Integrity Testing of Flexible Containers Using the Helium Integrity Testing (HIT™) Platform (2-D and 3-D Bags and Manifolds)

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ATMI

Goal

To demonstrate 10 micron defect detection capability of the Helium Integrity Testing platform - HIT™.

Introduction

Switching to single-use systems (bags and hardware) can have financial and performance benefits. However, one of the critical challenges for complete acceptance of single-use systems is assurance of bag integrity which in turn means assurance of product sterility and operator safety.

Single-use technologies (SUT)are used frequently in large scale -1000L+ scale. Main risk with SUT is leaks as transport and handling can induce leaks[1].

Assemblies must be integrity tested by a physical test correlated to a bacterial challenge test – VOC

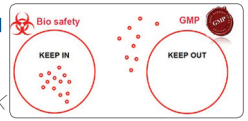


Figure 1. Biosafety versus GMP

Scientists at Viral Industrial Bulk, GSK Biologicals, Belgium, mention in their article[2], "Main problem in terms of biosafety is the loss of integrity of the disposable bag leading to a leak of the viral contaminant, and potentially operator contamination ".

The second greatest concern regarding the use of disposables was "Breakage of bags and loss of production materials" (which grew to 62.5% from 54.9% last year)[3].

1.ABSA Orlando 2012. Karin Hedebo Wassard, Henriette Schubert, NNE Pharmaplan. / 2.Jean-Francois Chaubard, Sandrine Dessoy, Et Al, BioPharm International, 2010, Issue 11, pp. 22-31 / 3.Langer E., Pharma Manufacturing, April 2009 (http://www.pharmamanufacturing.com/articles/2009/126.html?page=1

Limitations of Pressure Decay Test Method

Pressure decay is the most commonly used integrity test method for flexible containers at present, in which, a test bag is filled with a high pressure gas, usually dry air or nitrogen. Then the test part is isolated from the gas supply and, after a stabilizing period, its internal pressure is monitored over time. The pressure drop (Δp) is measured in the time (Δt).

PROPERTY	PRESSURE DECAY FREE INFLATION	PRESSURE DECAY CONSTRAINED PLATE	HIT System
			
TYPES OF BAGS	2D, 3D	2D, 3D	2D, 3D AND MANIFOLDS
WHAT IS TESTED	FULLY ASSEMBLED BAG	BAG COMPARTMENT ONLY (NO TUBING, CONNECTORS)	FULLY ASSEMBLED BAG
SPECIFIC DEFECTS	FILM/FILM SEAL, FILM FITMENT SEAL, FILM PINHOLES, MISSING COMPONENTS	FILM/FILM SEAL, FILM/FITMENT SEAL, FILM PINHOLES	FILM/FILM SEAL, FILM/FITMENT SEAL, MISSING CONNECTORS, HALF CLOSED CONNECTORS, BLOCKED JOINTS
DETECTION LIMIT	500 µm (≥ 1000L) 100 µm (~ 500L)	100 µm (≥ 350L) 20 µm (< 200L)	10 µm (≤ 500L)
TEST TIME	3D (6-15 MINUTES)	2D (< 1 Minute)	2D (2 MINS) 3D (6-8 MINS) MANIFOLD (6-8 MINS)
UTILITY	COMPRESSED AIR	COMPRESSED AIR, MECH.FIXTURE	COMPRESSED AIR, COMPRESSED He (6x @ 50, & 5x @ 2000), MECH. FIXTURE
SAFETY	GOOD	BETTER	BEST

Table 1: Comparison of different Integrity testing methods

Pressure Decay Test cannot detect defects down to 10 micron in large flexible containers and manifolds.

Correlation Between Defect Size and Microbial Ingress

Aerosol Microbial Challenge

Challenge Organism: Escherichia Coli, Staphylococcus aureus, Bacillus spizizenii, Candida albicans, Aspergillus brasiliensis
Microbe Conc. : 106 cfu/ml

Growth Media: Trypticase Soy Broth
Aerosol Exposure Time: 10 Minutes, 60 Minutes
Incubation Time: 14 days
Test Bag: 1L, 2D Bag
Positive Sample : Sample bag inoculated with 100 cfu.
Showed positive growth on 2nd day.
Negative Sample : Sample bags with no-defect.

Figure 2. Sketch of product in test

10 Minute Exposure *60 Minute Exposure*

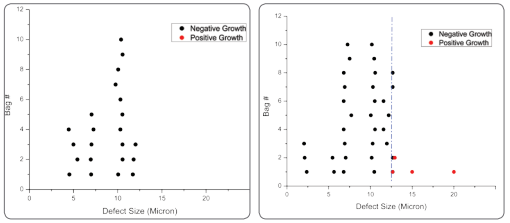


Figure 4. Observation of microbial ingress after 10 minute exposure (left) and 60 minute exposure (right)

Microbial ingress not observed in defects smaller than 12.65 microns irrespective of microbial aerosol exposure times.

