

# Monitoring Particulate Contamination in Medical Devices

## INTRODUCTION

Particulate contamination from any medical device should be minimized to avoid possible negative health consequences to the patient. The health risks from unwanted particles depend on the device and where they end up in the body. Particles that enter the venous system can cause harm through mechanisms including phlebitis, pulmonary granulomas, local tissue infarction, and embolisms. Some medical devices may not actually come in contact with blood and may end up anywhere in the body. In this case the medical risk depends both on where the device is placed and the physical/chemical nature of the particles. A main concern with nonvascular implanted devices is foreign body reaction, an immune response that can cause fibrosis, inflammation, and possible device rejection. With these risks in mind, medical device manufacturers should monitor and minimize particulate contamination.

## STANDARDS

Many standards, guidance documents, and information reports provide advice and requirements for testing particulate contamination on and from medical devices. These documents range from broad guidance to very specific test requirements and pass/fail criteria.

AAMI TIR 42<sup>1</sup> provides guidance on analytical methods for testing, identifying, and developing limits for particulate contamination on vascular devices. Liquid particle counters and microscopic assay of particles caught on filters are mentioned as potential testing techniques, but no specific advice is given on the topic of maximum allowable particle count. Instead, it suggests manufacturers should set their own limits based on the nature of the particles and clinical application of the device. This document does refer to an FDA guidance document for testing stents and associated delivery systems<sup>2</sup> and USP <788><sup>3</sup> for advice on setting particulate contamination limits.

The ANSI/AAMI standard AT6<sup>4</sup> for autologous transfusion devices describes a method where the device is filled with low particle water. The water is then collected on a membrane filter for microscopic particle count of fibers and all particle sizes greater than 10 µm.

The ISO standard 8536-4:2010<sup>5</sup> describes a test process and acceptance criteria for single use gravity feed infusion sets and intravenous equipment. The basic testing process is to flow clean water through 10 devices until 500 mL is collected on a vacuum filter. Then perform a particle count on the filter and record the count in the size ranges shown in Figure 1.

Particle parameters	SIZE CATEGORY		
	1	2	3
Particle size in µm	25 to 50	51 to 100	over 100
Number of particles in 10 infusion sets	$n_{a1}$	$n_{a2}$	$n_{a3}$
Number of particles in the blank control group	$n_{b1}$	$n_{b2}$	$n_{b3}$
Evaluation coefficient	0.1	0.2	5

Figure 1. From ISO 8536.

To calculate if the parts pass multiply the counts in each size category minus the blank counts times the evaluation coefficient. Add those values, divide by 10 and this result must be less than 90. The equations given in the standard are:

$$N_a = n_{a1} \times 0.1 + n_{a2} \times 0.2 + n_{a3} \times 5$$

$$N_b = n_{b1} \times 0.1 + n_{b2} \times 0.2 + n_{b3} \times 5$$

$$N = N_a - N_b \leq 90$$





Figure 4. AccuSizer SIS liquid particle counter.

When following the USP <788> procedure a 5 mL sample is measured four times. The first result is discarded and the second through fourth results are averaged. The allowable concentration limit specified for large volume injectables (LVI) is:

- 25/mL  $\geq 10 \mu\text{m}$
- 3/mL  $\geq 25 \mu\text{m}$

Using the USP <788> LVI limits bases the pass/fail criteria on particle concentration/mL. The alternative approach is to calculate the number of particles per device, and then use the USP <788> small volume injectables (SVI) criteria of:

- 6,000 particle per device  $\geq 10 \mu\text{m}$
- 600 particles per device  $\geq 25 \mu\text{m}$

This procedure is used for testing Entegris' Aramus™ single-use bags.<sup>12</sup> Here the bags are filled with clean water, placed on a 3D rocker and agitated for a set amount of time. The procedure used is:

1. Connect bag to test-system plumbing
2. Flush process line with ultrapure water through a 0.45  $\mu\text{m}$  filter, bypassing the single-use bag
3. Pump ultrapure water through a 0.45  $\mu\text{m}$  filter into the single-use bag
4. Agitate the bag using the 3D rocker for two minutes
5. Pull two 50 mL samples from the effluent stream to be subjected to USP <788> testing
6. Repeat with next sample

This same procedure could be applied to a multitude of medical devices. The test can be adapted to other devices by determining the optimal approach for releasing particles from the product surface by either flushing through the device or placing the device in clean water and applying energy to release any particulate contamination.

