Inspection of Injectable Products for Visible Particulates

Guidance for Industry

DRAFT GUIDANCE

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TABLE OF CONTENTS

Inspection of Injectable Products for Visible Particulates Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Visible particulates in injectable products can jeopardize patient safety. This guidance 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.[2] The guidance also clarifies that meeting an applicable United States Pharmacopeia (USP)[3] compendial standard alone is not generally sufficient for meeting the current good manufacturing practice (CGMP) requirements for the manufacture of injectable products. The guidance does not cover subvisible particulates[4] or physical defects that products are typically inspected for along with inspection for visible particulates (e.g., container integrity flaws, fill volume, appearance of lyophilized cake/suspension solids).

For the purpose of this guidance:

- *Particulates* refer to mobile, undissolved particles other than gas bubbles that are unintentionally present in an injectable product.[5] They vary in nature (e.g., metal, glass,

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, Center for Veterinary Medicine, Office of Regulatory Affairs, and Office of Combination Products in the Office of the Commissioner and in consultation with the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] Visual detection of a particulate is a probabilistic process that depends on, among other things, the product and the size and shape of the particulate (see United States Pharmacopeia General Chapter <1790> *Visual Inspection of Injections*). Therefore, threshold studies should be conducted to determine the size of visible particulates that can be reproducibly detected by trained personnel with near normal visual acuity. For more information about threshold studies, see section IV in this guidance.

[3] USP references in this guidance refer to USP 42–NF 37.

[4] In general, subvisible particulates are those that cannot be seen with the naked eye. See USP General Chapters <788> *Particulate Matter in Injections* and <787> *Subvisible Particulate Matter in Therapeutic Protein Injections* for information about subvisible particulates control.

[5] See, e.g., USP General Chapter <788>.

dust, fiber, rubber, polymer, mold, degradant precipitate) and can be divided into three categories[6]:

- *Inherent particulates* are particulates that are an innate product characteristic.
- *Intrinsic particulates* are particulates that are derived from the manufacturing equipment, product formulation, or container system.
- *Extrinsic particulates* are particulates that originate from the manufacturing environment and are foreign to the manufacturing process.

- *Injectable products* generally refer to injectable human drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), injectable animal drugs approved under section 512 or conditionally approved under section 571 of the FD&C Act, and injectable biological products licensed under section 351 of the Public Health Service Act. In some cases, the injectable product may be a drug or biological product constituent part of a combination product, such as a drug or biological product prefilled into a syringe (see 21 CFR part 3).[7]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. STATUTORY AND REGULATORY FRAMEWORK

Under section 501 of the FD&C Act, a drug product, including an injectable product, is deemed adulterated if:

[6] See USP General Chapter <790> *Visible Particulates in Injections*, which describes inspection procedures used to demonstrate that injectable products are essentially free from particulates, and USP General Chapter <1790>, an informational chapter that provides recommendations on inspection programs for visible particulates covering the injectable product life cycle.

[7] This guidance generally cites regulatory requirements for drugs and biological products, but where appropriate, also cites relevant requirements for combination products. The regulatory requirements for combination products derive from the statutory and regulatory requirements applicable to their constituent parts, which do not lose their distinct regulatory identity when they become part of a combination product. See, e.g., draft guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (February 2019), which, when final, will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. See also FDA's Combination Products Guidance Documents web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/combination-products-guidance-documents.

- "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" (section 501(a)(2)(A)).

- "It is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess" (section 501(a)(2)(B)).

- "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" (section 501(b)).[8]

- It is a new animal drug that is unsafe within the meaning of section 512 (section 501(a)(5)).

Adherence to FDA's CGMP requirements as set forth in section 501 of the FD&C Act and 21 CFR parts 210 and 211 for drug, animal drug, and biological products; §§ 600.10 through 600.15 for biological products; and part 4 for combination products[9] is essential for the control of visible particulates in injectable products.

Adherence to compendial standards can also assist manufacturers in complying with CGMP requirements (see, e.g., §§ 211.194(a)(2) and 211.165(e)).

USP General Chapter <1> *Injections and Implanted Drug Products (Parenterals)—Product Quality Tests* states that "[t]he inspection process should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates" as defined in USP General Chapter <790> *Visible Particulates in Injections*. Injectable products with a USP monograph are required to meet the applicable criteria from these USP General Chapters (see section 501(b) of the FD&C Act). Noncompendial products should also be "essentially free from visible particulates" as defined in USP General Chapter <790>.

