USP/IQ Consortium Roundtable: Subvisible Silicone Oil Droplets on Particle Analysis

Meeting Summary

Disclaimer

Views and opinions expressed in this document are those of the speaker/participants and should not be construed to represent FDA's views or policies. Certain commercial equipment, instruments, or materials are identified in this presentation to foster understanding. Such identification does not imply recommendation or endorsement by FDA, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

Products with Increased Levels of Silicone Oil subvisible particles (SbVPs)

- Industry adopting a patient centric approach by using new devices that can be administered at home, etc. (usually coated with silicone oil), has contributed to a trend of increasing challenges from silicone oil and silicone oil particles (SiOPs) in DP
- Typically, for intravitreal products in pre-filled syringes (PFSs), Method 1 can fail due to presence of SiOPs, but Method 2 passes, and a 2-stage testing approach is adopted as routine testing.
    - In addition, use of orthogonal methods
    - This could also be discussed for products intended for other routes of administration
- Discussion about the historical context of compendial USP<788> limits and meaning for biologics (ICH 6B)
- 1mL/2mL PFS typically exhibit product-specific behavior for amount of silicone oil droplets.
- Options to minimize SiOPs and silicone oil in product.
    - Mitigation of issues related to silicone oil, considering a return to vial + syringe option.
    - Selection of a syringe that causes less silicone migration into solution (e.g. cross-linked silicone oil or baked-on silicone oil).
    - Silicone oil-free syringes (plastic, EZ cartridge): reduces amount of silicone oil particles but faces other challenges, e.g. sterility or other process-related particle types.
- Stand-alone syringe (without vial backup): should include not only confirmation of silicone oil presence but also quantitation and safety assessment.

- How to quantitate silicone oil: size/count-based quantitation versus direct measurement of silicone oil by NMR/ICP-MS.
- Assume worst-case condition, that the total amount of silicone oil that the manufacturer applied will ultimately end up in the DP (this does not appear to happen).

- Silicone-oil induced drug stability versus expel-induced SiOPs.
- If we want to determine how many SiOPs the patient was exposed to then expelling the sample in the same way it is delivered in the clinic gives this result. If for investigation purposes, we want to see how much SiOPs in solution the DP would have been exposed to during storage, removing from the back so as not to add more droplets from the sample handling is the appropriate method.

- Long history of application of PFS in industry, but larger volume (e.g. 2.25 mL) is more recently used, subvisible SiOP challenges usually associated with larger volume PFS

2. **Current Orthogonal Methods to Quantify Silicone Oil Droplets**

- Mostly Flow Imaging is being used because LO undercounts SiOPs and cannot distinguish SiO particles from others. While running samples for SiOPs one of the best practices is to run absolute and regular controls to establish the amount of SiOPs coming from the PFS. Absolute control is one where the drug sample is drawn directly from the vial in absence of the syringe. Regular control is one where the drug sample is drawn with the help of syringe. There are no good reference standards available for silicone oil SbVPs and this would be necessary to develop a robust method. The only available standards are for sizing and counting of SbVPs (e.g. polystyrene beads and ETFE)

- Classifying/Distinguishing SiOPs from other types of particles.
- Aspect ratio: 0.85.
- AI-assisted classification, image analysis.
- There is variability using flow imaging method. We need to understand the variability of the measurement by flow imaging

- Reproducibility: using same method for same sample across different companies to compare the difference of FI data across industry
- Flow Imaging runs generate thousands of particle images consisting of a mix of protein particles, SiOPs and other particle images. AI-based data analysis software can be

implemented to help distinguish, classify and categorize SiOPs based on a rigorous training set. While implementing AI it is important to test several runs to make sure AI is able to distinguish SiOPs with a confidence level of XX% higher.

- Morphology-based versus refractive index-based classification (Spheryx).
- Classification based on density (RMM) but current instrument no longer supported.

