CCI Testing to Develop ASTM Standard No. F3287-17: "Standard Test Method for Non-Destructive Detection of Leaks by Mass Extraction Method"

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INTRODUCTION

An interlaboratory study (ILS#1178) was executed to support development of ASTM Standard No. F2387-17: *"Standard Test Method for Non-Destructive Detection of Leaks by Mass Extraction Method"*. The study included three package types: glass vials, LDPE bottles and glass syringes. A sample set of 123 containers of varying targeted results were tested 3 times at 4 different laboratories for a total of 1476 test results.

Results indicate that Mass Extraction is capable of detecting a 1 µm simulated defect (micropipette) in a variety of containers.

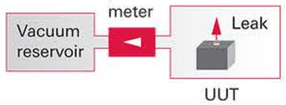
INSTRUMENTATION

All data collected for this study was generated using a Mass Extraction flow measurement instrument, model ME2, manufactured by Advanced Test Concepts (ATC), LLC a division of Pfeiffer Vacuum (patet protected)

- Each of the 4 laboratories used a different test instrument that was owned and operated by the respective laboratory.
  - No special instrumentation was supplied for the study.
  - Instruments used for completion of this study were used from 2 to 6 years in each of the laboratories.
- Each instrument was the same part number and same measurement range.
- All instruments used the same set-up parameters developed for each container type.
  - No special onsite set-up or parameter adjustment.
- ME2 instrument is very flexible and can be used to perform CCI testing on a wide variety of containers/packages.
- Included in USP1207 as a deterministic CCIT method

Mass Extraction Operation: Overall system includes a custom chamber that is specific to container being tested, Intelligent Molecular Flow Sensor (IMFS), and vacuum reservoir as shown in Figure 1. A container is placed inside a vacuum test chamber and chamber evacuated. Once the test system is evacuated, the system is isolated from the vacuum source. Mass extracted from the test container into the vacuum test chamber due to container leakage will flow to the vacuum reservoir. The IMFS measures mass flowing from the vacuum test chamber into the vacuum reservoir.

Figure 1: Mass Extraction Pictorial Diagram



CONTAINER TYPES

A sample set including 123 samples was prepared for the study including 6 container variations as shown below:

Glass Vial – Air Filled: 2 ml glass vial with stopper and crimped cap, air inside
Glass Vial – Liquid Filled: 2 ml glass vial with stopper and crimped cap, Liquid inside
LDPE Bottle – Air Filled: 4 ml LDPE bottle with a screw cap, air inside
LDPE Bottle – Liquid Filled: 4 ml LDPE bottle with a screw cap, liquid inside
Glass Syringe – Air Filled: 1 ml glass syringe, air inside
Glass Syringe – Liquid Filled: 1 ml glass syringe, liquid inside

The sample set included both negative and positive control samples. For each container type, a sample set was prepared with wfi (water for injection) inside or air only inside. Three positive controls of each diameter (1 µm, 2 µm, 5 µm, and 10 µm) were created for each container variation. Total sample set is shown in Table 1 below:

Empty Container – Sample Set					
	Manufactured Defect Sizes (micropipette)				Negative
Sample Type	1 µ nominal	2 µ nominal	5 µ nominal	10 µ nominal	Control
Glass Vial 2 ml	3	3	3	3	10
Syringe 1 ml	3	3	3	3	10
LDPE Bottle 4 ml	3	3	3	3	10
Liquid Filled Container – Sample Set					
	Manufactured Defect Sizes (micropipette)				Negative
Sample Type	1 µ nominal	2 µ nominal	5 µ nominal	10 µ nominal	Control
Glass Vial 2 ml	3	3	3	Eliminated**	10
Syringe 1 ml	3	3	3	Eliminated**	10
LDPE Bottle 4 ml	3	3	3	Eliminated**	10

**10 µm liquid filled samples were eliminated from the study due to liquid leakage into the test chamber failing gross leak check beginning of test

Table 1: ILS#1178 Sample Set

POSITIVE CONTROL GENERATION

There are multiple methods commonly employed for creation of positive control samples. Two typical methods used are insertion of glass micropipettes and laser drilling. Each method offers advantages and disadvantages as outlined in USP1207[1]. Extensive published studies were performed on the correlation of microbial ingress through micropipettes, as well as tracer gas flow rates[2]. The ability to generate consistent glass defects smaller than 2-3 micron (e.g. sub-micron to 1 micron) and historical published data on glass micropipettes were the primary reasons why micropipettes were selected for ILS#1178.

