

Filling the Pharmacopeial Gaps of Visual Inspection: Toward Standardization and Consistency of Visible Particle Testing

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Correspondence should be addressed to: Desmond G. Hunt,^g Principal Scientific Liaison, Science-General Chapters, US Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel: 1.301.816.8341; email: DGH@usp.org.

ABSTRACT

The presence of visible particles that are not anticipated to be present in drug products is one of the most common causes of recalls and warning letters (Parenteral Drug Association. Shabushnig, JG. PDA Survey: 2014 Visual Inspection. Bethesda, MD: Parenteral Drug Association; 2015 and Parenteral Drug Association. Shabushnig, JG. Hot topics in visual inspection on a cold January night. Bethesda, MD: Parenteral Drug Association - New England Chapter; 2015.). This critical quality attribute, which is typically determined during visual inspection (along with defects in the container–closure system), must be controlled to minimize its occurrence in all drug products. Conditions for visual inspection of visible particles in parenteral solutions, including the amount of light used to illuminate the sample, the black and white backgrounds against which inspection should be performed, and the amount of time allowed for the inspection, are addressed in the pharmacopeia. However, the determination of many parameters and operational conditions are left to the discretion of individual manufacturers and end-users. These include the size of the particles detected and defined as visible, the training set and procedure used to train the human inspectors, and the interpretation of results. Consequently, we observe variability among organizations in the stringency of the method and the limits applied, as well as inconsistency between sites, contract manufacturing organizations (CMOs), and products within a single organization. In this *Stimuli* article, we discuss the current state of visible particle assessment and propose a new USP chapter focused on assay suitability, enabled by universally available standards, that would fill the current pharmacopeial gaps and result in a universal, consistent definition of visible particles and the method by which they are analyzed.

INTRODUCTION/CURRENT STATE

Visual inspection of drug products is a compendial assay during lot release and stability testing, which encompasses not only visible particle assessment but also appearance (color and clarity) and container–closure defects. The presence of unintended visible particles in drug products is one of the most common causes for US Food and Drug Administration (FDA) recalls and warning letters ([1–2](#)). As part of routine lot release, visual inspection of drug products enables detection of visible particles, a critical quality attribute (CQA), and defects in the container–closure system. Strategies to control this CQA must be put in place to minimize its occurrence and impact. Visual inspection is a compendial method included in many pharmacopeias, for instance in the *United States Pharmacopeia* (USP) [Injections and Implanted Drug Products \(Parenterals\)—Product Quality Tests \(1\) \(3\)](#), [Visible Particulates in Injections \(790\) \(4\)](#), [Visual Inspection of Injections \(1790\) \(5\)](#), in the *European Pharmacopeia* (EP) 2.9.20 ([6](#)) and EP 5.17.2 ([7](#)) and in the *Japanese Pharmacopoeia* (JP) 6.06 ([8](#)). These chapters describe inspection of the drug product container and its contents against a white background and a black background and the conditions the human inspectors should use, such as light intensity, distance from the light source, inspection duration against both

backgrounds, and tests for visual acuity that the inspectors must pass. Suggestions for training sets and procedures are also included.

Many articles have been published to build on the requirements found in the compendia, and each company develops their own standard operating procedure (SOP) based on this information and their own product experience ([9-10](#)). Visual inspection is a probabilistic assay; in other words, the probability of detection increases with the size of the particle and other physical properties. Studies in which containers were spiked with spherical reference standard particles, especially polystyrene beads, demonstrated that the probability of detecting particles smaller than 50 μm is less than 5%. The probability of detection increases to 70% for particle sizes between 50 and 100 μm , and a >95% detection rate is realized with most particles greater than 200 μm in size ([10](#)). The lower limit for visible particles is not defined in the compendia and is decided by each organization based on the percentage of probability of detection and the variability in the results that they decide is acceptable. Thus, the size range of visible particles is ambiguous. This is further complicated by the achievable upper limit of the subvisible particle analysis. Subvisible particles are those that are smaller than visible particles, covered by the compendial methods in USP *Particulate Matter in Injections* ([788](#)) ([11](#)) and by EP 2.9.19 ([12](#)) and JP 6.07 ([13](#)). Light obscuration is the method of choice for the analysis of subvisible particles present in biotherapeutic drug products, with an upper limit of about 100 μm . This results in a “gray region” between 50 and 150 μm , the upper limit of the subvisible particle compendial analyses and the variable lower limit of visual inspection, in which particles are not reliably detected ([5,14](#)).

