Roundtable Session 2 - Table 18: Visible and Sub-visible Particles: New Approaches and Requirements

Facilitator: Yuting Huang, Legacy Seagen/Pfizer

Scribe: Susan Clardy, Mersana Therapeutics

Abstract:

Visible and sub-visible particles are a major concern for the quality and safety of injectable products, such as biologics, vaccines, and gene and cell therapies. They can affect the stability, efficacy, and immunogenicity of the product, as well as cause adverse reactions in patients. Therefore, it is important to have a robust and comprehensive approach to control, detect, and prevent particulate contamination in these products.

With the recent revision of USP 1788 and updated FDA draft guidance on inspection of injectable products for visible particulates this roundtable discussion aims to explore the new approaches and requirements for visible and subvisible particle testing, as well as the challenges and opportunities for the industry and regulators.

Discussion Questions:

1.) What type of techniques are being developed and implemented in orthogonal to light obscuration/HIAC? Is it expected to correlate the results between methods using stress conditions and stability time points?

2.) Current agency and industry expectations on sub-visible particles 2-10 um characterization?

3.) How to establish acceptance criteria for visible and sub-visible particles based on the product specifications, patient safety, and clinical relevance?

4.) How to use automated visual inspection systems to improve the efficiency, accuracy, and consistency of visible particle detection and classification?

5.) How to develop and maintain a library of reference particle data for different products and sources of contamination, and how to use this data for particle identification and root cause analysis?

Notes:

What type of techniques are being developed an implemented in orthogonal to light obscuration/HIAC? IS it expected to correlate the results between methods using stress conditions and stability time points?

Key takeaways:

- Unchained Labs- UNCLE- protein stability screening platform is more in the nm range—imaging is more in the µm
- DLS—nm size--- HIAC or flow imaging micro (MFI) bigger
- HIAC-FTIR

1. Current agency and industry expectations on sub-visible particles (2-10 µm) characterization. What phase do you introduce characterization?

Key takeaways:

- The agency has requested:
    - correlation between sub and visual particles with the assumption that sub is precursor.
    - development data correlating particles with stability
    - more characterization for 2-10 µm
        - Characterization has been requested for a long time—but it's not a requirement.
- As technologies improve, we should be using them to understand particles better.
- When do you introduce?
    - Characterization often is launched due to an investigation.
    - Others use characterization during stability testing by adding FTIR, flowcam and other assays on a yearly basis.
    - Small companies still perform characterization data by Phase 1 and 2
    - If you have a large enough lot, gathering the data is ideal but may be overkill if you do not have a particle problem.

2. How to establish acceptance criteria for visible and sub-visible particles based on the product specification, patient safety, and clinical relevance?

Key takeaways:

- SV particle specification were set and FDA accepted
    - 8 batches—calculated who many particles where given to patients and they didn't have any adverse effect
- EU compendial overarching document states that it does not apply to certain biologics (like vaccines)--there is no such disclaimer in the USP
- "Particle passport"
    - Gather as much historical data of particles as possible
    - what you have done to reduce—sometime impossible

    - correlate to the clinical data(safety, etc)
- Sometime particles in your DP are unavoidable.
    - Need to demonstrate:
        - Understanding of the particles—do this as early as possible
            - What is seeding particle, for example
            - Mass spec for ID
        - Control of the particles (process control)
        - Safety (clinical relevance)
            - Cant be your justification if you do not have control in your vials (must be homogeneous)
        - Everything that was done to reduce particles
        - Risk and benefit argument
- Specification setting for the Sub VP (upper range) people have experience with this.
    - 10-20µm requires characterization to understand and to set the specification
    - Dialogue with agencies---
    - Trying to show with and without particles—risk assessment for clinical
- Some experience with
    - submitting recent BLAs without specification.
    - post marketing agreement that we would drop the specification of report results.
- Harmanoize sub VP---too many variations of products—color, clarity, etc

3. How do get marketing authorization setting for “may have particles” or “essentially free” or “will contain” labels

Key takeaways

- Example of “will contain” for Oligonucleotides product was given—in line filters are required.
- For a “May contain” label
    - Sponsor had to show consistency, fully characterized, done everything to remove it---this is for proteinous particles

4. How to use automated visual inspection systems to improve the efficiency, accuracy, and consistency of visible particle detection and classification?

Key takeaways:

- Visual inspection is flawed—papers and examples were described were particles were missed by humans.
- You have to qualify and use manual confirmation by sampling to ensure the automatic machine works.—this still requires visual inspection
- Group gave examples of semi-automated inspection done in the development stage to catch things that then were screened by a human.
- Potential issues with Automation include:
    - artifacts(bubbles) from mixing too fast
    - Equipment not available at end user site
        - Visual inspection is the last line of defense at the clinic

- You need to define what the particle is and this can not be automated
- An inability to detect all particles due to difference in sizes
    - AI was suggested as a tool to overcome this limitation.
        - Handful of companies trying this
        - 1000-2000 particles are needed to train AI models—not possible for small companies.