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[1] 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[2] and USP <788>[3] for advice on setting particulate contamination limits.

The ANSI/AAMI standard AT6[4] 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[5] 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:

$$N_a = n_{a1} \times 0.1 + n_{a2} \times 0.2 + n_{a3} \times 5$$
$$N_b = n_{b1} \times 0.1 + n_{b2} \times 0.2 + n_{b3} \times 5$$
$$N = N_a - N_b \leq 90$$

The standards EN 45502[6] and ISO 14708[7] for active implantable medical devices such as pacemakers include a test to help assure there is no unacceptable release of particulate matter. The test described here involves immersing the device in a container holding a volume of clean liquid that is five times the surface area of the device. The container is agitated for between 8 – 18 hours at a temperature of 37°C (98.6°F). A reference container with the same liquid and stress conditions but without the immersed device provides a baseline for comparison. The liquid in both containers are tested with a liquid particle counter and the device counts minus the reference container counts must be below the concentration levels shown in Figure 2 to pass the test.

Size	Count/mL
2 µm	1000
5 µm	100
25 µm	5

Figure 2. From ISO 14708-3.

The ASTM standard 2394[8] for stents provides guidance for building a test stand with a path to simulate a moderately difficult degree of tortuosity, Figure 3.

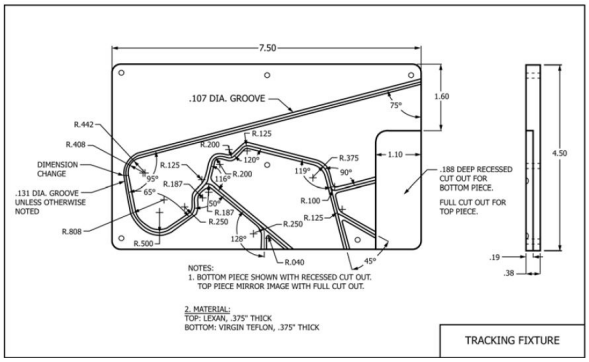


Figure 3. Test tracking fixture from ASTM 2394.

Several issued and draft FDA guidance documents[9, 10, 11] provide nonbinding recommendations for the size ranges to use for the microscopic assay of effluent liquid when testing stents using a tortuous path test fixture.

A typical procedure for this test would include the following steps:

1. Build the tortuous path device like seen in Figure 3
2. Place a sheath catheter in the grooves of the plate
3. Feed a test catheter through the sheath
4. Guide the stent into catheter
5. Expand the device(s) to maximum pressure or labeled diameter
6. Pump clean water through the device(s)
7. Capture the effluent on a filter
8. Perform a microscopic count of the captured particles

The captured particles should be reported in three size ranges: ≥10 µm, ≥25 µm, and at the largest size for which the validation tests yield >75% recovery. The minimum largest size should be >50 µm. The particles must be mixed/suspended during the sampling process. The validation tests involve introducing a suspension of known particle size and counts into the test stand and device(s). After the known concentration sample has passed through the device(s), perform another particle count test of the effluent. The particles in the effluent should be very close to the initial concentration. The recovery rate must be >90% at ≥10 and ≥25 µm for the system to be considered validated. Also determine the upper size at which recovery is >75% to determine the third size range for reporting results.

While a combination of ASTM 2394 and FDA guidance documents provides great detail into building the tortuous path test stand and size ranges to analyze, no recommendations are given for acceptable particle count levels. The device manufacturer is responsible for defining defendable limits.

None of the accepted standards or guidance discussed so far in this document are applicable to many medical devices. In this case, the USP <788> test for subvisible particles is often referred to for quantifying cleanliness after flushing the device with clean water. After flushing the device the removed particles are analyzed using a liquid particle counter such as Entegris' AccuSizer® SIS system, Figure 4.

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 ≥10 µm
- 3/mL ≥25 µm

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 ≥10 µm
- 600 particles per device ≥25 µm

This procedure is used for testing Entegris' Aramus™ single-use bags.[12] 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 µm filter, bypassing the single-use bag
3. Pump ultrapure water through a 0.45 µm 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 µm. This instrument is commonly used for various USP tests including USP <787>,[12] <788>, and <789>.[13] 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.

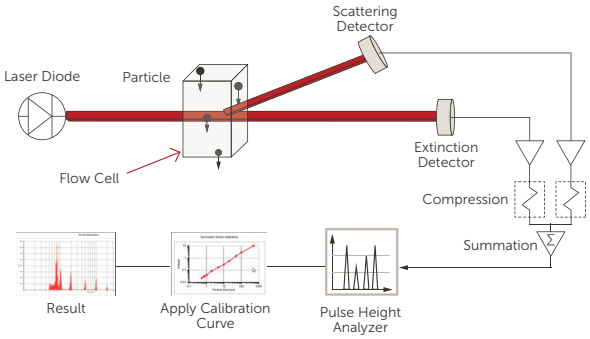


Figure 5. AccuSizer LE400 sensor principle of operation.

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 µm. The sizes below 25 µm 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 µm.

RESULTS

The results for the blank count are shown in Figure 6. Notice the counts are all zero for sizes greater than 10 µm. This implies no blank subtraction is required for the final calculations.