- When particles are <50 µm, more pronounced difference between LO/FI
- Combined Flowcam/LO instrument picks up difference in counts due to silicone oil
- It was mentioned that the Flowcam/LO instrument showed different LO results compared to HIAC.

3. **Siliconized Primary Container Control and Strategy**

- The selection of the primary container components iscritical to subsequent susceptibility of migration (leaching) of silicone oil into drug product.
- All components are critical including physical and chemical nature of the containers due to the primary consideration of silicone oil which is to minimize frictions during movement, thus both the container and stopper (e.g. syringe barrel and plunger stopper) must be evaluated as pairs.

- There are limited manufacturers of devices using modern day advanced manufacturing with particle controls meeting pharmaceutical grade standards, many aspects of manufacturing, e.g., glass (from delamination) might be more “industrial grade”
- However, this is not a challenge as many pharma, biotech and contract development manufacturing organizations leverage high quality platform devices, but silicone oil migration into solution is still highly variable and must be evaluated in the context of the drug, especially for high concentration and non-typical formulations (e.g., Cook, Abstract PEPTALK)

- Product Quality (viscosity) and Device performance (e.g., BLGF, selection of AI) must be taken into account including interactions of products with silicone oil, as well as migration of silicone oil during administration and longer term stability for physiochemical PQAs.
- To assure patient safety and meaningful product specific specifications, the approach to setting specification is thorough product characterization, including orthogonal

methods, of clinical material as well as drug admixtures (e.g., dispensed from syringes) that includes the counts **AND** also the composition of characterizable subvisible particles (e.g., how much SiOPs, how much proteinaceous particles, and the method of classification) during clinical development.

- The application of machine learning algorithms to analyses of these orthogonal data (e.g. Spheryx, MFI, Flowcam) is instrumental in understanding how clinical safety is related to the impact of silicone oil on products quality and device functions

- During product development, leveraging of data including multiple product configurations should be used to evaluate the inherent proteinaceous subvisible particles (in a vial) vs the intrinsic silicone oil in a device
- Innovations such as cross-linked silicone oil syringes should be evaluated (refs)
- CDRH input (tbd)

4. **Specification, Quality, Stability**

- PFS is a late introduction to clinical trials, typically in Ph3, resulting in insufficient time to react to issues related to SbVP or sufficient data generated to set a specification for silicone oil droplets.
- Building a new specification takes time, first report results, and establish AC based on ~50 lots.
- Typically, compendial acceptance criteria are used, even if the particle counts are much below compendial limits.
- Most companies use compendial specifications for SbVPs based on USP<788> while having internal acceptance criteria and action limits that are product-specific and can be lower than the compendial limits. Stability trending is typically monitored and acted upon in the quality systems.
- USP and FDA recommend setting product specific limits based on available data, manufacturing capability, clinical safety data and route of administration and to use orthogonal methods in addition.

5. **Toxicology of silicone oil and SiOPs**

- Additional clinical safe history and preclinical toxicological data are necessary to de-risk "high SiOP" counts.

- Analytical characterization of particles aids in toxicological qualification.
- Toxicology/E&L perspective - toxicology of silicone oil - Assessment through updated, appropriately designed preclinical studies using animal models
- Apply tiered approach to determine the leachable risk: clinical relevance in analytical study designs for toxicological assessment.
- Minimal absorption of silicone oil to human body, but it may impact kidney
- Possibility to leverage data from other clinical data for silicone oil impact (residual) in patients. Chemical characterization of silicone oil used in manufacturing of combination product devices.
- Product specific data can make assessment of toxicological risk of silicone oil more clinically relevant (this is challenging- product specific data is not always available).
- Toxicologically, differences in the chemical used between sprayed-on and cross-linked silicone oil in PFS are considered minimal.
- Immunogenicity impact is particle type dependent- chemical characterization of particles critical to correlate immunogenic reactions.
- Silicone oil subvisible particle counts and silicone oil content (analytical characterization), as well as particle size have a different impact on clinical safety.

