Characterization of FlowCam Sensor Resolution in Accordance with USP <1788>

SUMMARY

The concept of “sensor resolution” in any kind of instrumentation is an extremely important one. While there are many different ways to characterize resolution in an imaging system, the USP has very specific criteria for measuring sensor resolution for instruments used in the characterization of subvisible particulates in parenteral formulations. This document conclusively shows that FlowCam is compliant with the USP criteria for sensor resolution.

REFERENCES

A new revision of USP <1788> *Methods for Determination of Subvisible Particulate Matter* became effective May 1, 2021. USP <1788> is an informational chapter and introduces Flow Imaging Microscopy as an orthogonal test to Light Obscuration in <1788.3> *Flow Imaging Method for the Determination of Subvisible Particulate Matter.*

DEFINITIONS

Sensor Resolution (General):

The resolution of a sensor is the smallest change it can detect in the quantity it is measuring.

Sensor Resolution (as defined by USP <1788>):

“The particle size resolution of the instrumental particle counter is dependent upon the sensor used and may vary with individual sensors of the same model. Determine the resolution of the particle counter for 10-µm particles, using the 10-µm calibrator spheres.”

METHOD

NIST traceable calibrated microspheres (Thermo Scientific, Waltham, MA) were imaged by FlowCam and the resulting statistics were used to calculate “% resolution” for the FlowCam sensor.

The formula used for this calculation was as provided in the USP <1788> chapters referenced above:

“One commonly used method for calculating the percentage of resolution of the sensor is the following:

$$\% \text{ resolution} = (100/D \times [(S_{Obs})^2 - (S_{Std})^2]^{1/2}$$

in which S_{Obs} is the highest observed standard deviation determined for the sphere standard; S_{Std} is the supplier’s reported standard deviation for the spheres; and D is the diameter, in µm, of the spheres as specified by the supplier. The resolution is NMT 10%.”

The final sentence states that the % resolution calculated in this manner should be NMT (No More Than) 10% of the microsphere manufacturer’s specified diameter for the product.

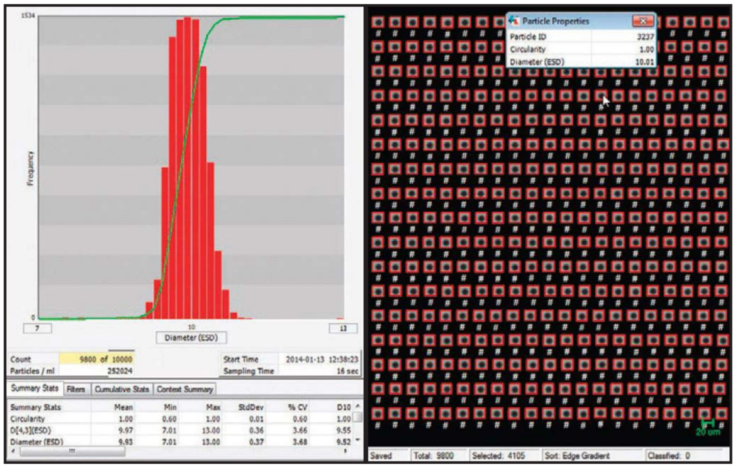

Figure 1. Typical results for a FlowCam run of 10 µm calibrated spheres. This run calculated a mean ESD of 9.93 µm, and a standard deviation of 0.37 µm.

RESULTS FOR 10 µm SPHERES

The first calculations were made using 10 µm calibrated spheres as called for by the USP <1788> chapters referred above. Five runs were made with roughly 10,000 particles captured in each run.

It is important to note that due to the sensitivity of FlowCam’s imaging system, a significant number of other particles (non-bead) get recorded, representing debris in the manufacturer’s carrier medium.