Immersion Microbial Challenge

Challenge Organism: Brevudimonas diminuta
Bacterial Conc.: 9.7 x 106 cfu/ml

Growth Media: Trypticase Soy Broth
Immersion Exposure Time: 30 Minutes and 3 Hours
Incubation Time: 14 days
Test Bag: 1L, 2D Bag
Positive Sample : Sample bag inoculated with 100 cfu.
Showed positive growth on 2nd day.
Negative Sample : Sample bags with no-defect.

Approximate level of microbial challenge outside test sample when immersed in bacterial suspension

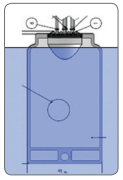


Figure 3. Sketch of product in test using immersion microbial challenge

30 Minute Immersion *3 Hour Immersion*

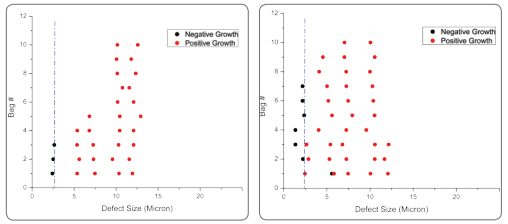


Figure 5. Observation of microbial ingress afetr 30 minutes exposure (left) and 3 hour immersion (right)

Microbial ingress not observed in defects smaller than or equal to 2.35 microns irrespective of microbial immersion time.

The Helium Integrity Testing Platform (HIT)

The HIT system consists of:

1. Control System
2. Chamber
3. Separator

Figure 6. ATMI LifeSciences Helium Integrity Testing platform

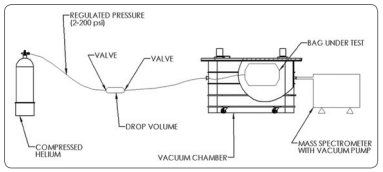


Figure 7. The HIT platform test schematic

Results

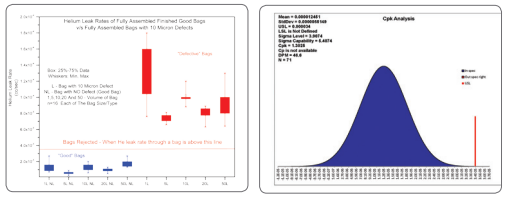
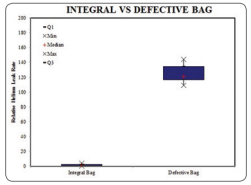


Figure 8. Defect detectability for single-use 2D bags

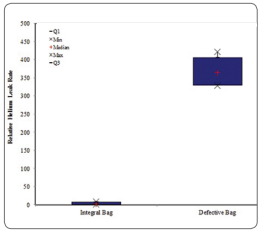
The leak rates of defective bags (10um) are statistically significantly higher than bags with no known defects, making "defective bag" detection possible.



200L 3D Bags with 10 micron Defect are easily detectable using the HIT platform.

Figure 9. Defect detectability for single-use 3D bags

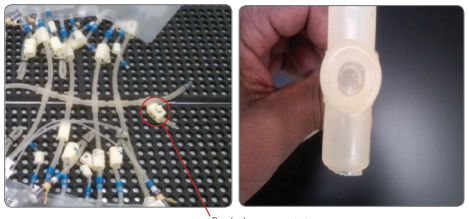
10µm Defect Detection - Manifolds



Manifolds with 10 micron Defect are easily detectable using the HIT platform.

Figure 10. Defect detectability for single-use manifolds

Manifold Backbone Defect



Pinch clamp was missing

Figure 11. Visual observation; Visual inspection of fourway connector. Manifold with No Defect : 2.0 (Relative Leak rate/Sec). Manifold with Missing Pinch Clamp : 4.5 (Relative Leak Rate/Sec)

Visual inspection of the fourway connector showed a film was present that blocked the flow of the helium to rest of the bags, creating net higher pressure and hence, higher He leak rate, which was detected instantly by the HIT system. The HIT platform detects missing or half closed connectors / Components, even where pressure decay test cannot.

Conclusions

1. Classical pressure decay tests cannot provide sufficient sensitivity for integrity test of finished complex manifolds or 3D bags.

2. Aerosol study shows that 10 micron detection is critical to ensure sterility of a package

3. Prior-to-use, Helium Integrity Testing platform (HIT) is capable of detecting defects of less than 10 micron size on complex manifolds, fully assembled 2D and 3D bags.

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