## EXPERIMENTAL: INFUSION SETS

A study of single use infusion sets was performed using Entegris' AccuSizer SIS liquid particle counter rather than the microscopic assay described in ISO 8536. The AccuSizer SIS counter has a dynamic range of 0.5 – 400  $\mu\text{m}$ . This instrument is commonly used for various USP tests including USP <787>,<sup>12</sup> <788>, and <789>.<sup>13</sup> Figure 5 shows the LE400 sensor principle of operation where particles passing through the sensor scatter and obscure the incident light and a calibration curve is then used to convert pulse height to particle size.

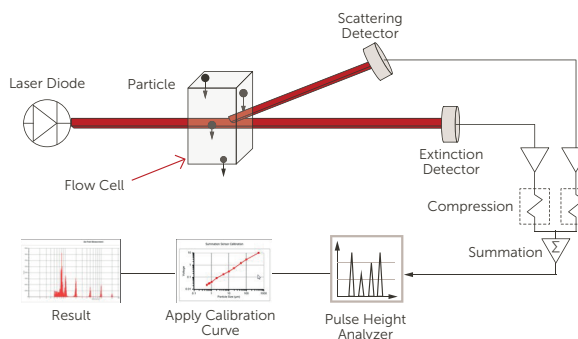


Figure 5. AccuSizer LE400 sensor principle of operation.

## PROCEDURE

First, the background counts (blank) were determined by cleaning a 500 mL bottle, filling it with filtered DI water, and then analyzing the DI water for particle size and count using the AccuSizer SIS instrument. Next, filtered DI water was gravity fed through the devices and collected in the clean bottle. In this study only three infusion sets were tested, so the results were scaled up to 10 sets before the final calculation. The original results are reported in particles/mL so the reported results were multiplied by 500 to reflect the total count in 500 mL.

The same measurement protocol was used for all measurements:

1. Pull a tare volume of 0.5 mL
2. Measure a 5 mL sample four times
3. Discard the first result
4. Average the second through fourth results
5. Report results in particles/mL

This measurement protocol is in compliance with USP <788>. Results were reported in size bins of greater than 0.5, 2, 5, 10, 25, 50, and 100  $\mu\text{m}$ . The sizes below 25  $\mu\text{m}$  are not required in ISO 8536 and not used in the final calculation, but the results in smaller size ranges can help quantify differences between infusion set cleanliness not noticed when only counting particles >25  $\mu\text{m}$ .

## RESULTS

The results for the blank count are shown in Figure 6. Notice the counts are all zero for sizes greater than 10  $\mu\text{m}$ . This implies no blank subtraction is required for the final calculations.

REGION	RUN 2	RUN 3	RUN 4
0.5 – 400 $\mu\text{m}$	76	77	71
2 – 400 $\mu\text{m}$	0	1	2
5 – 400 $\mu\text{m}$	0	1	1
10 – 400 $\mu\text{m}$	0	0	0
25 – 400 $\mu\text{m}$	0	0	0
50 – 400 $\mu\text{m}$	0	0	0
100 – 400 $\mu\text{m}$	0	0	0

Figure 6. Blank background counts.

The raw data results in particles counts/mL from comparing infusion set brand B vs. infusion set brand C are shown in Figure 7.

