SUBVISIBLE PARTICLES WORKING GROUP
CASE STUDY

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

A Multi-company Assessment of Submicron Particle Levels in Biotechnology-derived Protein Products

THE CHALLENGE

Subvisible particles (SVP, 2-100 µm) and submicron particles (SMP, 0.1-2 µm) in therapeutic protein products are topics of high interest for drug product developers and regulators due to their potential to elicit an immunogenic response that may affect drug safety and efficacy. Currently, there is no clear guidance on how and when to measure SMP. Limited information is available on the level of SMP in clinical and commercial products. Although SMP instruments are available, the robustness and performance of these detection methods and their proper use for routine characterization of clinical and commercial products still needs to be explored in more detail.

OBJECTIVES & APPROACH

The IQ Subvisible Particles Working Group aimed to determine the amount of SMP in currently marketed and clinical late-stage products. They leveraged the IQ Consortium's data sharing/storage infrastructure to collect and analyze 52 unique products (62 total samples) together with sample metadata (sample type, package type, protein concentration) using a double blinded approach.

The working group evaluated the robustness of the two most mature SMP characterization techniques, nanoparticle tracking analysis (NTA) and resonant mass measurement (RMM). They harmonized methods for the data collection and performed a "Round Robin" study with NIST traceable size standards and protein standard (BSA) to evaluate the precision and robustness of the techniques.

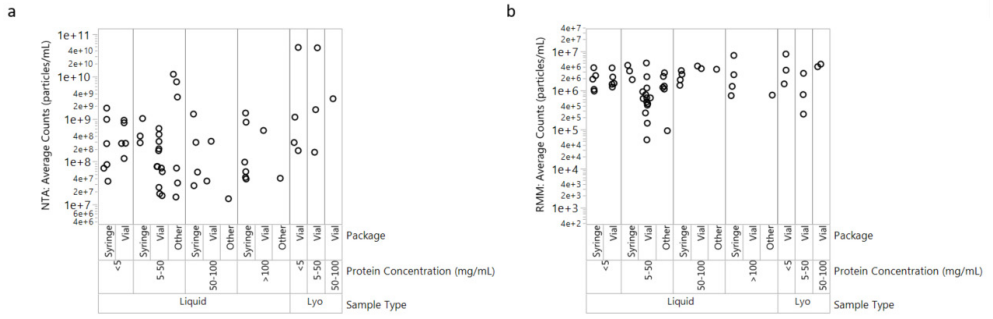

Figure 1. Variability charts showing particle concentration as a function of sample type, protein concentration, and container closure for (a) Nanoparticle Tracking Analysis (NTA), (b) Resonant Mass Measurement (RMM). Open circles correspond to the average particle count per sample (dosage form), determined from 3 or more replicates.

RESULTS

Observed particle concentration in therapeutic products ranged from $1x10^7$ – $1x10^{11}$ particles/mL for NTA and $4x10^4$ – $4x10^7$ for RMM. There were no practically significant differences in SMP concentration observed as a function of sample type (lyo vs. liquid), package type (vial, syringes or others), and protein concentration (<5 to >100mg/mL). Results obtained by NTA and RMM exhibit higher variability than well-established subvisible particle characterization techniques such as light obscuration (e.g., HIAC) and flow imaging (e.g., MFI).

More details about the results, discussion, and conclusion from this study can be found in the working group's publication in the *Journal of Pharmaceutical Sciences*[1].

IMPACT

The presented dataset and results provide development scientists with a baseline and expected range of SMP, as measured by NTA and RMM, to be able to benchmark their own programs.

The working group shared an aligned industry perspective on maturity and robustness of RMM and NTA analytical technologies.

The working group concluded that the techniques may provide relevant SMP data during product development but are not appropriate for quality control-related testing due to the higher variability.

[1] Hubert, M., Yang, D. T., Kwok, S. C., Rios, A., Das, T. K., Patel, A., ... & Cao, S. (2020). A Multicompany Assessment of Submicron Particle Levels by NTA and RMM in a Wide Range of Late-Phase Clinical and Commercial Biotechnology-Derived Protein Products. *Journal of Pharmaceutical Sciences*, 109(1), 830-844.

The IQ Consortium is a not-for-profit organization of pharmaceutical and biotechnology companies with the mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community.

iqconsortium.org

Subvisible Particles Working Group

The mission of the SVP WG is to discuss the regulatory requirements in the area of subvisible and submicron particles to aid development scientists in interpreting their data and inform risk assessment and regulatory strategy. Furthermore, the WG will gather data on clinical and marketed biotherapeutic products and share analytical experience with relevant technologies.

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