Table 3: Visible Particles - Just Another Critical Quality Attribute

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SCOPE:
Visible particulates need to be controlled in parenteral products to ensure patient safety. USP <1> and EP <7.0> provide guidance to visible particles in parenteral products. Furthermore, recent USP Chapter <790> and monograph <1790> specify conditions and clarify requirements of “essentially free from particulates” introducing AQL concept. However, there are many common challenges in industry practices and testing, such as setting practical acceptance criteria, analyst training/qualification, characterization of observed visible particles and adequate corrective action. This round table will serve as an interactive forum to discuss current issues and learnings across industry and regulators.

QUESTIONS FOR DISCUSSION:
1. Testing/Training
   a. What types and sizes of defects are included in visible particle testing for analyst/operator training and qualification?
   b. How do you differentiate proteinaceous/inherent particles versus foreign particles such as fiber, glass, metal, etc.? Can analysts be trained to differentiate these?
   c. Which methods are applied for particle characterization and determination of particle identity? When is it critical to characterize?
2. Acceptance criteria
   a. How do you define “essentially free from particles of foreign matter”? What does “essentially or practically free of visible particles” mean in your practices?
   b. What level of particulates is acceptable? How is this established?
   c. Can proteinaceous or other inherent particles (e.g. insoluble break down products of tween) be acceptable? How is this established and what are the criteria for this to be ok? How are particles qualified in particulate prone products, i.e. which data are needed to support/justify the use of a product prone to particulates?
   d. Does route of administration matter in acceptance criteria (Sub-Q, IV, intravenous)?
3. Pharmaceutical Development
   a. How do you prevent or mitigate the risk of visible particles in parenteral products?
      For example, do you use in-line filter throughout clinical development, after launch?
   b. Do you use polaxamer instead of tween in formulations?
4. In use particulate assessment
   a. How do you mitigate risk of positive results due to inadvertent introduction of visible particles to the product at release testing?
   b. For Lyos: Does your reconstitution method consider all components of the kit provided to patients (combination product)?
DISCUSSION NOTES:
Testing/Training for assessment of visible particulates:

- Companies use a panel of particles (intrinsic/process derived but some also inherent particles like e.g. protein particles) in various sizes, mainly between 100-400 micron, to train analysts.
  - Companies are relying on the analyst’s ability to detect and differentiate particles, which is subjective. Thus, visual inspection criteria must be clearly defined, training kits well maintained and representative, and inspectors must be routinely re-trained.
  - Examples/kits of foreign materials to be used for training have to be developed.
  - NIST is developing standards for visible particulates, but they are not readily available yet and may not be applicable to all products and representative for all particle types.
  - Automated visual inspection (AI) equipment may help reduce potentially problematic/subjective human based testing and is used already in the industry. This will require re-validation of the method and to establish link to the historical results.
    - In the future, AI could be used to detect the numbers of protein particles. However, the technology has to be further developed and qualified/validated for this purpose.
  - It is difficult to discern during the visual inspection which are intrinsic vs extrinsic particles. Thus, the particles origin has to be identified (ID) via an appropriate method (e.g. Raman or FT-IR) and a thorough understanding of product characteristics including potential inherent particles must be developed.
  - Train analyst and QA for what is considered “normal/typical” for a specific product, and accept certain types and numbers of inherent (e.g. proteinaceous or surfactant degradation products) particulates for release criteria and/or during stability. Some companies implement an inspection procedure which includes a decision tree for how to judge criticality of certain types of particles, i.e. define requirements for certain typical particle types and phenomena.
  - Internal standards for establishing semi-quantitative acceptable levels (such e.g. as an opalescence scale using actual product) have been developed and applied in some instances.
  - Some companies have established training kits for inherent particles (i.e. protein particles), although it remains unclear how these are qualified and maintained.
  - For certain products that may form particles, knowledge should be gathered during the development stages and a risk assessment regarding safety and product quality needs to be performed. Based on what is expected in the product and acceptable, certain particle findings during release and/or stability may be classified as typical and would not cause an OOS.
  - Descriptions for proteinaceous particles observed by some companies included: “They float (don’t sink like a metal or glass or fiber may), they are translucent and shapeless. Provide other visual characteristics/greater details and quantity based on the development data.

What analytical methods are used for identification?

- A lot of companies rely on optical characterization despite its subjective nature.
  - Visual assessment of DS is a challenge since it is in a bag or bottle that is not fully transparent. Analyst needs to move it from a bag to a glass container and it is hard to prepare particle free container in a lab.
• Precipitates can be ID’d using e.g. FT-IR and Raman spectroscopy to identify the chemical nature of the particles
• There are published papers using confocal Raman microscopy (Single Particle Explorer) to look into prefilled syringes and detect silicon derivatives or cellulose fiber.
• To ID particles, one can isolate particles on a filter, do IR or Raman spectroscopy or LIBS (Laser Induced Breakdown Spectroscopy) for elemental analysis