REGION	RUN 2	RUN 3	RUN 4
0.5 – 400 µm	76	77	71
2 – 400 µm	0	1	2
5 – 400 µm	0	1	1
10 – 400 µm	0	0	0
25 – 400 µm	0	0	0
50 – 400 µm	0	0	0
100 – 400 µm	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 µm	314	360	384	352.7
2 – 400 µm	19	18	15	17.3
5 – 400 µm	9	11	6	8.7
10 – 400 µm	3	4	2	3.0
25 – 400 µm	1	1	0	0.7
50 – 400 µm	0	0	0	0.0
100 – 400 µm	0	0	0	0.0

Brand C

REGION	RUN 2	RUN 3	RUN 4	AVERAGE
0.5 – 400 µm	2576	3538	5704	3939.3
2 – 400 µm	751	519	409	559.7
5 – 400 µm	15	15	15	15.0
10 – 400 µm	3	3	2	2.7
25 – 400 µm	1	0	0	0.3
50 – 400 µm	0	0	0	0.0
100 – 400 µm	0	0	0	0.0

Figure 7. Raw data comparing B vs. C.

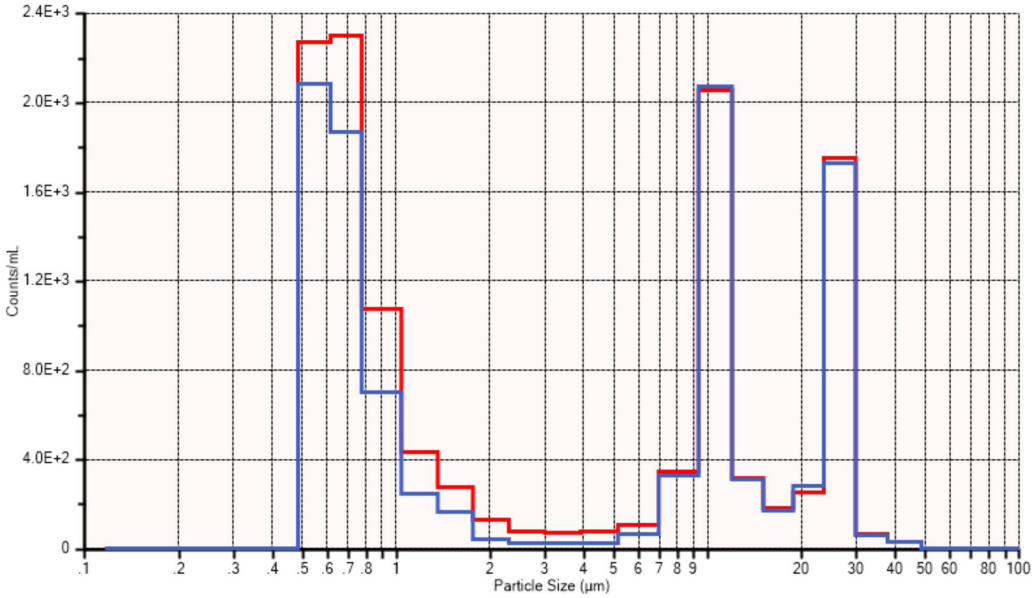
The averaged data was then used to calculate the final n value as described in ISO 8536. These calculations are shown in Figure 8.

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	**11.7**

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	**5.0**

Figure 8. Calculation of n per ISO 8536.

Method validation for this study was performed by preparing a mixture of 10 and 25 µm 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 µm	8132	9534	117.2%
2 – 400 µm	5116	5323	104.0%
5 – 400 µm	5047	5106	101.2%
10 – 400 µm	2580	2599	100.7%
25 – 400 µm	90	99	110.0%
50 – 400 µm	0	0	–
100 – 400 µm	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[14] 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 µm, 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 µm present, no background subtraction was required for the other experiments.

REGION	BLANK COUNT/mL	CLEAN BOTTLE COUNT/mL
0.5 – 400 µm	231	1876
1 – 400 µm	18	209
5 – 400 µm	1	5
10 – 400 µm	0	0
25 – 400 µm	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 µm	4281	4209	4122	4204.0
1 – 400 µm	699	672	655	675.3
5 – 400 µm	12	12	12	12.0
10 – 400 µm	4	2	4	3.3
25 – 400 µm	2	1	1	1.3

Bag 2

0.5 – 400 µm	3796	4176	3823	3931.7
1 – 400 µm	602	651	608	620.3
5 – 400 µm	18	12	11	13.7
10 – 400 µm	6	3	2	3.7
25 – 400 µm	2	1	1	1.3

Bag 3

0.5 – 400 µm	4157	4156	3925	4079.3
1 – 400 µm	698	713	670	693.7
5 – 400 µm	14	14	12	13.3
10 – 400 µm	4	3	1	2.7
25 – 400 µm	0	0	0	0.0

Bag 1 Agitated

0.5 – 400 µm	6807	7314	7309	7143.3
1 – 400 µm	1163	1249	1244	1218.7
5 – 400 µm	18	18	14	16.7
10 – 400 µm	3	3	2	2.7
25 – 400 µm	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.

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Entegris

Corporate Headquarters
129 Concord Road
Billerica, MA 01821
USA

Customer Service
Tel +1 952 556 4181
Fax +1 952 556 8022
Toll Free 800 394 4083