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Achieving “Zero” Defects for Visible Particles in Injectables

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ABSTRACT: The reduction of visible particles in injectable products is an important element in the consistent delivery of high-quality parenteral products. An important part of this effort is the control of particles that may emanate from the primary packaging materials. The Parenteral Drug Association (PDA), with the support of the Pharmaceutical Manufacturers Forum (PMF), has undertaken the task of developing test methods to assess the cleanliness of primary packaging components used in the manufacturing of sterile injectable products. Further work is focused on end-to-end analysis of the supply chain to identify additional points where particles may enter the finished product workflow. This includes shipment, receipt, transfer, and fill and finishing operations. This information and appropriate corrective actions and control methods, coupled with appropriate patient risk-based acceptance limits, are intended to provide better and more consistent supply of injectable products that meet current compendial and good manufacturing practice (GMP) expectations. Aligning control limits between supplier and pharmaceutical manufacturers will offer further improvement. This paper describes the formation of a task force to address these needs and current progress to date.

KEYWORDS: Injectable products, Primary packaging components, Process improvement, Risk assessment, Visible particles.

LAY ABSTRACT: Visible particles must be controlled in parenteral products. Such particles come from many sources including the primary packaging materials. The Parenteral Drug Association (PDA), with the support of the Pharmaceutical Manufacturers Forum (PMF), has formed a task force to review and improve particle measurement methods and perform an end-to-end analysis of how particles may enter into parenteral products. These activities are intended to lead to more consistent control limits for visible particles and ultimately more consistent supply of high quality injectable products.

1. Introduction

There has always been a demand for high-quality injectable drugs. Because injectable drugs bypass the body’s normal defense mechanisms, great care must be taken to control the risk of microbial, chemical, and particle contamination. This can typically be accomplished through careful formulation development, appropriate primary container selection, and the use of controlled manufacturing conditions—followed by a robust, visual inspection process. In recent years, there has been an increasing demand to reduce the residual particle load in injectable drug products, resulting in an increase in recalls associated with particles as can be seen in Figure 1 (1). In some cases, these recalls have led to the shortage of critical drugs, putting patients at risk (2). This is an industry-wide issue, and it is not limited to any one company, global region, or drug product format.

The United States Pharmacopeia (USP), European Pharmacopoeia (EP), and the Japanese Pharmacopoeia...
Although now closely aligned—have set the requirement for finished products, which are intended for parenteral use (3–5), and they provide no visible particle specifications for the materials that are used to produce these products. The USP and EP set requirements that are to be used, along with 100% inspection during the manufacturing process, to demonstrate the process, have produced a batch that is “essentially free” or “practically free” of visible particulates. The JP follows this approach, but it states that, “Injections or vehicles must be clear and free from readily detectable foreign insoluble matters” (5). A complete program for the control and monitoring of particulate matter in parenteral products remains an essential prerequisite to meet global pharmacopoeial requirements. The standards state that the inspected units must be essentially free of visible particulates when examined without magnification (except for optical correction as may be required to establish normal vision) against a black background and against a white background. No quantitative size limit or threshold has been established in the pharmacopoeias (3–5) to define what is visible. This lack of agreement on the definition of visible as applied to particles, coupled with inspector variability and the probabilistic nature of visual inspection, can lead to uncertain outcomes. Continued advancement in automated inspection technology and its deployment in the pharmaceutical industry have helped to reduce the variability often associated with manual inspection methods but do not fully address the uncertainty of these measurements. Adding to the difficulty of establishing an appropriate standard is the lack of an unambiguous measure of patient risk. The lack of controlled clinical studies assessing the impact of visible particles in human patients makes setting a safe limit for such particles difficult. These standards also treat all visible particles equally, regardless of their risk to the patient.

In early 2014, PDA assembled a team of physicians and visual inspection experts to review and assess the current clinical risks of visible particles in injectable drug products. The resulting publication (6) provided guidance on risk assessment to better align industry actions with specific products and patient populations. During this time, the USP was developing a general chapter to better guide the selection of inspection conditions and acceptance criteria to ensure that “every lot of all parenteral preparations is essentially free from visible particulates” as stated in USP General Chapter <1102> Injections and Implanted Drug Products (Parenterals)—Product Quality Tests. This led to the publication of USP General Chapter <790> Visible Particulates in Injections (3) which became an official chapter on August 1, 2014.