Acceptance Criteria:
• Presence of visible particles in certain types of products is acceptable provided that they are controlled, have been assessed regarding safety and product quality impact, and justified in front of health authorities. As an example, if a company specifies that up to 10 particles per vial is acceptable, then they have to validate the number and type of particles and provide explanation in the BLA. If quantitative acceptance criteria cannot be applied, companies have used a semi-quantitative opalescence scale with acceptable levels (that have been properly justified).
  • Justification would include assessment of particle identification data, clinical safety data, and data from in-use filtration studies to demonstrate to adverse impact to product strength (if filtration during administration is required).
  • USP 790 describes “essentially free of particles” as related to visual inspection test and presence of extrinsic and intrinsic particles (for some biologics protein particles are considered acceptable providing that its presence is measured and clinical safety proven). USP 1790 chapter (2017) provided further guidance on acceptable AQL for liquid and lyophilized products. There is a discrepancy in interpretation of these new USP chapters between regulators and industry. How many and which particulates are acceptable following introduction of USP 790 and 1790? These discrepancies have resulted in frequent observations at health authority inspections.
  • Many agencies (especially EU) define “essentially free” as zero level, whether proteinaceous in nature or not, for QC release for both liquid and lyophilized products.
• Manufactured lots undergo 100% visual inspection, then QA will allow a certain number of rejects per AQL, then QC does release testing. The dichotomy is that specification implies “no particle” - where AQL allows for some level of reject. The other issue is that for AQL 200-300 vials are examined, in QC you examine only 3 vials (such a small sample number; why do we need QC testing?).
• The level of particles allowed/specification limit may depend on patient population (e.g. immune disease vs vaccine to healthy children or cancer patients)

Risk assessment and mitigation:
• Use risk based approach with a focus on what is important for patient safety and how it is related to product class and manufacturing process. For example, observing a thin fiber may not be as detrimental as seeing an insect in the vial!
• Particles are a CQA - if observed, one should do risk assessment. For example, we are accepting 3% aggregates at product release because safety was established during clinical development, even if it is not desired. Is it a risk? Can same base risk assessment be applied for the particulates during clinical development?
• Regarding risk assessment, there was a discussion that products are actually released by sponsors under controlled manner, but after it is shipped out to the site, the level of control (e.g. handling and preparation for IV administration) may not be as rigorous. Dilution in an IV bag (in which there are many subvisible particles)
might lead to formation of proteinaceous particles during administration; this appears to be a higher risk that the released product.

- Adequate in use stability studies should be conducted to understand and mitigate this risk, e.g. the bag type and IV solution used.
- Particle risk is a subjective one. Risk is assumed without knowledge of what the impact of the particle may be. Has clear link between immunogenicity and particle level been established?

A suggestion was made to agree collectively as industry to better track adverse events and link them back to the lot used and particulate levels/types in that product.

**Combination products:**
- There is a risk product particle formation with use of devices. How do you control a potential addition of particulates from device usage? This should be understood during pharmaceutical development.
- Some lyophilized products are considered as combination products, e.g. if there are vial adaptors to reconstitute. Should all elements (i.e. in-use parts) be used for QC release?
  - “In-use studies” are done as part of Pharmaceutical development.

**Particle detection on stability:**
- Particles should be trended on stability to establish what is “expected” vs unexpected.
- If particles are observed occasionally/randomly on stability, how does one proceed?
  - The discussion was about a case where product that had passed 100% inspection and release testing, randomly showed a particle (e.g. a fiber) at a stability time point.
  - If it is not clear whether the particle is intrinsic or extrinsic, then ID testing has to be performed. A foreign particle is not a stability trend. In all cases, “unexpected” events should be investigated (even if within the specifications).
- Do you see any relation between growth of subvisible particles becoming visible?
  - Not necessarily, one would look to see if there is a stability trend.

**Pharmaceutical Development**
- Particles should be ‘qualified’ during clinical development to demonstrate that product is safe to use.
- Manufacturing process changes might impact particulate formation; this should be studied during development.
- Based on the FDA inspection experience, changes in raw material or process contact surfaces led to the formation of visible particulates in the final drug product.
- For virus-like-particles you get pairwise interactions and fractal aggregates in subvisible range that all of a sudden you can see.
- For siliconized prefilled syringes, a large set of particles may be seen that are different from container to container. Silicon nucleus forms particles or denatures the protein to form particles.
- How do you mitigate particles?
  - Understand the product. Visible protein particles contain very little amount of protein (usually does not impact protein concentration of the product), but they are a safety concern.
  - Controls to minimize generation of particles should be implemented consistently across employees/sites (controlled processing/storage temperatures, handling of the product, and production time).
  - In-line filters are often used for risk mitigation. However, use of a filter doesn’t mean you don’t control particles and allow for many particles in the product (must
demonstrate control of process). In-line filtration must be demonstrated to have no adverse impact to product strength / potency.

- The container/closure and device should be carefully examined during the development e.g. if glass delamination is observed it necessitates a change to better quality of glass or the presence of tungsten or presence of excess silicon oil in prefilled syringes may lead to protein precipitation.

- In some circumstances particle level increase right after reconstitution of a lyophilized product. Allow sufficient time before analysis for reconstituted solution to make sure it is equilibrated.