Applying acceptance criteria, such as the criterion outlined in USP General Chapter <790>, is an important component of the overall visible particulate control program, but meeting these acceptance criteria is not alone sufficient to ensure compliance with the applicable CGMP requirements identified above, which cover a broader array of manufacturing practices than product inspection. Full compliance with CGMP requirements is needed to ensure the continued supply of pure, safe, and effective injectable products.

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[8] *Official compendium* is defined in section 201(j) of the FD&C Act as "the official United States Pharmacopeia, official Homoeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them."

[9] 21 CFR part 4 establishes the CGMP requirements and postmarketing safety reporting requirements for combination products. See also guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).

In accordance with USP General Chapter <1>, injectable products should be prepared in a manner designed to exclude visible particulates, and the inspection process should be designed and qualified to ensure that the products are essentially free of visible particulates. Each final container must be inspected (100% inspection) using a qualified method to detect particles within the visible size range, and all units that are found to contain visible particulates must be rejected (§§ 211.160(b) and 211.110(c) and (d); see also USP General Chapter <1>).

Depending on the clinical risk profile associated with a specific product, FDA may expect that product to comply with stricter standards than those set forth in the compendia in order for those products to meet CGMP requirements.[10] Applicants implementing postapproval changes to their manufacturing processes that are intended to ensure a product is essentially free from visible particulates must follow existing FDA regulations and should follow existing FDA guidance.[11]

III. CLINICAL RISK OF VISIBLE PARTICULATES

The clinical manifestations of adverse events caused by particulate contamination vary and may depend on the route of administration (e.g., intravascular, intravisceral, intramuscular), patient population, and nature or class of the particulates themselves (e.g., physical size or shape, quantity, chemical reactivity to certain cells or tissues, immunogenicity, infectivity, carcinogenicity). Particulates in intravascular or intravisceral injections generally can cause more adverse events than those in subcutaneous or intramuscular injections. According to published case reports (Langille 2014; Doessegger et al. 2012), serious adverse events involving injectable products contaminated with visible particulates have included:

- At the systemic level, infection and venous and arterial emboli (thrombotic or nonthrombotic).
- Microscopic emboli, abscesses, and granulomas in visceral organs.
- Phlebitis, inflammatory reactions, granulomas, and infections at injection sites.

Furthermore, different patient populations may have different risks for developing adverse events after exposure to injectable products contaminated with particulates. Risk factors include age

[10] There are statutory CGMP requirements applicable to products addressed in this guidance. For human drug products, see sections 505(d)(3), 505(j)(4)(A), 505(b)(1)(D), and 505(j)(2)A)(vi) of the FD&C Act. For animal drug products, see sections 512(d)(1)(C), 512(c)(2)(A)(i), 512(b)(1)(D), and 512(n)(1)(G) of the FD&C Act. For biological products, see section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)(2)(C)). See also 21 CFR parts 210 and 211, §§ 600.10 through 600.15, and part 4.

[11] For approved new drug applications, see 21 CFR 314.70 and guidance for industry *Changes to an Approved NDA or ANDA* (April 2004). For approved biologics license applications, see 21 CFR 601.12 and guidances for industry *Changes to an Approved Application: Biological Products* (July 1997), *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997), and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021). For approved new animal drug applications, see 21 CFR 514.8 and guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANADA* (May 2007).

(e.g., pediatric and elderly patients), personal or family history of thrombophilia, major surgery, cancer, trauma, underlying infection, autoimmune disease, diabetes-associated late-stage vasculitis, obesity, and smoking.[12]

Applicants should consider these clinical risk factors when developing their quality target product profile and in establishing an appropriate control strategy and acceptance criteria for visible particulates.[13]

IV. QUALITY RISK ASSESSMENT

Visible particulates can have a negative effect on overall product quality. To ensure product quality and to limit clinical risk, manufacturers should conduct a risk assessment during product development.[14] During this risk assessment, manufacturers should identify the typical visible particulates that could contaminate the injectable product and characterize their size ranges, quantity, and composition; determine risks for each type; and provide a visual description (e.g., photographs or drawings of typical defects) to be used for training purposes.[15] Manufacturers should also consider the potential sources of particulates, appropriate analytical methods to monitor them, and mitigation strategies to prevent their presence in the final product.