Micropipettes were inserted into 18 gauge needles to protect the pipette from damage as they were inserted into containers. Each pipette was bonded inside the needle housing using epoxy as shown in Figure 2.

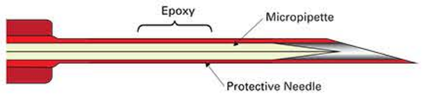


Figure 2: Micropipette Assembly

Air flow rate of each micropipette assembly was measured to ensure that the pipette was not plugged or damaged during assembly. Micropipette flow rate versus nominal diameter is included in Figure #1 below:

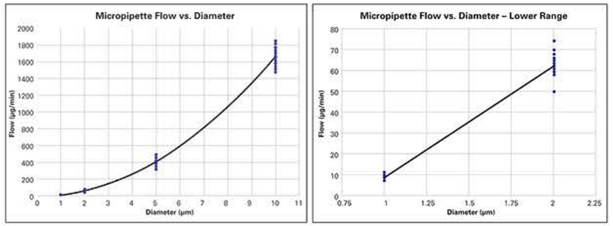


Figure 3: Micropipette Flow versus Diameter

Micropipettes are certified by the manufacturer to be within ±20% of nominal diameter. This manufacturers tolerance band results in the flow rate variation measured.

RESULTS

All air backed defects for all 3 container types were detected. All liquid backed defects vials and LDPE bottles were detected. The 1µm liquid backed syringe defects were not detected. It is theorized that silicone inside the syringe plugged the defect as test results were similar to intact negative control samples. Overall results are included in Table 2 below:

	Package Description	Sample Qty.	Qty. of Tests	Qty. of Failed Tests	Qty. of Passed Tests	Success %
Glass Vial 2 ml	Liquid Filled – Negative Control	10	120	0	120	100 %
	Air Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Liquid Filled	3	36	36	0	100 %
	1 µm micropipette – Air Filled	3	36	36	0	100 %
	2 µm micropipette – Liquid Filled	3	36	36	0	100 %
	2 µm micropipette – Air Filled	3	36	36	0	100 %
	5 µm micropipette – Liquid Filled	3	36	36	0	100 %
	5 µm micropipette – Air Filled	3	36	36	0	100 %
	10 µm micropipette – Air Filled	3	36	36	0	100 %
LDPE Bottle 4 ml	Liquid Filled – Negative Control	10	120	0	120	100 %
	Air Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Liquid Filled	3	36	36	0	100 %
	1 µm micropipette – Air Filled	3	36	36	0	100 %
	2 µm micropipette – Liquid Filled	3	36	36	0	100 %
	2 µm micropipette – Air Filled	3	36	36	0	100 %
	5 µm micropipette – Liquid Filled	3	36	36	0	100 %
	5 µm micropipette – Air Filled	3	36	36	0	100 %
	10 µm micropipette – Air Filled	3	36	36	0	100 %
Glass Syringe 1 ml	Air Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Air Filled	3	36	36	0	100 %
	2 µm micropipette – Air Filled	3	36	36	0	100 %
	5 µm micropipette – Air Filled	3	36	36	0	100 %
	10 µm micropipette – Air Filled	3	36	36	0	100 %
	Liquid Filled – Negative Control	10	120	0	120	100 %
	1 µm micropipette – Liquid Filled	3	36	0	36	0 %
	2 µm micropipette – Liquid Filled	3	36	36	0	100 %
	5 µm micropipette – Liquid Filled	3	36	36	0	100 %

Table 2: Results Summary

CONCLUSIONS

- Mass Extraction is capable of detecting a defect with similar flow rates as a 1 µm micropipette for containers included in this study.
- Multiple Mass Extraction instruments, with varying age, can be operated using same set-up parameters when testing the same containers.

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(1) First Supplement to USP 39–NF 34 General Information / (1207) Package Integrity Evaluation—Sterile Products 1, chapters 1207; 1207.1- United States Pharmacopeia (USP) Standard-2016.
(2) Kirsch, L.E., Nguyen, L., Moeckly, C.S. and Gerth, R., "Pharmaceutical Container/Closure Integrity II: The Relationship Between Microbial Ingress and Helium Leak Rates in Rubber-Stoppered Glass Vials", Journal of Parenteral Science & Technology, 51, 195-202 (1997)