New USP Informational Chapter <1787>: Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections

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USP<1787> is a new informational chapter intended to supplement USP<787> on Measurement of subvisible particulate matter in therapeutic protein injections. The chapter provides guidance on setting strategies for identifying and characterizing the various particle populations in such products, during development as well as lifetime of the product. Characteristics of proteinaceous particles include size/count, reversibility/dissociability, structure/conformation, chemical modifications and composition/identification. It includes a summary assessment of methods that can be useful in this effort.
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• Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections

• Informational chapter on methods and strategies for measuring and characterizing proteinaceous particles, size range 2 – 100 µm

• Objectives: Enumeration, Orthogonal characterization, identification, root cause analysis / nonconformance investigations…
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- Not a recipe for when to use the methods
- Not a recipe for which methods to use
- Proposes Categorization of Aggregates in aid of Objectives (as required)
  - Size / Count
  - Composition / Identification
  - Reversibility / Dissociability
  - Structure / Conformation
  - Chemical modification
  - Morphology

Aligned with USP definitions: SbVP can be assigned to one of three categories

- **Extrinsic particles** (from the outside) are materials that are not part of the drug product, package, or process, but are present due to contamination. These are truly foreign particles that are unexpected in drug product (e.g., insect parts, paint chips, clothing fragments, hair).

- **Intrinsic particles** (from the inside) are undesirable, non-protein material from degradation of formulation components, or related to the manufacturing and packaging processes and the device itself (e.g., glass lamellae, particles arising from packaging materials for drug product components, rubber from stoppers, silicone oil).
Aligned with USP SbVP definitions

- **Silicone oil droplets** are important intrinsic particles resulting from the silicone oil that is a necessary lubricant in pre-filled syringes. They can confound the analysis of the total subvisible particle population, and also have the potential to interact with the protein depending on formulation conditions\(^1-4\)

![Silicone oil droplet image]

- **Inherent particles** are particles which originate from the drug product, either the protein therapeutic itself or formulation components. These particles can be an expected characteristic of the drug product.

![Inherent particle images]
Aligned with USP SbVP definitions

- **Particles can also be heterogeneous**, consisting of mixtures of compounds from more than one of these categories.

- Heterogeneous particles are classified based on their non-proteinaceous component.
  - For example, glass particles coated with protein would be classified as an intrinsic particle
  - the characterization of these heterogeneous particles would include considerations based on both constituents
Particulates Strategy - 1

• Early Stages of Development
  – Guide candidate selection
    • Limitations – Amount of material
  – Understand particulation propensity
    • Risk assessment / product profile decision
  – Typical particle profile of product
    • Knowledge of particles in preclinical and clinical trials
    • Size/count and distribution
  – Typical morphology

Note: Archived samples are likely not very useful for particulates ⇒ Settle early on method(s)
Particulates Strategy - 2

• Later Stages of Development
  – Goal: Understanding and Controlling Risk
    • Risk Assessment, Control Strategy
  – Impact of Formulation, Manufacture, Storage, In-use, Stress conditions
    • Monitoring and trending size and counts
    • Aid in development of product and process that minimizes particles formation
    • Comparability, Investigations
  – Orthogonal / Enhanced characterization
  – Forced Degradation
    • Develop control strategy
Particulates Strategy - 3

• Commercial
  – Goal: Managing Change
    • Alignment with Control Strategy
  – Impact of changes (site, scale-up, strength, container/closure,…)
    • Monitoring and trending size and count
    • Comparability
## Attributes of Particles / Aggregates

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Analysis</th>
<th>Potential Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size and Count</td>
<td>Well established methods; Representative sampling easy; Primary information about particles</td>
<td>Broad – Trending; Risk assessment; Root cause analysis</td>
</tr>
<tr>
<td>Composition / Identification</td>
<td>Bespoke methods; Considerations about representative sampling; Secondary information about particles</td>
<td>Risk assessment; Root cause analysis; Understanding impact of changes or choices during process and product development; Inform process control; Immunogenicity …</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
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<tr>
<td>Reversibility / Dissociability</td>
<td></td>
<td></td>
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<tr>
<td>Chemical modifications</td>
<td></td>
<td></td>
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<tr>
<td>Conformation / Structure of protein</td>
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</tbody>
</table>
Non-Proteinaceous Particles

• Extrinsic and Intrinsic Sources
  – Control through process and components
  – Components can carry / shed particles
    • Stoppers
    • Fill equipment, especially if disposable containers etc. are used
    • Pump shedding
    • Filter shedding
    • ...

(Note: Silicone oil particle are generally intrinsic)

• Risk assessment of process to determine potential sources of particles and take steps to control

• Literature shows (exaggerated levels of) extrinsic/intrinsic particles can function as adjuvants
FDA Expectations ~2-10 µm Range  
(synopsis from Susan Kirshner’s presentation at Breckenridge, 2014)

• SVP between ~2-10 µm should be studied using quantitative methods (from early stages of development)

• No particular method is recommended  
  – Most frequently used is LO

• Particles should be characterized to inform method dev., risk assessment, specs setting  
  – Particle shape, type, size distribution  
  – Images helpful for review

• Include particle analysis in Forced degrdn. studies; risk assessment; control strategy
Summary

• USP<787> has been developed for subvisible particles in therapeutic protein products
• USP<1787> Guidance further elaborates the strategy
• Orthogonal methods required to characterize particles beyond size and count
  – id, composition, morphology, reversibility, conformation,
• Know your product. Monitor particulates (esp. size > 2 µm) in development to create a product (manufacturing and stability) history and understand liabilities, and thereby create proper control strategy.
Thank You

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Back-Ups
Particles: Categories

- Submicron
- Subvisible
- Visible

Size categories:
- 0.1 micron
- 1 micron
- 10 micron
- 100 micron
Particles: Risks

- Immunogenicity risk? (Protein particles)
- Capillary Occlusion risk (Foreign particles, Protein particles?)

Measure for Process and Product Characterization (Protein particles)
Particles: Control

Immunogenicity risk? (Protein particles)

Capillary Occlusion risk (Foreign particles, Protein particles?)

Measure for Process and Product Characterization (Protein particles)

SEC Specifications

Control gap

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Particles: Measurement

- Immunogenicity risk? (Protein particles)
- Capillary Occlusion risk (Foreign particles, Protein particles?)
- Measure for Process and Product Characterization (Protein particles)

- 0.1 micron
- 1 micron
- 10 micron
- 100 micron

- Measurement gap
- Control gap

- SEC, AUC etc

- USP<787>; <788>

- > 2 micron by LO, Flow Imaging