drug-Closure Compatibility	FluroTec® barrier film protects from drug-closure interactions Lot-to-lot extractables testing and analysis
Design Excellence	Available in tried-and-tested West designs suited to a range of vial types Critical dimensions specified in cpKs
Yield Maximization	Full vision verification to reduce end-of-line failure risks

Particulate Control

You can meet or exceed rising particulate standards with NovaPure® components so you will be more likely to reduce waste, increase throughput, and improve patient safety. This is achieved with:

- The tightest visible and sub-visible particulate specifications available for West elastomers.
- B2 coating, which helps you work toward reducing the amount of free silicone oil, which can interact with sensitive molecules in the form of protein aggregation.

Risk Mitigation

Every NovaPure® product is backed by robust risk mitigation strategies, which include:

- A dedicated particulate task force focused on identifying and implementing improvements to the NovaPure® component platform.
- Annual Quality and Operations product reviews.
- A Continuous Improvement Program that implements best practices across the West network through the process of define, measure, analyze, improve, and control.
- The scalable transition from the West Ready Pack™ containment system to full production NovaPure® components.

Drug-Closure Compatibility

As mentioned above in the Overview of the Draft Guidance, careful component selection is critical to particulate control and must ensure compatibility between the drug and the container closure. Customers can meet regulatory guidance by choosing:

- NovaPure® stoppers, coated with FluroTec® barrier film, which have been shown to reduce the risk of chemicals migrating from elastomers into the drug product.
- Lot-to-lot extractables fingerprint profile testing.

Design Excellence

Pharmaceutical manufacturers selecting packaging components can further mitigate risk by choosing products, such as NovaPure® components, that are manufactured under the principles of Quality by Design. This means that such components:

- Are available in tried-and-tested West designs suited to a range of vial types
- Meet critical dimensions specified in CpK

Yield Maximization

West customers rely on West's Envision™ automated vision inspection to maximize yield. This automated vision inspection process minimizes the risk that a packaged drug product will be rejected due to closure defects.

HOW WEST ANALYTICAL SERVICES AND INTEGRATED SOLUTIONS CAN SIMPLIFY YOUR JOURNEY

The West Pharmaceutical Services team is intimately familiar with injectable product containment and delivery systems. The services team works closely with customers to design studies and assist in navigating the challenging and evolving regulatory landscape. The West Analytical Services Particle team provides the following services:

- Subvisible particle testing on drug product and biologics that are BioSafety Level 2 or lower, including fluid imaging to allow for particulate characterization.
- Services such as USP <787>, USP <788>, and USP <789> testing with the ability to count and size sub-visible and visible particulate using technologies such as light obscuration, microscopy, and light microscopy/image analysis for automated particle detection.

YOUR PARTNER FOR PARTICULATES

As the market for biologic drugs continues to grow, manufacturers need to protect patient safety and comply with evolving regulatory requirements. In your drug development journey, keep the following points in mind:

- It is important to adopt a holistic, risk-based approach when considering the challenges of bringing a biologic drug to market and addressing the risk of particulate contamination.
- Quality by Design, a key principle in drug development, must also apply to drug packaging and delivery components.
- Drug manufacturers can rely on West for support in their efforts to comply with tighter regulatory expectations and for innovative solutions to the challenges posed by particulate control and testing.
- NovaPure® components and West Analytical Services and Integrated Solutions can help you meet tighter, evolving regulatory guidance regarding visible particulate.

If you would like to learn more about how West NovaPure® components, Integrated Solutions, and Analytical Services can help with your drug product containment and delivery challenges, please visit us online.

We invite you to Contact Us so that we can connect you with an account manager in your region or visit our online store, an easy and convenient way for you to order West NovaPure® components.

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