Table 22: New Challenges for an Old Problem: Tales of Subvisible Particles

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SCOPE:

Subvisible particles (SVPs) are a common drug product (DP) impurity. They are classified as either intrinsic, extrinsic, or inherent and must be controlled to meet regulatory requirements such as USP <787> and <1787>. Detecting, quantifying, and characterizing SVPs in a DP is essential to understanding the process, the product and product stability because different types of SVPs have different degradation pathways. The two most common analytical tools to quantify SVPs are light obscuration and flow imaging techniques. Additional tools are used to characterize the chemical composition of SVPs such as scanning electron microscopy with energy dispersive X-ray spectroscopy and attenuated total reflection Fourier transform infrared microscopy. In 2015, two white papers discussed the strategy and considerations for SVP analysis as well as case studies from the participating companies (J Pharm Sci. 2015 Jun;104(6):1899-1908 and Biologicals. 2015 Nov;43(6):457-73). In this roundtable, we will discuss how companies analyze SVPs, the challenges with SVP analysis, and how SVP data is used during process and product development. We will also discuss unique issues presented by polysorbate degradation.

QUESTIONS FOR DISCUSSION:

1. What analytical tools are used for quantifying and characterizing SVPs?
2. Is the primary focus particle counting, particle characterization or both?
3. What are the most common types of SVPs encountered during development?
4. Are different methods used to analyze different types of SVPs?
5. What are some of the challenges you face during SVP analysis and how do you overcome them?
6. What unique challenges are presented by transient, free fatty acid SVPs arising from polysorbate degradation?
7. How is SVP data used to guide biopharmaceutical product and process development?

DISCUSSION NOTES:

- HIAC is primarily used for release and stability, MFI for characterization only. IR/Raman technologies are used to ID the particles. Visible particles are picked and measured by FT-IR. Subvisible particles can be filtered and the filter analyzed. Caution needs to be exercised with filtration to avoid particle clumping and particle growing. In addition to traditional techniques, scanning electron microscopy can be used.
- Sample handling needs to be taken into account. The results often indicate a heterogeneous mixture of proteinaceous particles, fatty acid particles, and other intrinsic or exogeneous particles such as glass, rubber, and silicone oil.
- Discussion around sub-micron particles: different companies are using RMM and NTA for characterization purposes only. RPS is also used and provides a continuum distribution of particle concentration. People did not see good correlation between SMP numbers and SVPs or VPs. This is consistent with historical observations that particle formation tends to be product specific. Different products may form SMPs, SVPs or VPs and no real

connection – don't see that smaller particles grow into larger ones, but different and distinct degradation pathways.

- Validation of MFI methods: need for particle standards. The recent availability of ETFE standards might make this possible in the future.
- Particles concern not only safety, but also quality and manufacturability (blocked filter). Hence, the need for testing on a continuous basis.
- Types of particles: proteinaceous, Si oil (especially in syringes). Si Oil can be characterized by Raman in solution. However, IDing a protein particle in a protein solution might not be possible. Mixed particles can also be observed (i.e. Si Oil and protein particles). Transient free fatty acid particles have also been observed. Do we envision that MFI will become part of USP 787. Do USP limits need to be changed? Perhaps the better approach is not to work towards meeting the limits but rather set specifications and action limits
- How do we deal with DP that have high viscosity if we are concerned that dilution will dissolve the particles? Dilution strategy deals with the high viscosity, as long as the method is providing consistent results and orthogonal tools are used, reversibility of particles should not be a concern.
- Vial-to-vial variability and syringe-to-syringe variability needs to be taken into account. This becomes a real challenge when considering ophthalmological indications.