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General Commentary

A Risk- and Science-Based Approach to the Acceptance Sampling Plan Inspection of Protein Parenteral Products

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ABSTRACT

The requirement for visual inspection of pharmaceuticals has been a compendial expectation for over a century, with some advancement of visible particle control strategies in recent years. Current philosophies include a 100% inspection and an Acceptance Sampling Plan inspection. The particles found during these inspections are normally categorized simply by particle size (visible vs. subvisible), particle source (intrinsic vs. extrinsic) and particle type (inherent vs. extraneous). We believe that a more risk- and science-based approach is attainable, which is grounded in forensic data, toxicological/medical opinions and prior knowledge. We have provided an outline for how to determine patient safety impact of visible particles found in parenteral products and potential actions that could be taken within the quality system regarding lot disposition. We believe this approach focuses efforts on patient safety risks, enhances the use of prior knowledge and improves consistency in how particle observations are handled.

Introduction

Approaches to determine the need for reinspection of parenteral drug products because of an unexpected particle(s) have traditionally been based on particle size (visible or subvisible) and whether a particle is extrinsic, intrinsic, or inherent to the drug product manufacturing process. In the absence of detailed forensic analysis, toxicology assessments, and medical opinions, these criteria simplify the decision of how to react to an unexpected particle found during the acceptance sample plan (ASP) inspection.

A new risk-based approach is proposed that leverages extensive particle information as well as specific quality system actions to drive science- and risk-based decisions to ensure patient safety. This new approach is aligned with current and emerging regulatory guidance that encourages and increases the application of risk- and science-based approaches as well as leveraging prior knowledge. Although this approach could be applied across the particle size continuum, this article is focused only on the application to visible particles.

History and Current State

Visible particles in solution are defined by the USP (United States Pharmacopoeia) as "mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions"[1] and by the European Pharmacopeia as "extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions."[2]

Even though the USP was founded in 1820, it was not until 1915 that USP IX defined the term "true solutions" reflecting concerns with particulate matter. It was recognized then that defining a criterion of a solution that was free of particulates was not practical even though this state was desired. This was followed by the term "substantially free" which was defined in 1942, and it later became the release specification of "practically or essentially free from particles" in European Union and United States guidelines. The current expectation to achieve this specification is via a 2-step process consisting of a 100% inspection of units, followed by a statistically justified sampling plan also known as the ASP. Successfully passing the ASP verifies that the 100% inspection met the objectives and the lot is "essentially free from particles."[3]

In an effort to further refine the particle control strategy, several attempts have been made to divide particles into subcategories and provide applicable guidance. This resulted in nomenclature related to size (visible and subvisible) which was based primarily on the technical capabilities of the analytical instrumentation and the potential origin (inherent, intrinsic, and extrinsic) of the particles.

Although these definitions were a step forward from treating all particles as equivalent regardless of source and risk, this has resulted in unclear expectations of how to react in the quality

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Particle Composition	Cellulose
Product	Monoclonal Antibody
Largest Particle Size	257 µm Length / 5 µm Width
Largest Mass Calculation	5.40 x 10^{-6} g

Figure 1. Example forensic data. Note: data for illustration purposes only.

system to these broad categories. This approach is also not completely aligned with current risk- and science-based concepts that have been described in more recent guidance documents for our industry. In addition, the ambiguity associated with current guidelines has resulted in inconsistent interpretation and application across industry. Considering these experiences and the observation that the existing particle subcategory nomenclature lacks a practical connection to risk assessment approaches, a new methodology has been developed to deliver improvements in this area. This approach is built on the existing ASP inspection; no changes in the inspection process itself are needed or proposed.

Global Particle Library and Approach to Risk Assessment

Over the last several years, Amgen has incorporated detailed forensic data, toxicology evaluations, and medical opinions into investigations of unexpected particles found during the ASP. These comprehensive analyses have resulted in the generation of an extensive historical data set across our drug product manufacturing network. Consolidating this historical information into a single Global Particle Library (GPL) has created an opportunity to leverage prior knowledge and implement a risk- and science-based approach that can be applied to future particle investigations. The GPL is actively maintained, centrally owned, and managed through the quality system to reflect any updates in the accumulated knowledge across the drug product manufacturing network. This library has 3 major categories of information:

1. forensic data including particle composition, product that the particle was observed in, details of the largest particle size identified to date, largest particle mass identified to date, and a photo representative of the particle (Fig. 1);
2. risk evaluation criteria including a product's route of administration, toxicology assessment, and independent medical opinion (Table 1); and
3. patient safety risk that uses the totality of the forensic and risk evaluation information to determine the patient safety risk associated with the particle.

The toxicology assessment (performed by a toxicologist not associated with the product or the organization that determines disposition outcomes) described previously determines the potential patient safety impact from a toxicological perspective and is based on the composition and mass of the particle. The assessment estimates daily exposure to the composition based on the forensic data gathered about the particle and then compares that to published permissible daily exposure limits. The subsequent independent medical opinion assesses numerous elements, including the outcome of the toxicology assessment, the product dosage, prior product complaints, relevant medical literature,

Table 1
Patient Safety Risk Evaluation Criteria

Criteria	Result
Number of particles	1
Intrinsic/extrinsic/inherent	Extrinsic
Primary container type	Glass syringe
Route of administration	Subcutaneous
Potential sources	Tape used in the autoclave, label, cleaning wipes, or printer paper
Patient population	Adult
Toxicology assessment	Not a toxicological concern
Medical opinion	The potential risk to patients from a particle of this type is very low

Note: Data for illustration purposes only.