While these actions have helped to reduce the number of recalls due to visible particles, as can be seen in Figure 2 (1), further action is still needed. This figure also highlights the results of the increasing concerns by regulators and increasingly conservative actions taken by industry, rising to a peak in recall numbers in 2014. With the publication of USP General Chapter <790> in that year, both regulators and producers had a better understanding of the inspection conditions and the quality levels expected for the finished product, which resulted in a drop in the number of recalls in the next few years. Much of the work done to date has focused on the inspection requirements for filled and finished products. Further work is still required to improve the filling process and to address concerns upstream in the manufacturing process, including primary packaging materials. As with the filled and finished drug product, it is important to have defined test methods and clear requirements and specifications for the components used to manufacture these products. This is needed for both the component producers to develop reliable and appropriate processes as well as end manufacturers to assess the quality of these components before use.

Primary packaging components are not usually subjected to the 100% inspection that is required for the finished and filled product, but these are often assessed by inspecting a sample of each batch. Particle detection can also be more difficult in these components because they cannot be put in motion as with particles.
in a liquid product. Movement aids detection by both the human eye (7) and automated inspection systems. All of these are complicated by the probabilistic nature of detecting particles in or on product or components. Generally, the probability of detection in filled solutions increases with increasing particle size and is approximately 50% for a single 100 \( \mu \text{m} \) spherical particle in a clear solution packaged in clear vials and approaches 100% for particles 200 \( \mu \text{m} \) in diameter (8).

The routine 100% inspection of filled products specified by the Pharmacopeias (3–5) emphasizes detection and does not require identification or sizing. When an analytical technique, such as that offered by recovery, isolation, and microscopy is applied, an accurate measurement of particle size can be obtained and should be assessed relative to the required visual inspection detection performance. This leads to the need to set a visible threshold for counting, similar to the subvisible threshold of 10 \( \mu \text{m} \) and 25 \( \mu \text{m} \) currently in common use (9).

In September 2016, the PDA organized a meeting between suppliers of glass and elastomeric components and pharmaceutical manufacturers to define a viable pathway for a collaborative effort to further reduce the number of recalls in the market. The participants overwhelmingly voted to focus on achieving zero defects for visible particles in injectables.

To achieve this objective, a task force was established, which was sponsored by PDA and the Pharmaceutical Manufacturers Forum (PMF). A cross-functional industry task force of industry experts was established to lead this initiative. The project would look at the process from end-to-end, including suppliers of components, as well as the pharmaceutical manufacturing processes, and focus on identifying potential sources of particles, accurate detection and measurement methods for visible particles, and methods to mitigate the presence of visible particles in injectable drug products. The project was named Achieving “Zero” Defects for Visible Particles in Injectables. Zero was intentionally placed in quotes, recognizing that no product or material is absolutely free of particles. The test and inspection methods used will ultimately determine what is visible or detectable. Appropriate measurement methods and risk-based specifications are required to reliably deliver safe and effective products to patients.

The task force will focus on visible particles in:

- ready-to-fill (RTF), ready-to-use (RTU), and ready-to-sterilize (RTS) materials and components (bulk components will be addressed in a later phase);
- glass containers such as vials, syringes, and cartridges;
- elastomer components such as stoppers, plungers, and syringe tip caps; and
- secondary packaging associated with packaging components such as bags.
Bulk components are those that are subjected to further cleaning and sterilization processes by the pharmaceutical manufacturer in-house prior to use, while RTF, RTU, and RTS components are used without further cleaning but are subjected to sterilization in the case of RTS components.

The taskforce intends to establish a clearly defined visible particle specification (e.g., size, type and quantity) based on the potential risk of harm to patients. While such specificity in a visible particle specification is desirable, the lack of relevant clinical trials owing to obvious ethical considerations limits the ability to establish unequivocal safety limits as is typically done for other “impurities.” However, an initial review suggests that a visible threshold limit for particles between 100 and 150 μm and a separate limit for fibers between 300 and 500 μm may be appropriate. However, additional assessment work will be required to establish practical limits. Such limits, while related to visual inspection capability, will be based on the performance of an alternate analytical method (such as membrane filtration coupled with microscopic observation). These limits would be established and qualified through planned testing of the proposed measurement methods.