Different considerations are relevant depending on the category of particulates found during the risk assessment:

- **Inherent particulates** are associated with specific products or their formulations—such as proteinaceous particulates, liposomes, or agglomerates—and are considered part of the quality target product profile. Their presence should not be cause for rejection of individual units or product batches if they are a property of the approved product and product release specifications are met. For hard-to-inspect products containing inherent particulates, such as suspensions or emulsions, manufacturers should develop supplemental testing methods to ensure adequate detection of visible particulates (see section V, Visual Inspection Program Considerations). In addition, manufacturers should monitor time-dependent changes during stability testing that may lead to increases in size or number beyond the approved acceptance criteria.

- **Intrinsic particulates** can be related to the manufacturing process. Such particulates could come from components, containers and closures (e.g., glass vials, rubber stoppers), and product contact processing equipment (e.g., tubing, filters, gaskets). Manufacturers should control such particulates before the actual manufacturing process through careful

[12] The potential clinical risk is further supported by animal studies from the literature (Pesko 1996; Barber 2000; Langille 2014). In animals massively infused with particulates, histopathology findings include endothelial cell injury in pulmonary capillaries, pulmonary capillary microscopic thrombi, pulmonary microscopic granulomata, and inflammatory hepatitis (Liu et al. 1992; Jones and Warren 1992; Bautista et al. 1992).

[13] See International Council for Harmonisation (ICH) guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

[14] See section II.3 of Annex II in ICH guidance for industry *Q9 Quality Risk Management* (June 2006).

[15] See section V.C in this guidance for information about training.

selection and quality control of components, containers and closures, packaging materials, and manufacturing equipment. Additionally, manufacturers should conduct studies to determine whether their manufacturing processes generate particulates. Similarly, manufacturers should study and understand the impact of handling, washing, and sterilization processes on manufacturing equipment (i.e., wear and tear) that could lead to particulate generation over time. Such process development studies can minimize intrinsic particulates by informing selection of the appropriate handling, washing, and sterilization procedures and establishing equipment life spans. Manufacturers should also evaluate trends in reject data at designated manufacturing facilities and use a life cycle management approach to monitor and control process-related intrinsic particulates in their final products.

Intrinsic particulates can also be related to the formulation or stability of the product or its container closure (e.g., particulates formed because of precipitation of active pharmaceutical ingredients, glass delamination, or protein-silicone oil interaction). These types of particulates can form after product release and can change in size or number when the product is stored. Manufacturers should study the risk of this type of intrinsic particulate forming under accelerated or stressed conditions in the product development phase to determine particulate characteristics and any time-dependent particulate formation or growth that can occur. In addition, an analytical method suitable for characterizing and monitoring product-specific particulates should be developed. A robust product design achieved through formulation optimization and container closure screening during development is critical to reduce the formation of product-related intrinsic particulates. Information obtained from these studies can be used to support product-specific inspection processes (e.g., particulate seeding for test kits with known product-specific intrinsic particulates, particulate identification, and rejection classification).

- **Extrinsic particulates** arise from sources other than the formulation's components, the containers and closures, or the manufacturing equipment's product contact surfaces. These particulates, derived from materials not intended to be in contact with the injectable product, can negatively affect product quality and could indicate possible microbial contamination or another CGMP issue. Their presence in the final product can occur because of poor conditions in the manufacturing facility (e.g., poor environmental control; equipment design, age, and maintenance; facility location, construction, and maintenance; material and personnel flows). Manufacturing facilities must be CGMP compliant and of appropriate design to support the manufacture of injectable products (see 21 CFR part 211, subpart C; § 211.63; and part 4).

Manufacturers should not rely on downstream adjustments during manufacturing to justify a poorly designed product or process. Instead, quality should be built into the manufacturing process, starting with the development phase and continuing during scale-up, process qualification studies, and commercial manufacturing.[16] Successful management of visible

[16] See guidance for industry *Process Validation: General Principles and Practices* (January 2011).

particulates also includes vigilant assessment of the state of control, early detection of poor process performance, and effective process improvement throughout the product's life cycle.

