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PARTICULATE CONTAMINATION IN SINGLE-USE SYSTEMS: MEASUREMENT CHALLENGES

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Summary
In the application of single-use systems (SUS), the pharmaceutical manufacturer “outsources” process cleanliness to the manufacturer of the SUS, since no rinsing or cleaning occurs prior to implementation. While visual inspection may detect “visible” (≥ 100 microns) particulate contamination, the probability of detecting particulates on fluid contacting surfaces within single-use components remains low due to the difficulty of seeing through translucent or turbid plastics. Extraction (flushing, washing) of fluid contact surfaces allows collection of particles for quantitative microscopic analysis. Here we present studies comparing extraction methods (agitation/rinsing), and extraction fluids (solvents/aqueous media). These studies highlight challenges in the development of methods for measurement of particulate contamination in SUS.

Definitions and Methodology
Visible Particulates (particles and/or fibers) ≥ 100µm
Sub-visible Particulates 10-100µm
ISO 16232 (VDA 19) determination of extraction efficiency:
- Repeated extraction of same component under constant conditions
- Calculate relative particle counts (%):
\[ C = \frac{\sum L_i}{\sum L_t} \times 100 \]
where \( C \) is the cleanliness value, \( L_i \) the number of the extraction, \( L_t \) total number of extractions
Extraction is efficient if 10% achieved within 6 extractions

Test System: Single-Use Bags
Extraction critical parameters:
• extraction fluid (solvent/water/water plus surfactant)
• agitation (intensity, liquid volume): fill bag with liquid, controlled rocking, drain
• rinsing (flow rate, liquid volume): flush bag with liquid, controlled flowrate
Extracted liquid containing extracted particulates is filtered onto membrane
Visible particulates counted and sized using automated microscopy

Effect of Extraction Fluid (agitation/rinsing held constant)

Effect of Extraction Conditions (extraction fluid held constant)

Identification
We apply optical microscopy (polarized light), infrared microscopy along with electron microscopy for the identification of particulates:

Conclusions
Challenges arise in development and validation of methods for extraction of particulate contamination within the interior of single-use bags. The complex geometries of single-use bags often hinder easy removal of particulates, and a combination of agitation and rinsing may be required. Under the specific agitation/rinsing conditions and for the specific types of single-use bags studied here, efficient extraction is achieved with water alone, solvent, or water plus surfactant according to ISO 16232. Particle counting and sizing is only the first step in the particle analysis process: particle identification, source identification and design optimization are required for guiding improvements in cleanroom processes and operations.

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