Thus far, a large body of anecdotal information has been used to guide the understanding of clinical risk of visible particles. These are useful and provide guidance, but not an exact limit, for setting acceptance criteria for injectable products and the primary packaging used in their preparation. The lack of a specific definition of what is a visible particle, coupled with the normal variability of visual inspection processes, has led to a wide range of practices and acceptance limits applied to particles in injectable drug products and their packaging materials.

The uncertainty associated with both clinical risk and detection must be considered when undertaking a project of this nature, but it should not prevent the development of practical guidance, which will be intended for use along with existing compendia and regulatory and industry standards.

Because of its broad scope, the project was broken into two phases, and the first phase would limit the scope to RTF, RTU, or RTS components. This was identified as a critical gap in the process leading to filled product, as these widely used primary packaging components are often not evaluated or subjected to additional washing prior to use, and are not regulated by the current standards with regard to visible particle load. The assessment of bulk components will be considered in a later phase.

A significant part of this project will also include an end-to-end assessment of where particles may be introduced into finished filled product, either directly or through contact with other component materials. This will use failure mode and effects analysis (FMEA) methodology to quantify particle sources with regard to occurrence, detection, and severity. This analysis will look upstream into the component manufacturing process and continue through the assembly of filled units. This model is intended to provide guidance for process improvement from lessons already learned.

The task force will prepare a document summarizing their findings and recommendations. Publication is anticipated once method development and qualification have been completed and associated risk assessments have been completed. A second phase is anticipated to address bulk components that are processed by the end user.

2. Project Structure

Figure 3 provides an overview of the many process steps between raw materials, finished drug, and the patient.

The first phase of the project, associated with RTF, RTU, and RTS components, was further divided into four key steps:

- Understanding the current criteria used to define patient risk, visible particle size and number and their associated acceptance limits;
- process mapping with associated FMEA analysis;
- developing qualified methods with which to evaluate components; and
- aligning and promoting these methods and acceptance criteria within the industry.

Figure 4 provides further detail regarding each of these project steps in Phase 1 and a description of each of these steps follows.
2.1. Understanding and Defining the Current State of Visible Particle Measurement and Control for Primary Packaging Components and Establishing a Patient Risk-Based Particle Size Threshold and Acceptance Criteria

The focus of this part of the project is to establish a clear definition for what constitutes a “visible” particle and to develop standardized methods that can be used by both suppliers and the pharmaceutical manufacturers to evaluate RTF, RTU, and RTS components.

This involves examining two distinct but complementary paths for glass and rubber/elastomeric components. Risk assessment methodologies and the commonality of the process steps for both these components will be used as the starting point for self-evaluation and mitigation strategies. These in turn will result in the definition of

Figure 3

End-to-end process view for sterile injectable drug product.

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Figure 4

Phase 1: Achieving “zero” defects for visible particles in injectables.
risk-based acceptance criteria for visible particles for these components.

2.2. Developing Qualified Methods With Which to Evaluate Components

The work in this next step includes the review of existing methods for detecting and quantifying visible particles on or in the primary packaging materials described earlier. Included in the scope of this project is a review of current practices with the intent to qualify and harmonize these methods. This will be done within the constraints of existing manufacturing capabilities and best practice sharing without violating current antitrust regulations.

2.3. Aligning and Promoting the Acceptance Criteria and Methods Within the Industry

On completion of the initial phase of work, the task force will partner with existing standard-setting bodies to institutionalize the best practices and limits identified here. Established by consensus and supported by bodies equipped to develop industry standards, we will help drive our industry toward the desired goal of zero visible particles in injectable products.

The task force will then extend this approach, addressing issues and solutions in the areas of active pharmaceutical ingredient (API) and drug product (DP) manufacturing and process equipment, as well as addressing bulk packaging components in later project phases.