Proactively addressing risk is an important part of a life cycle approach to visible particulate control. Formal risk assessments conducted during product development contribute to process understanding and form a foundation for knowledge management. Their results should be used to establish adequate product-specific production controls and clearly defined in-process alert and action limits for particulates. Threshold studies should be conducted to determine the characteristics (e.g., size, shape, color) of visible particulates that can be reproducibly detected by trained personnel. These threshold studies can also be the basis for establishing particulate standards that will be used to establish inspection procedures, help avoid inspection bias, and allow manufacturers to verify their manufacturing processes are in a state of control.

V. VISUAL INSPECTION PROGRAM CONSIDERATIONS

Visual inspection can be viewed as part of a larger program to ensure that injectable products are essentially free of visible particulates.[17] During injectable product development, manufacturers should establish procedures for inspecting the product, statistical sampling plan(s), acceptance/rejection criteria, and procedures for evaluating inspection results. Inspection procedures carried over from another site or another product may not always be suitable for a new product.

During process scale-up or transfer to contract manufacturers, the visual inspection methods should be assessed to confirm they are still appropriate and valid at the new scale or manufacturing site. The visual inspection program should allow for appropriate adaptations based on knowledge gained throughout the product's life cycle. For example, the inspection procedures and/or analytical and statistical methods may need revision if the batch size, manufacturing process, or conditions change.

In addition to inspection, a visible particulate control program should include the training and qualification of operators and investigation of discrepancies, including root cause analysis, corrective actions, and preventive actions.

Trained and qualified personnel, automated inspection technology, or a combination of both should be used to inspect each unit of injectable product for visible particulates (hereinafter *100% inspection*). In addition, the quality unit should sample each batch for acceptance quality limit (AQL) testing.[18] A visual inspection program should ensure that any visible particulates present in the batch at the time of release are only those that have a low probability of detection because they are of a size approaching the visible detection limit. This section covers 100% inspection, statistical sampling, training and qualification, quality assurance through a life cycle approach, and actions to address nonconformance.

[17] See, e.g., USP General Chapter <1790>.

[18] *Acceptance quality limit* refers to the "quality limit that is the worst tolerable process average when a continuing series of lots is submitted for acceptance sampling" (see ASTM E456, Standard Terminology Relating to Quality and Statistics).

A. 100% Inspection

Manufacturers should conduct 100% inspection during the stage at which there is the greatest likelihood that visible particulates will be detected in the final container (e.g., before labeling to maximize container clarity). Manufacturers should ensure that the equipment used and the physical environment where visual inspection will be performed are designed to minimize variability and maximize detectability in the inspection process.

Important factors to consider follow.

1. Components and Container Closure Systems

Visible particulate contamination could be traced to components or container closure systems. To ensure visible particulate control, manufacturers must have written procedures for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and product containers (including devices and device components that contact injectable products) (§ 211.80; see also part 4). Such procedures must ensure that components and containers and closures are tested or examined and approved, as appropriate, before use in manufacturing (§ 211.84). Containers and closures must not alter the product's safety, identity, strength, quality, or purity (§§ 211.94(a) and 600.11(h); see also part 4).

2. Facility and Equipment

To comply with CGMP requirements, manufacturing facilities must be designed, constructed, and outfitted with equipment to prevent injectable products from being contaminated with particulates. Applicable CGMP regulations include:

- Buildings and facilities (§§ 211.42 through 211.58 and 600.11).
- Equipment design, size, and location (§ 211.63).
- Equipment construction (§§ 211.65 and 600.11).
- Equipment cleaning and maintenance (§§ 211.67 and 600.11).

Inspections can be conducted manually and/or using a range of automated inspection techniques:

- For **manual inspections,** the inspection station should have a backdrop of one or more solid colors (e.g., black and white) to provide adequate contrast and to allow maximum visibility of product contents. The light intensity of the inspection station is also critical to achieving maximum visibility. Manufacturers should consider container color, size, and shape as well as product characteristics when determining the ideal intensity.

- During **semi-automated inspections,** a machine rotates the product at a constant rate past a trained inspector's field of vision. Rejected products are removed mechanically or by hand.

- **Automated inspection technology** can be used as part of an investigation in the inspection process for injectable products, as a replacement for manual inspection, or as an additional quality assurance step. Automated inspection technology can use different wavelengths and sensors to detect hard-to-see particulates in sterile powder, suspensions, or light-protected injection products for which visual inspection is not completely effective.