### Brand B

REGION	RUN 2	RUN 3	RUN 4	AVERAGE
0.5 – 400 $\mu\text{m}$	314	360	384	352.7
2 – 400 $\mu\text{m}$	19	18	15	17.3
5 – 400 $\mu\text{m}$	9	11	6	8.7
10 – 400 $\mu\text{m}$	3	4	2	3.0
25 – 400 $\mu\text{m}$	1	1	0	0.7
50 – 400 $\mu\text{m}$	0	0	0	0.0
100 – 400 $\mu\text{m}$	0	0	0	0.0

### Brand C

REGION	RUN 2	RUN 3	RUN 4	AVERAGE
0.5 – 400 $\mu\text{m}$	2576	3538	5704	3939.3
2 – 400 $\mu\text{m}$	751	519	409	559.7
5 – 400 $\mu\text{m}$	15	15	15	15.0
10 – 400 $\mu\text{m}$	3	3	2	2.7
25 – 400 $\mu\text{m}$	1	0	0	0.3
50 – 400 $\mu\text{m}$	0	0	0	0.0
100 – 400 $\mu\text{m}$	0	0	0	0.0

Figure 7. Raw data comparing B vs. C.

The averaged data was then used to calculate the final n value as described in ISO 8536. These calculations are shown in Figure 8.

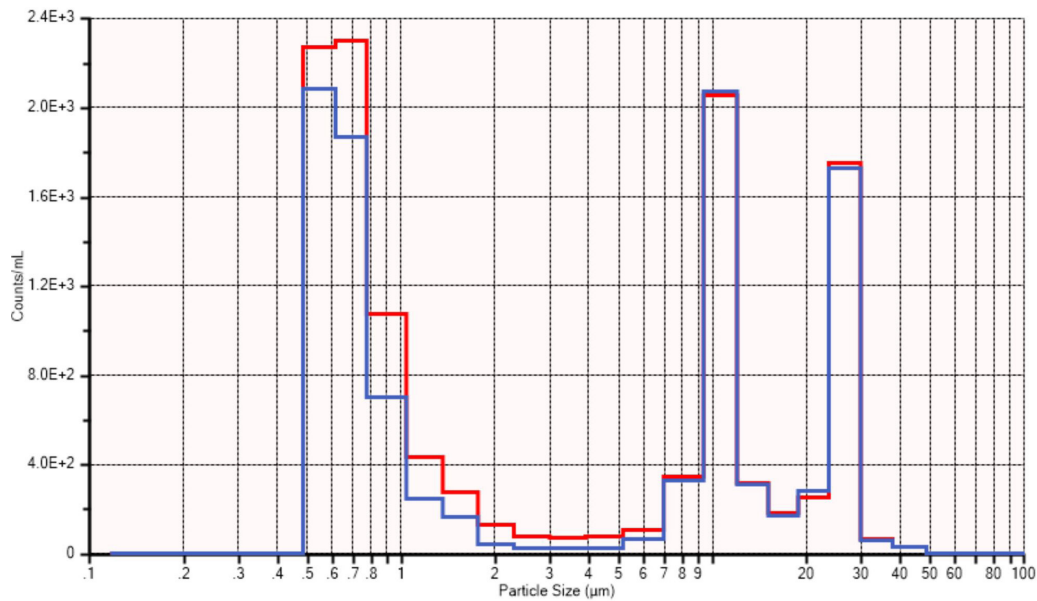
SIZE RANGE	COUNT/mL (3 DEVICES)	COUNT/mL (10 DEVICES)	COUNT IN 500 mL	EVALUATION COEFFICIENT	n
25 – 50 µm	0.7	2.331	1165.5	0.1	116.6
50 – 100 µm	0	0	0	0.2	0
>100 µm	0	0	0	5	0
				Total	116.6
				Total/10	<b>11.7</b>

SIZE RANGE	COUNT/mL (3 DEVICES)	COUNT/mL (10 DEVICES)	COUNT IN 500 mL	EVALUATION COEFFICIENT	n
25 – 50 µm	0.3	0.999	499.5	0.1	50.0
50 – 100 µm	0	0	0	0.2	0.0
>100 µm	0	0	0	5	0.0
				Total	50.0
				Total/10	<b>5.0</b>

Figure 8. Calculation of n per ISO 8536.

Method validation for this study was performed by preparing a mixture of 10 and 25  $\mu\text{m}$  polystyrene latex (PSL) standards. The initial concentration was analyzed, gravity fed through an IV set, collected and analyzed again. The results in particles/mL for the initial (blue) and retained sample (red) are shown in Figure 9.