Debris particles are not typically a problem in less-sensitive instrumentation such as light obscuration devices, since these systems will not detect their presence. In order to eliminate the bulk of these non-bead particles, the statistics were limited to particles approximately 10 µm in diameter. In order to ensure that no beads were eliminated, runs were first manually checked for beads that would be excluded by this process. Further restriction of the counts could have been accomplished by filtering the remaining particles by aspect ratio or circularity. This was not done in order to keep the data as close to “raw” as possible. However, had it been done, the corresponding diameter statistics would have been had even lower variance.

The overall results can be seen in Figure 1. The data was filtered to show particles between 7 µm and 13 µm in size for the reasons stated above. The overall statistics and calculated sensor % resolution can be seen below in Table 1.

Run #	n	D_{Obs}	S_{Obs}	D_{Std}	S_{Std}	% Res-olution
1	9,800	9.93	0.37	10.00	0.08	3.612
2	9,797	9.93	0.36	10.00	0.08	3.510
3	9,791	9.94	0.37	10.00	0.08	3.612
4	9,790	9.94	0.37	10.00	0.08	3.612
5	9,793	9.94	0.37	10.00	0.08	3.612

Table 1. Results for 10 µm microspheres

The results in Table 1 show that FlowCam is well within the specification as outlined by USP <1788> for % Resolution with 10 µm microspheres.

RESULTS FOR 5 µm SPHERES

While not specifically called for by USP, the sensor resolution was also measured using the same technique with smaller (5 µm) microspheres.

The results are shown in Figure 2. The data was filtered to show particles between 3 µm and 7 µm in size for the reasons stated above. The overall statistics and calculated sensor % resolution can be seen in Table 2.

These results show that FlowCam is well within the specification as outlined by USP <1788> for % Resolution, even when using 5 µm microspheres, a significantly smaller size than is called for in the USP document.

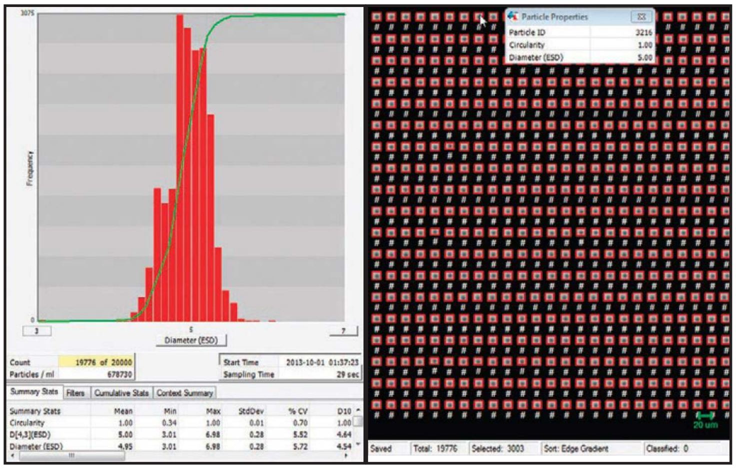

Figure 2. Typical results for a FlowCam run of 5 µm calibrated spheres. This run calcualted a mean ESD of 4.95 µm, and a standard deviation of 0.28 µm.

Run #	n	D_{Obs}	S_{Obs}	D_{Std}	S_{Std}	% Res-olution
1	9,878	4.94	0.28	4.993	0.05	5.518
2	9,886	4.95	0.28	4.993	0.05	5.518
3	19,746	4.95	0.29	4.993	0.05	5.721
4	19,746	4.94	0.28	4.993	0.05	5.518
5	19,776	4.95	0.28	4.993	0.05	5.518

Table 2. Results for 5 µm microspheres

CONCLUSIONS

FlowCam easily meets the sensor resolution requirements for characterization of sub-visible particulate matter in injections and ophthalmic solutions. In fact, it is able to do so using beads half the size of what the specification calls for.

Since imaging particle analysis systems also measure particle shape, and are more sensitive to transparent particulates, they are much more capable of characterizing protein aggregates and also distinguishing other types of particulates (such as silicone droplets) from those aggregates.