# PARTICULATE CONTAMINATION IN SINGLE-USE SYSTEMS: REAL VERSUS PERCEIVED RISK

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Certainly final drug products must be “essentially free” of visible particulate contamination and visual inspection systems must meet USP 790 criteria. In addition, final drug products must meet USP 788 limits for sub-visible particles. It is however important to distinguish final drug product standards from requirements for single-use process containers and equipment, even though it is common to claim single-use systems (SUS) “meet USP 788 requirements”. USP 788 does not describe a method for determination of particulate counts in SUS process containers and equipment (1).

Visible particles are “visible” and thus a visual indicator of SUS quality, and consequently sometimes lead to visceral reactions and the perception of major or even critical risk to product safety. However, guidance from PDA TR66 (2), ASME BPE-2016 (3) and the BPSA (4) published in the last few years provide valuable information on assessment of particulate risk in SUS processes. In most situations where SUS are currently applied, filtration and purification steps occur downstream, which essentially reduces the risk to zero for transfer of particulate contamination from SUS to the final drug product. However, any applications of SUS after final filtration (such as in ascetic processes or final filling operations) present significant risk to drug substance or drug product. So is risk to final drug product from SUS an essentially a binary situation: Prior to final filtration low risk, and after final filtration high risk?

While assembly of SUS is a “clean build” process usually done in ISO 7 classified cleanrooms, incoming components and cleanroom processes such as cutting, welding and human assembly are unfortunately not particulate-free with current SUS manufacturing technologies. In addition, visual inspection of SUS components and assemblies is nowhere near 100% effective at detecting visible particles, especially for large complex assemblies or stirred tank reactor systems. Sartorius is currently implementing a “Visible Particle Test” (VPT: liquid extraction and microscopy) for process monitoring and continuous improvement efforts. Thus while most SUS manufactures strive to minimize particulate contamination, absence of particulates remains a goal but is not a currently feasible SUS specification.

Particle contaminants may lie within the interior surfaces of SUS (in the fluid contact path), may be embedded within bag films or plastic components, or lie on the exterior surfaces of SUS. Particulates fall into two general categories: intrinsic (particles from SUS manufacturing process and component materials) and extrinsic (particles from human operators or the environment). Extrinsic particles potentially contain microbiological or viral contamination. These classifications of location and particle type lead to different assessments of risk.
One concern are potential “secondary effects” of particulate contamination. Particle contamination could potentially nucleate protein aggregation. Particles embedded in SUS films or plastic components, or on the interior surfaces of the SUS assemblies could potentially leach out chemicals or release microbiological or viral contamination into the bioprocess fluids.
In this presentation, the topic of particulate contamination risk is approached holistically and scientifically using literature data along with calculations. The goal of the presentation is to gain feedback from end users, and to facilitate the discussion between suppliers and end users based upon real rather than perceived risks.

(1) Particulate Contamination in Single-Use Systems, J. D. Vogel and K. Wormuth, Bioprocess International, 15(9) 2017
(2) Application of Single-Use Systems in Pharmaceutical Manufacturing, PDA Technical Report No. 66, 2014
(3) Bioprocessing Equipment, ASME BPE-2016, American Society of Mechanical Engineers, 2016
(4) Recommendations for Testing, Evaluation and Control of Particulates from Single-Use Process Equipment, Bio Process Systems Alliance, 2014.