Table 32: Visible and Sub-visible Particles: Practical Experiences in Manufacturing Support and Quality Control

Facilitators –

George Bou-Assaf, *Biogen*

Jan Olaf Stracke, *F. Hoffmann - La Roche Ltd.*

Scope:

Sub-visible and 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.

With regard to subvisible particle testing, low volume DP presentations (for example AAV products or dosage forms for intra-vitreal administration with fill volumes as low as e.g. 0.25 mL) are gaining importance in the industry. New testing strategies and technologies are required to deal with these challenges.

This round table will serve as an interactive forum to discuss current issues and learnings across industry and regulators.

Questions for Discussion:

1. Visible particle Testing/Training
    a. What types and sizes of defects are included in visible particle training sets?
    b. How to differentiate inherent particles versus foreign particles?
    c. Which methods are applied for characterization and determination of particle identity?
    d. Can visible particle standards (NIST) be used to enhance training toolkit?
    e. Manual or automated visual inspection? Advantages (and maybe limitations) of automated visual inspection instruments over manual inspection?
2. Visible particle acceptance criteria
    a. What does "essentially or practically free of visible particles" mean?
    b. What level of particulates is acceptable?
    c. How are particles qualified in particulate prone products, i.e. which data are needed to support/justify?

3. Subvisible particle considerations for low-volume products
    a. What different strategies are each of the companies adopting?
    b. Beyond light obscuration, what are other techniques are companies looking into? Acceptable by regulatory agencies?
    c. What other considerations need to be taken into account?

Discussion Notes:

January 26 and 28, February 1 and 3, *combined* –

Visible particles definition and characterization

- In development, no training set but QC has dark fiber, large piece of metal, translucent bead, fairly obvious visible particles in training set, which does not always prepare for real samples.

- 100-150 um is observable by inspectors. Cutoff size below that is difficult for most but some can detect down to 50-70 um. Grey area is 50-150 um. Probability of detecting a particle goes up with the particle size. 20% at 100um, 100% at 500 um.

- Distinction between particle and container defects which might be ~300 um in size: Inspectors should be trained to distinguish between the two.

- If particle is observed, or if product prone to form particles, a second analyst is called to confirm the observation. This is for product specific or study/characterization specific case, not all.

- Differentiation between inherent and foreign particles: methods should be descriptive to tell particles apart. Inherent (proteinaceous) particle have irregular shapes and are translucent. Orthogonal methods are used for characterization.

- If 1 particle is observed, yes, characterization is always performed.

- If particles are identified, we would identify for morphology, and FTIR, particle ID is done by Raman because FTIR has a filter and this could squeeze the particles.

Visible particles acceptance criteria

- What does it mean “essentially free from particles of foreign matter”? There are acceptance criteria to meet. Russia does not accept "essentially" and so there is no exception and it's difficult to justify. Russia pharmacopoeia have a different definition of particles, that are not the proteinaceous one. Japan might be another country with specific requirement.

- What is the cutoff for acceptable number of particles? What does essentially free of visible particles means? Is 10 particles acceptable? No clear answer. The definition of "essentially free" evolves with the lifetime of the product development: permissive in early stage, more restrictive in late stage, and strongly dependent on clinical experience and the indication (ophthalmology USP 789 more restrictive)

- If particles grow on stability, because it interacts with an excipient, or degradant like polysorbate, how do we handle it?

  - 10-20 vials tested for SVP (Roche), 10 (GNE)

- If comparability shows differences, for example for polysorbate oxidation, we need a clear ID of the particles, and what is the risk/impact of the presence of those particles.

  - Roche asked by FDA to set the specs based on batch history, not based on compendial limits. GNE also confirmed that for commercial process we would be asked to tighten to process knowledge.

- Compatibility with the same filter sourced from multiple markets would be used to avoid calling out the filter supplier name, and therefore avoid calling combination product.

Methods for characterization of visible particles

- What technology is used for characterization? In development, extensive characterization performed. MFI, tweezer technology to isolate particle with Raman analysis

- Hound instrument comes with database or can purchase but typically need to build own by stressing material for example, add known potential source of particle i.e. glass, plastic etc

- Morphology. Easiest is fibers, elongated, easily identified. Proteinaceous particles are more tricky to describe

- RI system Spheryx technology can be used for particle ID. New technology

- Particles observed at the clinic site. Risk assessment performed. Beyond realm of CMC(?)

Manual vs. Automated visual inspection:

- Manual is required for Japan and typically catches more defects.

- Automated visual inspection is used during manufacturing. Can it be used for release and stability? Roche has a robot that picks up vials to place them in front of a light source, but not yet used. Automation would allow for increased consistency but also increased number of vials that can be analyzed.

- Compendia method is manual.
- Automated is used for 100% visual inspection during manufacturing. If we were to move to automated for release, this would not be covered by compendia.
- Current methods for SVP are destructive, so cannot used in process.

• Standard beads are used for system suitability checks. But they have optical properties different than those of proteins. That's why ETFE particles (NIST) might be more suitable because they mimic proteinaceous standards.

• Specifications are linked to USP methods. We cannot judge how big the particles are "in the moment", everything that can be seen is considered visible.

• NIST standards. Would you intent to use are system suitability or for training? Good idea, stimuli article coming out Mar-May to talk about what we need, may be included in monograph.

• Companies put training in place for inspectors. Methods are usually validated with not more than precision.

• Attribute for automated inspection/automated method. Currently calling for participating instrument companies to build prototypes. 30k fee for companies to be part of the consortium and another 30k to participate in the study (?)

• Automated platform is already used in industrial setting for vial inspections. Limitation with air bubble interference, which is frequent, may trend towards over sensitivity. Semi-automated system exists, typically wipes outside of the vial, shakes the vial, use camera to take picture, AI based analysis.

Subvisible particles: challenges with small volumes.

• There are two compendial methods for SVP, HIAC and a filtration method. The HIAC biggest problem is the sample prep. Precision also decreases as particle size decreases, so not very precise for 2-5um.

• SVP what is the range: GNE would report 10-25-(50 for ophthalmology) and internally we trend 2-5. methods are not reliable at size smaller than 2

• Silicon oil: not considered harmful so could be justify an OOS, but not acceptable to be constantly above the ranges allowed by the compendia. Control in place at the raw material (syringes controlled minimum and max level of silicon oil).

• Subvisible particles. With gene therapy, sample size is small. How do you perform testing? 0.2 mL for HIAC is reasonable. Validate methods for smaller volumes. Backgrounded membrane imaging technology (BMI, HaloLabs) for AAV products is promising. It uses significant less

volume than the HIAC. Since this is a filtration method and you count particles on a filter, it could be sold as "compliant with the Ph.Eur. Requirements

- New methods need to be validated to show they are suitable. We do not have to use compendial methods, but have to bridge between compendial and new method.
- A new method combines MFI and HIAC.
- Instead of pooling several vials. Can we pool less vials and dilute to make up enough volume for the assay and then back calculate? Dilution is viable but it may result in overestimating the number of particles due to principal of back calculation.