The ability to detect particles varies with their shape and morphology (fibers can be more difficult to detect) and on their orientation in solution relative to the inspector’s eye. When the optical properties (such as the refractive index) of any particle, but more specifically of proteinaceous particles, are comparable with those of the background solution, detection becomes very challenging. Automated or semiautomated 100% inspection are often implemented, with human visual inspection reserved for acceptance quality limit (AQL) inspection and inspection of the units rejected by the automated systems. Human error caused by eye strain and fatigue of the human inspector will also affect the probability of detection. Finally, the definition of visible particles varies among individual manufacturers based on product specifications and capabilities as well as the inspection and training conditions that are used. Therefore, the definition of visible particles is inconsistent among the therapeutic drugs that patients receive from different companies.

As described in the compendia, different particle types can present different risks to patients. Particles can be classified as extrinsic, intrinsic, or inherent. Extrinsic particles arise from outside of the normal manufacturing process, such as insect parts, whereas intrinsic particles come from the normal manufacturing process or container closure, such as silicone oil. The USP further differentiates inherent from intrinsic particles: those which are expected and originate from the formulation excipients or the active ingredient itself, such as protein aggregates ([5,14](#)). In the EP, inherent particles are simply classified as intrinsic. The highest risk is linked to extrinsic particles because their presence may compromise product sterility. Intrinsic/inherent particles are typically associated with a lower risk, especially when the historical product and clinical development data as well as prior product knowledge support this claim. Based on the results of the visible particle inspection, a drug product is defined as “essentially free”, “practically free of particles”, “without visible particles, unless otherwise justified”, or “free of readily apparent foreign material” ([6](#)). The presence of visible particles in drug products is a critical defect that must be minimized and controlled, and the acceptance of a product that “may contain particles” requires justification from either the manufacturer ([15](#)) or a similar molecule for a similar therapeutic indication.

The original compendial methods were developed for small molecule (synthetic) parenteral drug products and focused on foreign material (extrinsic matter). With the increasing prevalence of biotherapeutics, such as monoclonal antibodies (mAbs), the application of these methods has changed. Proteins tend to self-associate, especially at high concentrations, and the detection of protein aggregates becomes more challenging because of their amorphous shape and their refractive index, which is similar to that of aqueous solutions. With the advent of newer modalities, such as complex engineered proteins and cell and gene therapies, these methods

require further adaptation, and more appropriate specifications should be set for these novel therapeutic entities.

The compendial methods are focused on lot release and analysis of commercial product, as they should be. During drug process and development, the particle content should be minimized by implementation of a control strategy. The purpose of the visible particle assay is to ensure that each lot conforms to the expected particle profile. Inspectors must be able to detect the presence of a single particle, under very stringently controlled conditions that are identical among inspectors and testing sites. However, as visible particles are a CQA, it is critical to monitor and track the formation of these species early on during development, where the information can be used to inform the choice of product candidate, the process, the formulation, and the container closure or device. This data also enables the generation of a particle profile for the material used in preclinical and clinical trials, thus establishing a standard or a benchmark and defining what is normal for product and patient exposure. In early development, larger amounts of particles are more likely to be present in solution, especially proteinaceous particles that may be difficult to detect. Phase-appropriate changes in the inspection conditions are often implemented during development, such as longer inspection times, more intense lighting, etc., in order to provide enhanced detection and data to support decisions and risk assessments.

The situation described above resulted in visual inspection methods that conform to the pharmacopeia, but differ from one company to another and even sometimes between different sites and departments within the same organization. Specifics regarding training, the training set, and the definition of a visible particle are left to the discretion of individual analytical groups. Consequently, a level of uncertainty arises not only for the companies who manufacture and file the drug applications, but also for the regulators who review them, thus leading to differences in risk assignment, drug product quality, and patient safety.

A compendial chapter, hopefully harmonized, with an emphasis on the use of universally available standards to train inspectors, qualify the method, and validate the results expected with these standards, would go a long way toward increasing the assay consistency and the ability to compare results and analytical capabilities across products, departments, and organizations. Ultimately, a unified definition of the minimum size of a visible particle, perhaps dependent on particle type would further enhance the consistency of products as well as process control. In addition, this definition will take into consideration the drug product itself and the stringency of detection based on the therapeutic indication. A uniform approach to risk assessment based on particle type and amount, patient population, and route of administration should also be considered ([16](#)). This chapter would also enable bridging between human inspection and any new technology in development and the application of the new guidance to newer modalities. The focus of this *Stimuli* article is the visible particle aspect of visual inspection. Container–closure defects and appearance (color, clarity) that are also components of visual inspection have been adequately addressed ([17–18](#)) with appropriate and readily available standards and are therefore out of scope in this article. The main factors to be considered in the development of the sought chapter are discussed later in this article.