REGION	INITIAL	RETAINED	RATIO
0.5 – 400 $\mu\text{m}$	8132	9534	117.2%
2 – 400 $\mu\text{m}$	5116	5323	104.0%
5 – 400 $\mu\text{m}$	5047	5106	101.2%
10 – 400 $\mu\text{m}$	2580	2599	100.7%
25 – 400 $\mu\text{m}$	90	99	110.0%
50 – 400 $\mu\text{m}$	0	0	–
100 – 400 $\mu\text{m}$	0	0	–

Figure 9. Particle retention study.

Although the author of this application note has over 35 years of experience making particle size measurements, this retention study was a difficult challenge and only the best results are shown in Figure 9. Purchasing commercially available particle count standards<sup>14</sup> is recommended to facilitate this procedure.

The infusion sets examined in this study were very clean and easily pass the ISO 8536 criteria. While the microscopic assay has the advantage being able to better define fibers, the liquid particle counter test is quicker, easier, and can report results down to 0.5  $\mu\text{m}$ , often providing additional detail into comparative cleanliness levels.

### EXPERIMENTAL: ENTERAL BAGS

Several 1200 mL enteral delivery feeding bags were purchased online for this study. Although no standards or limits exist for these specific medical devices the purchased products included both an IV type bag and delivery set, providing an inexpensive and characteristic delivery system for particulate contamination testing. A similar test procedure to the infusion sets was employed for testing these devices. A clean background was first established by testing the filtered DI water and bottles used for the study. The bags were filled with 1000 mL of clean water, gravity fed through the entire device, and then collected in a clean bottle. The collected water was analyzed on the AccuSizer SIS system following the USP <788> protocol where four 5 mL samples are measured and the average particle concentration/mL of runs two through four are calculated and reported.

The results for the clean water and bottle are shown in Figure 10. Since there were no particles  $>10 \mu\text{m}$  present, no background subtraction was required for the other experiments.

REGION	BLANK COUNT/mL	CLEAN BOTTLE COUNT/mL
0.5 – 400 $\mu\text{m}$	231	1876
1 – 400 $\mu\text{m}$	18	209
5 – 400 $\mu\text{m}$	1	5
10 – 400 $\mu\text{m}$	0	0
25 – 400 $\mu\text{m}$	0	0

Figure 10. Blank and clean bottle counts.

The particle results of concentration in counts/mL of the collected effluent after flowing through three bags and delivery systems are shown in Figure 11. Bag 1 was then refilled with water and manually agitated to determine if adding additional energy to remove particle from the bag surface increased the effluent particle count.

#### Bag 1

REGION	RUN 2	RUN 3	RUN 4	AVERAGE
0.5 – 400 $\mu\text{m}$	4281	4209	4122	4204.0
1 – 400 $\mu\text{m}$	699	672	655	675.3
5 – 400 $\mu\text{m}$	12	12	12	12.0
10 – 400 $\mu\text{m}$	4	2	4	3.3
25 – 400 $\mu\text{m}$	2	1	1	1.3

#### Bag 2

0.5 – 400 $\mu\text{m}$	3796	4176	3823	3931.7
1 – 400 $\mu\text{m}$	602	651	608	620.3
5 – 400 $\mu\text{m}$	18	12	11	13.7
10 – 400 $\mu\text{m}$	6	3	2	3.7
25 – 400 $\mu\text{m}$	2	1	1	1.3

#### Bag 3

0.5 – 400 $\mu\text{m}$	4157	4156	3925	4079.3
1 – 400 $\mu\text{m}$	698	713	670	693.7
5 – 400 $\mu\text{m}$	14	14	12	13.3
10 – 400 $\mu\text{m}$	4	3	1	2.7
25 – 400 $\mu\text{m}$	0	0	0	0.0

#### Bag 1 Agitated

0.5 – 400 $\mu\text{m}$	6807	7314	7309	7143.3
1 – 400 $\mu\text{m}$	1163	1249	1244	1218.7
5 – 400 $\mu\text{m}$	18	18	14	16.7
10 – 400 $\mu\text{m}$	3	3	2	2.7
25 – 400 $\mu\text{m}$	0	0	0	0.0

Figure 11. Particle count in enteral bags.