3. Progress to Date

3.1. Literature Search and Risk Assessment

A review of relevant literature associated with visible particles in injectable pharmaceutical products was undertaken to assess the current state of particle control. It was important not to duplicate or create conflict with existing guidance. This review included published benchmarking studies, regulatory and compendial guidance, and standards and test methods. Application to both filled and sealed units, as well as primary packaging components, was included in the scope of this review. The search was based on previous searches, personal experience of the team members, online Internet searches using Google, and keyword search of the following databases: Books@Ovid, BIOSIS Previews, Embase, and Ovid MEDLINE. The search yielded 43 relevant documents that were sorted into the following categories: General, Medical Risk Associated with Visible Particles, Regulatory and Compendial Requirements, Test Methods and Acceptance Criteria for Primary Packaging Components, and Finished Product Inspection Methods and Acceptance Criteria. The team considered undertaking a survey to gather additional information on current industry practices, but it found sufficient information in the PDA surveys conducted in 2014 and 2015 to support this work. A list of the key documents identified can be found in Appendix 1.

The general findings were that no new relevant references were identified and that no new test methods or acceptance criteria were found. Furthermore, no specific regulatory requirements or test methods for visible particles in primary packaging components were found. The existing test methods for primary packaging favor collection followed by sizing and counting of particles to assess suitability of a component or a batch. The general findings also indicate that there is support for a lower limit to the visible range between 100 and 150 μm in diameter from studies that assess the probabilistic nature of human inspection performance in filled and sealed containers (8). A reduced detection ability for fibers may require a higher (or larger-size threshold) for this type of particle.

Existing risk assessment tools and methods associated with visible particles in injectable pharmaceutical products are currently being assessed. It is recognized that this is complicated by the wide variety of products and the number of patients served, and care must be taken to understand such risks. Such a tool should be used to focus resources on the areas of the greatest risk rather than to diminish the need for rigorous current GMP controls for particles in general.

3.2. Understanding Failure Modes, Probability of Occurrence, and Particle Detection

Current industry particle control practices will be benchmarked and patient risk-based acceptance criteria will also be established. One focus is on understanding the main particle generation mechanisms and/or entry routes within the entire production chain, from suppliers (container and closure) to the final drug product (fill and finish). Based on industry surveys, the five most common visible particle types (in order from most common to the least common) that are identified in parenteral products are fibers, glass, product-related, rubber/elastomer, and metal (10).
FMEA methodology will be used to identify the most critical process areas and mechanisms that result in particle contamination for the five most common particle types. Process steps will be generalized to be broadly applicable, but these will include specific best practices that can be applied in common manufacturing settings. The team will leverage their experience and industrial knowledge to contribute to this effort with the goal of sharing best practices broadly and aligning on critical processes that can benefit from additional focus and improvement with the goal of driving improvements across industry.

Deliverables include:

- FMEA for manufacturing process (glass, elastomer, and fill and finish); and
- identification of most critical process steps within manufacturing process for top five particles, focusing on RTF, RTU and RTS materials.

Thus far, significant observations include the criticality of glass handling and limiting glass-to-glass contact, robust environmental controls throughout the process, careful transfer of materials between areas of different classification and cleanliness, and the importance of controlling the shedding and transfer of particles from secondary packaging.

3.3. Develop Risk-Based Visible Particle-Size Threshold

The focus is the establishment of what should be considered a visible particle when performing analytical testing on primary packaging components. In drug products’ containers, extraneous matter is considered “visible” when it is seen by the unaided human eye under standard inspection conditions. For primary packaging components, there is a desire to set acceptance criteria for particles that ensure the drug product requirements for visible particles are met; however, there is no clear method or definition on what should be considered a visible particle if found on incoming component testing. Further adding to the challenge, it is very typical for primary packaging component suppliers to perform particulate testing with analytical methods that have the capability that goes far beyond that of the unaided human eye.