STANDARDS

The importance of standards for training inspectors and ensuring uniformity of the assay has been discussed in the pharmacopeia [[1790](#)] ([5](#)), for instance] and in several review articles ([9–10,19](#)). The most common particle standards are polystyrene beads, which are commercially available in limited sizes that span the range from submicron to visible. These spherical particles are the easiest to detect primarily because they have optical properties that are very different from those of the normal aqueous formulations of parenteral drug products. They can be uniformly produced at a defined size, making them suitable for use as a single standard particle per unit for determining the limit of detection; however, they do not look like typical particles routinely observed during visual inspection. They are often a part of a larger standard set with multiple particle types. Standard sets should include representative extrinsic and intrinsic particles such as glass lamellae, similar to those generated in glass vials under particular buffer conditions; fibers which can be

shed from gowning and packaging; and rubber, which can come from stoppers and tubing. Many, if not most, of these particles are common to all therapeutic manufacturing processes.

A standard set composed of typical extrinsic and intrinsic particles, such as those described above, if available to the industry as a universal standard set, has several advantages. It will be easier for smaller organizations to adopt the training set and methodology because they do not need to invest time and money into assay development for their visual inspection program. It also enables consistency in training, better defines particle size categories, allows clearer specification-setting, and enhances risk assessment. In addition, material specific to the product could be used to supplement the universal standards. Whereas components of this second set should be standardized within the organizations employing them, their use could be optional and depends entirely on the nature of the product. These specific standards should be prepared in an identical manner and in the same solution as the commercially available standardized sets. All particle standards used should be tested at one time as a single set.

An example of a supplemental standard is one that mimics protein particles in biotherapeutics. In these products, the detection of intrinsic/inherent particles can be challenging because they have typically irregular, amorphous shapes with optical properties (refractive index) similar to those of the surrounding solution; in other words, they “blend” into the background. Because of their intrinsic instability, proteins have a tendency to aggregate and form particles over time. The use of actual protein aggregates as standards is very difficult due to the fragility and instability of these species. The National Institute of Standards and Technology (NIST) has spent several years exploring different materials and ways of creating particles that mimic proteinaceous ones and is leading a cross-company study to have them assessed by several different organizations ([20-21](#)). One candidate standard may be useful for establishing a detection threshold for inspectors and for better defining what is “visible” for a particular product. The second candidate may be useful for semi-quantitatively tracking and monitoring proteinaceous particle content in biological products that are justified to have low levels of proteinaceous particles ([21-22](#)). Both particle types can be instrumental in training analysts to monitor visible, proteinaceous particles more consistently in biotherapeutics. It is known that different stresses and formulation conditions often lead to different types of aggregates (sizes, morphology, conformation, etc.). Therefore, although these standards look proteinaceous, they may not be representative of all types of proteinaceous particles that may form. Companies should verify that the standards appear sufficiently similar to the proteinaceous particles they typically encounter in their product before implementing their use. Additionally, bridging studies should be carefully considered to link historical data with any new data collected with these new standards.

In the prospective USP chapter, we propose a discussion depicting the importance of a universally available standard set to evaluate assay and system suitability. The universal standard set is suggested for training purposes only and should be composed of the following: container–closure defect vials (not the scope of this work) and defect vials containing typical extrinsic and intrinsic particles. Additionally, a third category of defects, not part of the universal set, should contain product-specific defects (i.e. mimics of inherent particles) only if those are part of the drug profile. The standard sets will not replace company specific standards or procedures unless the same particle type is included in both sets. For example, if the company set includes glass particles, these could be replaced by the glass particles in the universal commercial standard set to eliminate redundancy and streamline testing. Factors to consider when including standards specific to the product and process and when performing the assay on the product samples themselves will also be analyzed. The discussion will describe details pertaining to sample preparation and conditions recommended for bringing the sample to room temperature, lag time between sample preparation and analysis, and storage conditions.