The AccuSizer SIS software can automatically report the USP <788> large volume injection pass/fail criteria as seen in Figure 12 for the Bag 1 test. All of the devices tested passed the USP <788> LVI limits.

Sample	Run date/time	Sample volume	Pre DF	≥10 µm	≥25 µm
Bag 1 run1 rep. 2	10:36 08/13/2020	5.0 mL	1.00	4/mL	2/mL
Bag 1 run1 rep. 3	10:37 08/13/2020	5.0 mL	1.00	2/mL	1/mL
Bag 1 run1 rep. 4	10:38 08/13/2020	5.0 mL	1.00	4/mL	1/mL
			Mean	3.3/mL	1.3/mL

Test criteria	Result
(Mean #/mL ≥10 µm) ≤25/mL and (Mean #/mL ≥25 µm) ≤3/mL (Pass)	Pass

Figure 12. USP <788> LVI report for Bag 1.

## CONCLUSIONS

A wide range of standards, USP tests, and FDA guidance documents provide test methods and acceptance criteria for particulate contamination in medical devices. But the end user often needs to interpret the documents, apply the principles to their specific devices, and determine acceptable particle limits. The use of Entegris' AccuSizer SIS liquid particle counter automates the measurement and reporting of particle size and count, often making the analytical measurements the easier part of the overall process.



## References

- <sup>1</sup> AAMI TIR42:2010, *Evaluation of Particulates Associated with Vascular Medical Devices*, available at: <https://webstore.ansi.org/Standards/AAMI/AAMITIR422010TIR42>
- <sup>2</sup> FDA Guidance for Industry and Staff, *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*, available at: <https://www.fda.gov/media/71639/download>
- <sup>3</sup> USP <788>, *Particulate Matter in Injections*, available at: [https://www.uspnf.com/sites/default/files/usp\\_pdf/EN/USPNF/revision-GeneralChapter788.pdf](https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revision-GeneralChapter788.pdf)
- <sup>4</sup> ANSI/AAMI AT6:2013, *Autologous Transfusion Devices*, available at: <https://webstore.ansi.org/standards/aami/ansiaamiat62013-1510027>
- <sup>5</sup> ISO 8536-4:2010, *Infusion equipment for medical use – Part 4: Infusion sets for single use, gravity feed*, available at: <https://www.iso.org/standard/55799.html>
- <sup>6</sup> BS EN 45502, *Implants for surgery – Active implantable medical devices*.
- <sup>7</sup> ISO 14708-3:2017, *Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators*, available at: <https://www.iso.org/standard/60539.html>
- <sup>8</sup> ASTM F2394-07 (2017) – *Standard Guide for Measuring Securement of Balloon Expandable Vascular Stent Mounted on Delivery System*, available at: <https://www.astm.org/Standards/F2394.htm>
- <sup>9</sup> FDA Guidance for Industry and FDA Staff – *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*, April 2010, available at: <https://www.fda.gov/media/71639/download>
- <sup>10</sup> FDA Guidance for Industry – *Coronary, Peripheral, and Neurovascular Guidewires – Performance Tests and Recommended Labeling*, available at: <https://www.fda.gov/media/113959/download>
- <sup>11</sup> FDA Guidance for Industry (Draft) – *Peripheral Percutaneous Transluminal Angioplasty (PTA) and Specialty Catheters – Premarket Notification (510(k) Submissions*, available at: <https://www.fda.gov/media/134016/download>
- <sup>12</sup> USP <787>, *Subvisible Particulate Matter in Therapeutic Protein Injections*.
- <sup>13</sup> USP <789>, *Particulate Matter in ophthalmic Solutions*.
- <sup>14</sup> Micro Measurement Labs, see : <http://www.mmlabs.com>

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