Regardless of the technique—manual, semi-automated, or automated—the inspection environment should be free from distractions and extraneous light, and the inspection rate should be qualified and should allow for thorough visual inspection. Manufacturers can operate independent inspection stations as separate units or units that are connected in a series. Some inspection equipment does not require controlled separate facilities for visible particulate inspection.

For manual and semi-automated inspections, the inspection environment should be ergonomically designed for inspector comfort.

For semi-automated and automated inspections, equipment must be routinely calibrated, inspected, or checked in accordance with a written program designed to ensure proper performance, and records of those calibration checks and inspections must be maintained (§ 211.68). Equipment should also be properly qualified. See section V.C, Training and Qualification, for more information.

When compared with manual inspection, automated inspection technology may improve detectability of visible particulates because machine variability is generally easier to control than the variability individual personnel can bring to tasks performed repetitively over time. In some cases, the technology can detect higher levels of specific visible particulates. In others, it can detect particulates at the lower end of the visual inspection range with greater statistical reliability when compared with manual and semi-automated inspection of the same product (Melchore 2010).

Automated inspection technology may allow manufacturers to better control product quality. Manufacturers may need to adjust in-process action and alert limits if they change from manual to automated inspection. Adjustments should be based on statistical process and batch data analysis obtained during evaluation and validation of automated inspection equipment.

Among the automated inspection technologies currently in use (e.g., high-speed industrial camera, visible diode array, X-ray, near-field radar, ultraviolet and near infrared spectroscopy), each has its advantages and disadvantages but, if properly implemented, all can substantially improve the accuracy of visual inspection.

3. Process

Manufacturers should conduct inspection feasibility studies for visible particulate detectability, unit inspection duration, illumination, and fatigue time frame. These studies should be scientifically based and analyzed using appropriate statistical methodology. Depending on the

study results, manufacturers may need to adjust particulate standards or inspection processes or, in some cases, change equipment to improve accuracy and reduce patient risk.

Manufacturers must implement written procedures for production and process controls (§ 211.100), which should cover each aspect of the visual inspection process. Such procedures should cover handling of the units (e.g., swirling, inversion, distance from light), maximum length of the inspection period without a rest break, and disposition and documentation of products that were rejected based on the results of the visual inspection.

A complete program[19] for the control and monitoring of particulate matter must include written procedures for production and process control, sampling and testing of in-process materials, and control of microbiological contamination that are designed to minimize the occurrence of visible particulates, identify affected batches of injectable product, and facilitate investigation to determine the sources of visible particulates (§§ 211.100, 211.110, and 211.113).

Written procedures should also cover how to conduct 100% inspections to ensure batches are essentially free of visible particulates. All records must be documented in accordance with applicable regulatory requirements (§ 211.188(b)(5); see also § 600.12). Adequate written procedures can contribute to a more thorough understanding of the potential sources and quantity of visible particulates, leading to improvements in process design. The increased level of understanding would also promote a more robust particulate control program and higher quality investigations (see § 211.192).

4. Special Injectable Product Considerations

Large volume parenterals should undergo the same level of inspection as small volume injectable products. In many cases, patient risk from particulate contamination is higher for large volume parenterals than for small volume injectable products because of the volume of product administered and the potential for a patient to receive a continuous administration over many days. Packaging and labeling of large volume parenterals (e.g., overwraps and printing on the flexible bags) can interfere with visual inspection. Large volume intravenous bags that have an outer bag can be particularly challenging to inspect. Manufacturers should take appropriate measures to ensure adequate 100% inspection of these products. Supplemental destructive testing may also be warranted to ensure these products are essentially free of visible particulates if the packaging does not allow for the identification of particulates within the accepted visible size range.

Opaque products and containers (e.g., lyophilized powders, suspension products, tinted vials) present obvious challenges to visual inspection. Using advanced technologies such as those described in section V.A.2 in this guidance (e.g., X-ray spectroscopy) can help, as can supplemental destructive testing after the 100% inspection, which provides additional assurance of product quality. Supplemental destructive testing may not be warranted, however, if the technology used in the 100% inspection is validated to meet or surpass human inspection

[19] USP General Chapter <790> notes that "a complete program for the control and monitoring of particulate matter remains an essential prerequisite," but it does not describe such a complete program.

capabilities. Manufacturers should conduct a feasibility study to demonstrate the suitability of the technology selected for the specific product.