TRAINING

Limited instructions on training of inspectors are included in the current pharmacopeia. The commercial availability of standard sets would allow this training to be more comprehensive and allow the testing to be more consistent across organizations because of the implementation of stringent requirements for all

inspectors. The contents of the training kit should include the universal standards, any product-specific standards required, and the method for the qualification of the set. Sample handling instructions such as dispersion of the particle samples, storage conditions, etc., should also be detailed. In addition to defining expectations on inspectors' visual acuity, we suggest that inspectors be certified according to the percentage of particles detected when analyzing different types of particles in the standard training set. This training procedure provides uniform certification for all visual inspectors and ensures that particles are being detected and identified with the same sensitivity across organizations, thus making the assay more consistent and quantitative. Training could be enhanced with real-world samples with known particle counts. For instance, pictures and videos of commonly encountered inherent or intrinsic particles and those of (hopefully less common) extrinsic ones are strongly encouraged. The chapter will also dictate how often inspectors should be re-certified.

As mentioned previously, visual inspection performed during development can be more rigorous than the compendial method. In fact, during development, the purpose of the test is to capture all particles present as completely as possible, to build up a library of "normally expected particles" for this product, and to simultaneously develop a control strategy by evaluating means to minimize particle content. It should be noted that different types of particles may be present to different extents at various stages of developing a product. For example, formulation scientists are often concerned with proteinaceous particles (inherent), whereas GMP visual inspectors are more alarmed by process-specific particles (intrinsic). Therefore, a core training set and procedure should be used consistently across all samples and phases, with additional phase-specific training that is tailored to the phase-appropriate assays being performed. Any phase-specific differences regarding visual particle assessment/training, including that performed as part of the annual report inspection, should be clearly described so that results can be bridged as the project moves through the product life cycle.

PARTICLE SIZE

Particles occur as a continuum across the size range from nanometers to hundreds of micrometers. This is especially true for protein aggregates that can vary in size from dimers to very large agglomerates. The current classification of subvisible and visible particles is solely based on the limitations of the available technology and does not rely on any scientific understanding of differences in biological consequences or impact to patients. As described previously, the definition for visible particles lacks consistency primarily because it is defined by each manufacturer based on internal Knapp studies that record the probability of detection as a function of size for a cohort of inspectors and the probability that the company accepts as the lowest limit, usually between 100 and 200 μm . Many companies simply forgo this approach and set their limits based on historical data for other molecules for which clinical studies and patient safety information is already available. Others may even set their limits based on what they have heard from other companies.

The availability of universal standards would make it possible to compile industry-wide data and gather consensus on a harmonized definition of visible particles based on size and particle type. To aid this objective, NIST is leading a collaboration between several organizations to evaluate their "protein-like" ethylene tetrafluoroethylene (ETFE) and photolithographic standards and is in the process of collecting data that will hopefully enable this type of statistical analysis. Concomitantly, another industry effort is just getting started and aims to evaluate the mixed standards set (consisting of extrinsic, intrinsic, and protein-like mimics) from Micro Measurements Labs to determine the level of detectability for individual standards and their mixtures. Ultimately, information gathered from these two efforts will be used to establish a consistent definition of visible particles that can be uniformly applied to all drug products.

TYPES OF PARTICLES AND RISK ASSESSMENT

Risk assessment for visible particles is an important part of a well defined control strategy just as it is for all CQAs. Categorizing particles as extrinsic or intrinsic (and in the case of the USP, as inherent) can help guide a streamlined risk assessment for visible particles. Developing a robust particle profile during development is crucial. This effort can be enhanced by the use of prior knowledge including the creation of a particle library

(23). The library should compile information on particles found in drug products, especially during lot release and stability, with all analytical results including images, spectroscopy, and preferably videos of the particles in motion after swirling. This information is useful not only for risk assessment but also for root cause analysis and subsequent inspector training.

Morphology is an important characteristic of particles that can be used to differentiate between microbubbles, protein particles, and foreign material (24). In-depth morphological characterization of particles that 1) occur during development, 2) are found in reject units during 100% inspection at lot release, and 3) come from the standard sets enable streamlined identification of particle type and source simply by matching morphology and appearance of the test article to those in an existing library. Current imaging systems for subvisible particles, or those under development for visible particles, have the potential to routinely provide morphological parameters for each particle detected, and the proposed chapter should include provisions for taking full advantage of this data.

