Achieving “Zero” Defects for Visible Particles in Injectables


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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 manufacture 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 (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

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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 (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.
1. INTRODUCTION

There has always been a demand for high quality in injectable drugs. Since injectable drugs by-pass the body’s normal defense mechanisms, great care must be taken to control the risk of microbial, chemical and particle contamination. This is typically 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 shortages of critical drugs, putting patients at risk [2]. This issue is industry-wide and not limited to any one company, global region or drug product format.

Figure 1: Analysis of Sterile Drug Product Recalls 2010-2017 [1]

The United States Pharmacopeia (USP), European Pharmacopeia (EP) and the Japanese Pharmacopeia (JP), although now closely aligned, only set the requirement for finished products which are intended for parenteral use [3,4,5] and provide no requirements for the materials which are used to produce these products. USP and EP set requirements which are to be used, along with 100% inspection during the manufacturing process, to demonstrate the process has produced a batch “essentially free” or “practically free” of visible particulates. JP follows this approach, but states that, “injections or vehicles must be free from readily detectable particles”. A complete program for the control and monitoring of particulate matter remains an essential prerequisite. 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 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

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has helped to reduce the variability often associated with manual inspection methods but does not fully address these concerns. 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 makes setting a limit difficult. These standards also treat all visible particles equally, regardless of their risk to the patient.

In early 2014, The Parenteral Drug Association (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 PDA Points to Consider document [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 assure that injectable drug products were “essentially free from visible particulates”. This led to the publication of USP General Chapter <790> [3] as 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 result 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 <790> in that year, both regulators and producers had a better understanding of the inspection conditions and quality levels expected for finished product and the drop in recalls is evident in following years. Much of the work done to date has focused on the inspection requirements for filled and finished product. 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 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.

Figure 2. Sterile Drug Product Recalls Due to Particles by Year 2010-2017. [1]
Primary packaging components are not usually subjected to the 100% inspection that is required for the finished and filled product but are often assessed by inspecting a sample of each batch. Detection of particles 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 and automated inspection systems. All of this is 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 single 100 µm spherical particles in a clear solution packaged in clear vials and approaches 100% for particles greater than 200 µm in diameter [8]. The routine 100% inspection of filled products specified by the pharmacopeias 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 sub-visible threshold of 10 µm and 25 µm 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. Overwhelmingly, the participants voted to focus on achieving zero defects for visible particles in injectables.

To achieve this objective, a task force was established, 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 ultimately 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: vials, syringes and cartridges
- Elastomer components: stoppers, plungers and syringe tip caps
- Secondary packaging associated with packaging components: 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 task force intends to:

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• Establish a clearly defined visible **particle specification** (e.g., size, type and quantity) based on the potential **risk of harm** to patients

In relation to the potential risk of harm to patients, while such specificity in a visual particle specification is desirable, the lack of relevant clinical trials due to obvious ethical considerations limits the ability to establish unequivocal safety limits as is typically done for other “impurities”. However, an initial review suggests a visible threshold limit for particles between 100-150 µm and a separate limit for fibers between 300-500 µm may be appropriate. However, additional assessment work will be required to establish practical limits. Such a 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.

A large body of anecdotal information has been used thus far 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 should not prevent the development of **practical guidance**, which will be intended to be used along with existing compendia, regulatory and industry standards.

Because of its broad scope, the project was broken into two phases, 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 since 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 has been completed and associated risk assessments have been completed. A second phase is anticipated to address bulk components which 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.

**Figure 3. End-to-End Process View for a Sterile Injectable Drug Product**
The first phase of the project, associated with RTF, RTU and RTS components, was further divided into four key steps:

- Understanding and defining the current state, including establishing patient risk-based particle size threshold and acceptance criteria
- Process mapping with associated FMEA analysis
- Developing qualified methods with which to evaluate components
- 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.

**Figure 4. Phase 1 Achieving “Zero” Defects for Visible Particles in Injectables**
Understanding and defining the current state and establish 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 which 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 assessments 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 risk-based acceptance criteria for visible particles for these components.

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. A review of current practices with the intent to qualify and harmonize these methods is included in the scope of this project. This will be done within the constraints of existing manufacturing capabilities and best practice sharing without violating current antitrust regulations.

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 towards 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 address bulk packaging, components in later project phases.

PROGRESS TO DATE

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, standards and test methods. Application to both filled and sealed units as well as primary packaging components were included in the scope of this review. The search was based on previous searches, personal experience of the team members, online internet search using Google and a keyword search of the following databases: Books@Ovid, BIOSIS Previews, Embase and Ovid MEDLINE. The search yielded 43 relevant documents which 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 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. Further, 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 batch. The general findings also indicate that there is support for a lower limit to the visible range between 100 to 150μm in diameter based on studies to assess the probabilistic nature of human inspection performance in filled and sealed containers [8]. A reduced detection ability for fibers may require a higher (larger size threshold) for this type of particle.