B. Statistical Sampling

Following 100% inspection, manufacturers should employ statistically sound sampling plans, validated inspection methods, and appropriate acceptance criteria to ensure that each product batch meets a pre-established AQL for visible particulate contamination. This is consistent with USP General Chapters <1> and <790>; however, a more stringent sampling plan and acceptance criteria may be appropriate for higher risk products.

A sampling plan allows the user to make a specific statistical quality statement[20] about the attribute of interest (e.g., a defect) in a batch based on the sample size and sampling locations. Manufacturers should select their sampling plans in accordance with the risk for a particular type of product defect. CGMP regulations require manufacturers to ensure that batches of injectable products meet appropriate specifications and statistical quality control criteria as a condition for their approval and release (§ 211.165).

Manufacturers should quantify the following parameters with respect to design and use of sampling plans[21]:

- Operating characteristic curves developed for each defect classification or quality attribute that is being tested.

- Accept/reject criteria, AQL, and unacceptable quality limit (also referred to as *rejectable quality limit*, *limiting quality*, or *lot tolerance percent defective*).

The methodology and acceptance criteria for the statistical sampling plan should consider patient risk, particulate type, and product and container characteristics that may interfere with particulate visibility. For example, an adequate sampling plan with an acceptable AQL for nondestructive/destructive testing could follow ASTM E2234.[22] Firms that wish to propose an alternative minimum standard for their specific product should ensure that there is a risk-based justification for the proposed standard.

Extrinsic particulates identified during 100% inspection or AQL of the batch—which suggests the presence of filth, sterility assurance issues, or other CGMP violations—may result in product that could be considered adulterated, even if the statistical sampling acceptance criteria are met. Likewise, multiple visible particulates (extrinsic or intrinsic) within a single container may be indicative of manufacturing problems and should trigger increased scrutiny of the batch.

[20] A statistical quality statement could be, for example, “There is 95% confidence that there are no more than X% defects in the batch.”

[21] See ASTM E2234, Standard Practice for Sampling a Stream of Product by Attributes Indexed by AQL; ASTM E456, Standard Terminology Relating to Quality and Statistics.

[22] ASTM E2234 is equivalent to the ANSI/ASQ Z1.4 standards referenced in USP General Chapters <790> and <1790>.

If retained samples are used to evaluate the suitability of product in distribution (such as in the case of product complaints), manufacturers should consider additional factors such as historical data for the facility and/or product when evaluating the suitability of a given product batch.

According to § 211.194(a)(2), "the suitability of all testing methods used shall be verified under actual conditions of use." Manufacturers also must validate and document tests used to ensure that each batch of the product conforms to final specifications for release and distribution (§ 211.165(e)).

C. Training and Qualification

Only certified inspectors and qualified equipment should be used to inspect injectable products for visible particulates. Personnel conducting inspections (100% inspection and AQL inspection) must be adequately trained (including, as appropriate, periodic retraining or requalification) (§§ 211.25 and 600.10(b)).

Formalized training and qualification programs promote consistent performance by individual inspectors or automated inspection machines and help minimize variability among different inspectors or machines (Melchore 2011). The program can include a combination of training materials, standard operating procedures (SOPs), on-the-job training, and testing. Inspector candidates should be trained in the relevant CGMP requirements and should have normal near visual acuity (with or without the use of corrective lenses) and no impairment of color vision (Ricci et al. 1998).

Regarding inspection equipment:

- The specific backdrop and light intensity selected for manual inspection stations should be qualified.

- Semi-automated inspection equipment should be properly calibrated and qualified at a specific vial-spin and belt speed. Lighting should also be qualified to allow for accurate human detection of defective products.

- Automated inspection machines should be validated to meet or surpass human inspection capabilities and can be qualified using training standards or artificial intelligence technology.