6. **Product Quality concerns from Silicone Oil introduced into the drug product or drug admixture from materials/devices during clinical administration – In use compatibility perspectives based on risk of exposure**

The Potential for safety adverse events from silicone oil for biologics is comprehensively reviewed in Saggu et al. Overall, the case studies in the Saggu paper indicate the presence of silicone oil is “low risk” for adverse events in the clinic.

- Comprehensive characterization of the SbVP profile of your product and the potential impact of long-term exposure to silicone oil in the delivery device on drug product quality is critical to ensure the drug developer understands the sensitivity of the product quality to silicone oil from medical devices. Some manufacturers are using a co-packaged approach for improved control of the devices used with their product

- One emerging trend is the use of closed system transfer devices (CSTDs), which can have many moving parts that can introduce Si oil
  - silicone oil is being more prevalently used due to state and national laws
  - Amount and type of silicone oil from CSTDs can be variable, thus vendor information is critical. Also understanding how they can introduce silicone oil from various interactions (recon, compound, admin)
  - CSTDs have been the subject of a previous roundtable, and multiple publications. An important issue is whether the CSTDs should even be employed with biologics, where there is little chance of toxicity but the devices itself can result in administration of a decreased dose of drug, etc. This is out of the scope for this particular article.
- Filtering should not be considered a control strategy, because filtering is not a substitute for thorough understanding of subvisible particle load and it is the responsibility of drug manufacturer to reduce particle counts. The expectation is that the drug product and admixture using the designated route of administration will meet subvisible particle limits. It is the responsibility of the drug developer to understand the silicone oil risk and contribution of these many clinical devices and how it impacts the drugs. The goal is to have a thorough understanding of the total silicone oil load including SiOP distribution and characteristics (e.g. adsorbed protein on the surface of the SiOPs) going into the patients, addressing them both through risk assessments and testing.
  - Filtering can be used to “reduce” particle load, as a redundant safety precaution, but not a formal control strategy.
  - The Drug Product and clinical admixture need to meet the SbVP specification or critical quality attributes “expectation”, and particles should be minimized and controlled
  - If there is high particle count, determine the root cause and implement a control strategy around this.
- One member suggested that the USP<788> spec for DP can be applied to IV preparations that are used without inline-filter
  - One must understand the compounding and Route of Administration (RoA) strategies need to be evaluated for particle load (impact of bags Materials of Construction (MoCs), dilution factors, diluent etc)
- Feedback during discussion: need to define a level of silicone oil/SiOPs that is acceptable for IV administration. While we would like to have that, it is difficult to set

the bar at the right level for all products. It should be ideally clinically relevant, meaningful to the product and minimized as long-term safety of exposure is difficult to be determined.

- Start with the default specifications, but minimize and control all particles shed from the IV bag and tubing (often adds particles of material from IV bag), as part of compatibility study for IV bags. RoA routes and other primary container (e.g. cartridge) need to be evaluated as well.
- The concern should be total amount of silicone oil that is injected into patient (dose), and any immediate impact of silicone oil addition to the protein product quality. Then consider long-term chronic exposure

7. **Looking forward**

- Next steps (proposal) - USP drafts stim article and informational chapter on guidance of silicone oil analysis/control in PFS products (reasonable limit, Dependence on modalities/indications)
  - USP position: should have an analytical method for measuring silicone/silicone oil first. After a method is defined, then we can talk about developing a new chapter for silicone oil. USP<788> is a harmonized chapter – aligned with EP and JP. Do not want to change this chapter.
- Road show/Conference, e.g. AAPS or CASSS, to expand the learning from USP/IQ meeting discussion (e.g. West coast to accommodate for time difference)
- Suggestion: FDA and other agencies have the submitted data on subvisible particles. Could they look into flow imaging data and give a summary to understand the trending? Could this be published, at least as a stim article in the PF?
- IQ consortium – already collected flow imaging data from pharma companies for benchmarking, data analysis completed and manuscript in preparation