USP <787> Testing Therapeutic Protein Injections

AccuSizer® Syringe Injection System (SIS)

Figure 1. Single sensor AccuSizer SIS

OVERVIEW

The USP <787> subvisible particulate matter in therapeutic protein injections test is very similar to USP <788> for parenteral drugs. The standard AccuSizer® Syringe Injection System (SIS) meets and/or exceeds all requirements in USP <787>, but new improvements have been added to accommodate specific requirements of this new sample type. In addition, the new two sensor FX Nano SIS system can be used for both USP <787> testing plus research into the mechanisms of protein aggregation.

INTRODUCTION

USP <787> is meant for therapeutic protein injections, making changes for smaller test product volumes and smaller test aliquots. Here is a summary of how to test a sample following the new USP <787> procedure:

Follow the Same Standardization Steps as Described in USP <1788>:

- Volume accuracy
- Flow rate
- Sensor resolution
- Calibration
- Count accuracy

Two System Control Tests are Recommended:

- Blank test: Measure five aliquots of degassed particle-free water, the count must be less than 1 particle/mL >10 µm.
- System suitability verification; analyze the USP particle count reference standard and pass the count limits.

Sample Preparation:

- If there is enough volume test individual units.
- If the volume is too small, mix units and combine the contents to obtain the required volume (typically 0.2 – 5.0 mL).
- Degas the sample and gently mix again.

ANALYSIS

- Analyze four aliquots.
- Count the particles in the size range of interest, including particles >10 and 25 µm.
- Disregard the first result and average the next three results.

PASS/FAIL CRITERIA

- If the container volume <100 mL; less than 6000 particles/container >10 µm and 600 particles/container >25 µm.
- If the container volume >100 mL; less than 25 particles/mL >10 µm and 3 particles/mL >25 µm. Also not exceed the per container limits for the <100 mL criteria above.

Many of these system preparation and measurement steps are identical to USP <788>. The standard PSS AccuSizer SIS system (Figure 1) is perfectly suited for performing these tests.[1] One important difference is the acknowledgement that sample volumes may be as small as 0.2 mL (200 µL). The SIS sampler can accurately measure samples as small 150 µL,[2] making this uniquely suited for analysis of small volume protein samples.

The two sensor configuration combines the FX Nano sensor with the LE-400 sensor used in the single sensor system. The same syringe sampler is used along with two pulse height analyzers (counters). Separate research software combines the two results to provide the sensitivity down to 0.15 µm. Along with the small sample volume and recovery features, this is proving to be the preferred system for performing protein aggregation studies.

FDA GUIDANCE ON PROTEIN INJECTIONS

In August 2014, the FDA issued a guidance for industry document immunogenicity assessment for therapeutic protein products.[3] Within this document, the FDA comments that "it has been recognized that subvisible particulates in the size range of 0.1 – 10 microns have a strong potential to be immunogenic, but are not precisely monitored by currently employed technologies. As more methods become available, sponsors should strive to characterize particles in smaller (0.1 – 2 microns) size ranges." The desire to measure at these smaller sizes is driven not only by FDA suggestion, but also by common understanding that investigating protein aggregation phenomenon requires measuring well below the 10 and 25 µm sizes required for USP <787> testing.

ACCUSIZER FX NANO SIS SYSTEM

It is now possible to easily and accurately perform particle count measurements down to 0.15 µm (150 nm) using the two sensor AccuSizer FX Nano SIS system (Figure 2).

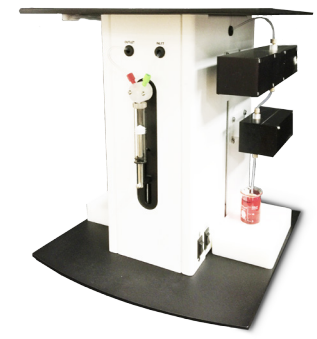

Figure 2. Two sensor AccuSizer FX Nano SIS

RESULTS

Immunoglobulin G (IgG), ~150 kDa, 1% was prepared in filtered PBS. The sample was measured undiluted using the AccuSizer FX Nano SIS two sensor system. The protein sample was then passed through a 0.2 µm filter and analyzed again on the AccuSizer FX Nano SIS system. The results comparing before and after filtration are shown in Figure 3. The results for the PBS is also shown in black. The concentration reduced from 9.7 to 3.1x10^8 particles/mL after the filtration step. The decrease in the tail of aggregated particles is clearly visible and easily identified by the AccuSizer FX Nano SIS system.

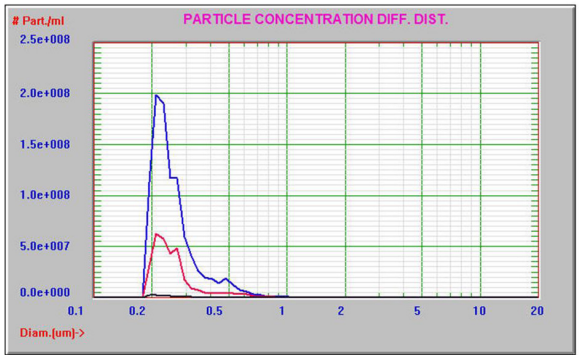

Figure 3. IGG before (blue) and after (red) filtration

References

[1] *USP <788> Particulate Matter in Injections, Entegris Application Note, July 2019*

[2] *Low Volume Particle Size and Count Analysis, Entegris Technical Note, 2019*

[3] *Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products*, August 2014, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

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