For personnel qualification and automated inspection systems validation, a mixture of good injectable product units and defective units containing visible particulates should be used (Melchore 2011). This test set should be prepared and approved by quality assurance staff. Manufacturers should develop libraries of defective units from samples collected throughout the product life cycle, samples created to simulate production defects, or samples purchased to be representative of the types of particulates likely to occur for the drug product and its manufacturing process. Quality assurance staff should review the library of defective samples and compare the samples to established standards for proper classification. The library should contain examples from the lower limits of visual detection determined in the threshold studies. If

a new particulate matter defect is identified, it should be analyzed to determine its source and added to the training library.

Typically, the percentage of defective units in a test set should not exceed 10–20 percent, and the test set quantities should be sufficient to provide an adequate degree of confidence in the test results. Trained inspectors should review defective units before they are included in the test set to determine if the visible particulates in them can be detected under normal conditions, and the identity of defective units should be masked to test subjects. The quality unit should control the test sets to ensure that qualification tests are not manipulated or biased.

The quality unit should also establish and approve qualification protocols that identify the sample test sets, test duration, grading method for test results, documentation of test results, acceptance criteria for certification, and actions to be taken for test failures. The protocols should also specify requalification testing methods and frequency.

D. Quality Assurance Through a Life Cycle Approach

Process performance and product quality monitoring systems should provide information to ensure process control throughout a product's life cycle. Process performance measurements (e.g., deviations, in-process defect results, statistical process control reports, equipment and facility breakdowns) provide information on the state of control during manufacturing. Product quality indicators (e.g., stability test results, complaints, returned product) can help determine whether particulate matter in the product caused an event. Similarly, field alert reports and adverse event reports could reveal possible particulates-related quality issues. This information should be used to evaluate the effectiveness of visible particulate control strategies.

Trends of increased particulate contamination, identification of new types of particulates, or particulates that exceed alert or action limits may indicate a flaw in product or process design. For example, inconsistent product quality could be caused by any one or a combination of these factors:

- Inadequate controls of components, containers, or closures.
- A product formulation that is not stable.
- Uncontrolled changes to the manufacturing process.
- Equipment and facilities that are not suitable for their intended use.
- Personnel practices that generate particles.

If an investigation reveals a flaw in product or process design, it is important to redesign the product or process to ensure reproducible product quality and reduction of particulate matter.

E. Actions To Address Nonconformance

Manufacturers must investigate quality discrepancies identified through the inspection process, quality control testing, complaints, or as a result of a batch failure and extend their investigation to other batches that may be affected (§§ 211.192 and 211.198). Such investigations should seek

to identify the particulates and categorize them (intrinsic or extrinsic) because the presence of certain categories of particulates could indicate CGMP issues or sterility failures.

Investigations can include tightened sampling plans, examination of particles to understand their origin, and evaluation of batch release impact. The investigation should determine the sources of the variation and identify appropriate corrective actions and preventive actions. The investigations may also reveal opportunities to enhance the robustness of particle detection (e.g., improvements to the 100% inspection or AQL inspection program).

Investigations of manufacturing inspection outcomes should be conducted in situations such as the following:

- Individual or total defect limits are exceeded.
- A batch fails to meet AQL limits.

Atypical trends should also be investigated. This includes examining defective units removed from a batch that are within in-process specifications but outside of statistical (historical) trend limits for the manufacturing process or defective units with visible particulates that have not been commonly observed.

Reinspection of product batches may be permissible with appropriate scientific justification and should be conducted according to approved SOPs with tightened acceptance criteria. FDA does not recommend more than one reinspection in an attempt to release a batch with atypical defect levels. Samples failing the AQL reinspection should be counted along with rejects from any other inspection of the product (e.g., such as 100% inspection and the original AQL visual inspection) in calculations to account for and reconcile all units of final product in the batch.

Corrective actions, such as reinspection, should be justified based on risk and have quality unit oversight and must be documented consistent with applicable written procedures (§ 211.100(b)).

Customer complaints must be handled according to applicable CGMP regulations (§ 211.198) and should result in particulate identification whenever possible, an investigation into the potential source of the particulate, corrective actions (if necessary), and analysis of the batch's retain samples for evidence of visible particulate contamination.

Ensuring the effectiveness, safety, and quality of injectable products is of utmost importance. Therefore, FDA recommends the use of a holistic, risk-based approach to visible particulate control. This approach includes the use of a robust visual inspection program along with the implementation of other relevant CGMP measures to help ensure that injectable products are not adulterated and are essentially free of visible particulates.

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