The team is currently assessing existing risk assessment tools and methods associated with visible particles in injectable pharmaceutical products. It is recognized that this is complicated by the wide variety of products and patients served and care must be given to understand such risk. Such a tool should be used to focus resources on the areas of greatest risk rather than to diminish the need for good cGMP controls for particles in general.

Understanding failure modes, probability of occurrence and detection of particles

The team will benchmark the current state and establish patient risk-based acceptance criteria. 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 (5) most common visible particle types (in order from most common) that are identified in parenteral products are fibers, glass, product related, rubber/elastomer and metal. [10].
Failure mode and effect analysis (FMEA) methodology will be used to identify the most critical process areas and mechanisms that result in particle contamination for the five (5) most common particle types. Process steps will be generalized to be broadly applicable but 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, fill and finish)
- Identification of most critical process steps within manufacturing process for Top 5 particles, focusing on RTF, RTU and RTS materials

Significant observations thus far 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.

Develop Risk-Based Visible Particle Size Threshold

The focus of this team 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 ensures that 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 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 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.

Glass Analytical Methods and Qualification Strategy
Completion of this team’s work will result in a proposal for an analytical method for the collection and quantification of visible particles in RTU glass containers.

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 the customer 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 the method, which will include a qualification strategy, which demonstrates the effectiveness of the method, thus ensuring repeatable and accurate results industry wide.

Development of analytical methods and qualification strategies for stoppers and bags

The goal of this team is to align the stopper analytical methodology used for 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 utilized by both stopper supplier and the pharmaceutical manufacturing customer. There is no requirement to test stoppers from final packaging, which causes a 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.

The team’s 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 sub-team 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 sub-team 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. Methodology to be applied to bags will follow the same development and qualification strategy as that for the elastomeric components themselves.

CONCLUSIONS

On completion of the work of this cross functional team a common definition of what is a visible particle (size, 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. 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 possible moving us towards meeting the goal of zero particles in injections.

The completion of this first phase is planned for 2018. 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 whose names are listed report there was no conflict of interest related to the development of this manuscript; (no competing interests). The authors whose names are listed also acknowledge that they have no involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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APPENDIX 1. Literature Search document list.

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Particulate Matter in Injectable Drug Products

Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Process Equipment
Bio-Process Systems Alliance (BPSA), (2014)

Good Practice Paper: Visual Inspection of Medicinal Products for Parenteral Use

Particulate Matter in Parenteral Products: A Review

Investigation of Foreign-Particle Contamination

A Biopharmaceutical Industry Perspective on the Control of Visible Particles in Biotechnology-Derived Injectable Drug Products

A Proposed Working Standard for Validation of Particulate Inspection in Sterile Solutions

Visual Inspection and Particulate Control
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2. Medical Risk Associated with Visible Particles

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Glass Particles in Intravenous Injections

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Particles in Intravenous Solutions: A Review

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

Federal Food, Drug and Cosmetic Act, FD&C Act Chapter V: Drugs and Devices, Section 510

Code of Federal Regulations, Title 21 Food and drugs, Chapter 1 – Food and Drug Administration
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43 FR 45077, Sept. 29 (1978)

4. Test Methods and Acceptance Criteria for Primary Packaging Components

ISO 8871-3 Elastomeric Parts for Parenterals and for Devices for Pharmaceutical Use — Part 3: Determination of released-particle count

IEST-STD-CC1246E: Product Cleanliness Levels – Applications, Requirements, and Determination Institute of Environmental Sciences and Technology (IEST), (2013)

PDA Technical Report No. 43, Revised 2013, Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing Covering Ampules, Bottles, Cartridges, Syringes and Vials
Asselta, R., et. al, Parenteral Drug Association (PDA), (2013)

PDA Technical Report No. 76 Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging

The BPOG (Biophorum Operations Group) Stopper Quality Team: Harmonized Requirements
Biophorum Operations Group (BPOG), (2015)

USP <381> Elastomeric Closures for Injections

USP <1381> Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems (DRAFT)

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5. Finished Product Inspection Methods and Acceptance Criteria

Generalized Methodology for Evaluation of Parenteral Inspection Procedures

Implementation and Automation of a Particle Detection System for Parenteral Products


USP <1> Injections and Implanted Drug Products (Parenterals) – Product Quality Tests

USP <660> Containers - Glass

USP <787> Subvisible Particulate Matter in Therapeutic Protein Injections

USP <788> Particulate Matter in Injections

USP <790> Visible Particulate in Injections

USP <1660> Evaluation of the Inner Surface Durability of Glass Containers

USP <1790> Visual Inspection of Injections

EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use:
Annex 1 Manufacture of Sterile Medicinal Products
European Medicines Agency (EMA) (2008)

EP 01/2008:0520 Parenteral Preparations

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JP 6.06 Foreign Insoluble Matter Test for Injection

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Test for Visible Particle in Injections
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