The report produced by the task force will include an assessment of existing technical literature on the science of particle detection in drug products, and they can, from that information, establish an industry standard for what should be considered a “visible particle” for analytical testing of primary packaging components. More specifically, the report intends to establish an industry-standard-size threshold for analytical testing of particulate matter in primary packaging components, and only particles above the size threshold should be “counted” as visible particles. This size threshold could be used in both analytical testing during component release by suppliers and can be used during incoming material acceptance testing by pharmaceutical manufacturing companies. Sampling from various points in the supply chain will be useful for process optimization to better understand the contribution of each operation and ultimately lead to better control. The size threshold developed by the task force will not be intended to be applied to inspection of filled drug product inspection and should not be applied when the test method is simply inspection by the unaided human eye.

3.4. Glass Analytical Methods and Qualification Strategy

Completion of this work will result in a proposal for an analytical method for the collection and quantification of visible particles in primary packaging components.

Today, there is no standardized industry method or limit for visible particles that is used by both the glass container suppliers and pharmaceutical manufactures, and specifications are established between suppliers and customers for each product supplied. This is further complicated by the diversity of potential manufacturing defects generated by both glass primary packaging suppliers and pharmaceutical manufactures. The sensitivity of any such method is affected by many variables including the size, shape, color, and reflectivity of the particle, as well as the specific container size and shape.

The task force is developing an implementation strategy for a visible particle assessment method for empty glass containers, which will include a qualification strategy, which shows the effectiveness of the method, thus ensuring repeatable and accurate results industry wide.

3.5. Development of Analytical Methods and Qualification Strategies for Stoppers and Bags

The goal is to align the stopper analytical methodology used for the detection of visible particles released
from processed components (RTF, RTS, and RTU) and from their final packaging. Currently, there is no standard analytical methodology that is used by both stopper supplier and the pharmaceutical manufacturing customer. There is no requirement to test stoppers from final packaging, which causes disconnect between what is tested by suppliers and what is received by customers. Additionally, there are no standardized specifications for visible particles on RTF, RTS, and RTU stoppers, rather specifications are agreed upon between customer and supplier for each product.

Furthermore, the goal of aligning the suppliers and customers on an analytical method used for visible particles will be achieved through the implementation of a method qualification strategy. The method qualification will serve to demonstrate the ability of the analytical method to be used by the entire industry to generate accurate and repeatable results for visible particles greater than the identified and agreed-upon size threshold.

FMEA will also be applied to production and use of elastomer components. A study comparing the methods used by each of the stopper suppliers will be performed to determine gaps and identify best practices. Work by this subteam will include development and qualification of an appropriate test method for visible particles released from elastomer components. A qualification strategy has been agreed upon and a qualification protocol is in the process of being developed for use in this study.

Work in this subteam extends to the bags used to package elastomer components, as these can be a significant source of particles. Gaps in the current testing methodology have been identified, and a guidance for particle testing in bags has been completed. The methodology to be applied to bags will follow the same development and qualification strategy as that for the elastomeric components themselves.

4. Conclusions

Upon completion of the work of this cross-functional team, a common definition of what is a visible particle (size and type) and how to evaluate if visible particles are present (quantitative methods) will be available for use by both component suppliers and pharmaceutical manufacturers. These will permit a common approach to process evaluation and mitigation strategies. Process mapping and risk analysis will further identify opportunities to reduce particle entry throughout the supply chain. With this alignment, quantification and ultimately reduction and improved control are possibly moving us toward meeting the goal of zero particles in injections.

The completion of this first phase is planned for 2018 and planning for the second phase has already begun. This initiative welcomes new task force members who can contribute to this project in the current or subsequent phases.

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Conflict of Interest Declaration

The authors declare no conflict of interest related to the development of this manuscript (i.e., no competing interests). The authors acknowledge that they have no involvement in any organization or entity with any financial or nonfinancial interest in the subject matter or materials discussed in this manuscript.

References


4. Chapter 2.9.20 Particulate Contamination: Visible Particles, European Pharmacopeia (EP), Eudralex,


APPENDIX Literature Search Document List.

1. General


2. Medical Risk Associated with Visible Particles


3. Regulatory Requirements

Note: requirements found in pharmacopeias are listed in sections 4 and 5.


4. Test Methods and Acceptance Criteria for Primary Packaging Components


conformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging; PDA: Bethesda, Md., 2016.


5. Finished Product Inspection Methods and Acceptance Criteria


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