Particles between 50 and 150 μm fall into the gray zone between visible and subvisible particles (5-6,12,14) and should be explicitly addressed in the proposed chapter. Particles of this size often appear to visual inspectors as a haze or a sparkling tornado after swirling the sample. They are often inherent particles that originate from the aggregation of the active protein ingredient, and for which protein engineering to minimize their tendency to self-associate is not feasible because it decreases the drug product efficacy. Classifying these particles raises a dilemma. If they fall below the threshold defined as visible particles by the compendia but are still detected by the inspectors, can they be listed as subvisible particles and treated as such in terms of lot release and nonconformance? Or perhaps they should be classified under a unique category of particles with assigned specifications and directions for reporting? Based on the risk assessment performed, the therapeutic indication, and the route of administration of the drug product, individual companies might determine that the presence of particles in this subcategory is acceptable based on existing development and clinical data. Because these particles tend to be too large to be detected and analyzed by the typical subvisible particle analysis instrument, the creation of a subcategory to classify these types of particles might be a more pragmatic solution.

Another factor to consider is the reversibility of some particles. Free fatty acids, which can occur from hydrolysis of the surfactants in biotherapeutic formulations, often reverse upon storage at room temperature. Protein aggregates can also be temperature-dependent. If particles disappear under conditions that mimic those of patient dosing and administration or if dosing itself is designed to eliminate any particles that might have formed during the drug product shelf life (such as the use of syringe filters), the risk associated with these particles should be decreased. These issues should be discussed, and direction should be provided, in the proposed chapter.

ACCEPTANCE CRITERIA AND SPECIFICATIONS

More specific guidance for setting phase-appropriate acceptance criteria and/or specifications for visible particles is needed. Specifications should be based on particle type and phase of development (clinical versus commercial). For instance, we know that extrinsic particles are not allowed at any point of the product life cycle. Intrinsic particles pose a lower risk but are generally still not acceptable during lot release and stability testing. Therefore, the proposed chapter specifications should primarily focus on concern of the inherent particles. European Union (EU) guidelines for monoclonal antibodies attempted to provide some clarity to the definitions of “practically free of particles” versus “may contain particles” but at the same time increased the stringency of the proposed specifications without clear support from clinical data. These definitions remain qualitative, and the assignment of “few particles” and “some particles” is still ambiguous (15). These current guidelines are often the source of confusion and discussion between regulators and sponsors during the filing process (25). Implementation and use of universal standards (which should include a semiquantitative set) will eliminate some of the ambiguity in terminology used for particle quantification and allow the transition to a more quantitative analysis. Prior product knowledge and risk assessment of the particles present should be considered when determining an acceptable particle profile for a given product. This process should be

iterative and should evolve over the product life cycle, as more direct data on patient safety becomes available. Here, it is noteworthy that the therapeutic indication of the drug product plays a big role in defining this acceptable particle profile. For instance, immunocompromised patients (oncology) might tolerate a higher particle content than a patient population undergoing treatment for a different indication (rheumatology, for example), and acute administration could carry different risks than ongoing chronic administration of the therapeutic.

The strategy for particle detection should adopt a phase-appropriate approach to specification setting. In other words, specifications should be tailored to the phase of development. Guidance on factors to consider throughout the product life cycle would be a welcome addition to the suggested chapter. For instance, in the early phases of development, a wider range might be acceptable. Later in development, more product-specific data becomes available and enables implementation of an appropriate control strategy to minimize the occurrence of visible particles. At this point, as clinical data on patient safety is gathered along with prior product knowledge, a tighter specification can be set during the advanced stages of development.

CONCLUSION

Visible particles are a CQA that must be minimized and controlled. Although several compendial chapters address them and provide guidance for testing them, the analysis remains very subjective primarily because the training of inspectors, training sets used, and size range tested are determined by individual manufacturers. In this *Stimuli* article, we have proposed a new USP chapter for which we hope to receive endorsement from regulatory agencies and the industry. This chapter would focus on assay suitability and factors that must be considered for visual inspection, accompanied by the establishment and implementation of universal, commercially available standards. The chapter would ideally provide a consistent definition of visible particles as delineated by a lower limit. In addition, clear instructions around the standard training set and the minimum requirements for inspector certification, including results from the training standards, will be outlined. Finally, the chapter will also provide clear guidance on risk assessment for different particle types, including those in the “gray area” and those which are reversible, which in turn allows the setting of acceptance criteria/specifications.

DISCLAIMER

These opinions, recommendations, findings, and conclusions do not necessarily reflect the views or policies of NIST or the United States Government.

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