Common Approaches to Meeting Requirements for Packaging Validations

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Agenda

- Purpose of Packaging
- Package validations / Test Methods
- Worse Case/Failures/Revalidation

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Purpose of Packaging (Sterile Barrier System)

- Introduced ISO 11607 in 2006, newest edition 2019/2020.
- Designed to allow sterilization
- Provide an acceptable microbial barrier
- Demonstrate strength and integrity characteristics
- Allow for aseptic presentation
- Is a requirement

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The document divides the testing into two separate areas:

- ✓ Performance Characteristics
  - ➢ temperature, humidity, pressure, light, cleanliness, and electrostatic conductivity

- ✓ Package Properties
  - ➢ microbial, physical and chemical properties, sterilization, and biocompatibility

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Responsibilities – Material Supplier

- Provide information regarding physical properties (porosity, flammability, etc.)
- Assistance with validation runs
- Validation data on preformed sterile barrier systems

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Responsibilities – Medical Device Manufacture

- All seals on Form Fill Seal (FFS)
- Final seal on purchased pouches
- Final package performance – including distribution testing and validation report

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Material classification

Porous – a material used in medical packaging which is intended to provide an environmental and biological barrier, while allowing sufficient air flow to be used in gaseous sterilization methods

- Paper
- Flashspun Polyolefin

Non-porous – material which does not have pores or minute openings to allow volumetric air flow.

- Plastic film
- Rigid trays
- Metal foils

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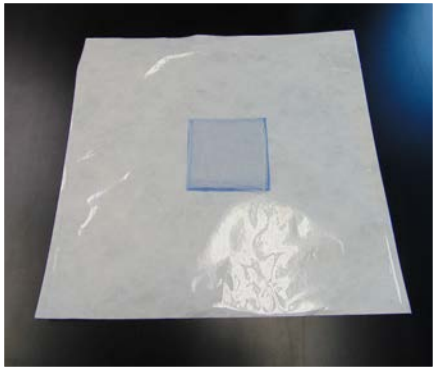
Right Size Packaging

Too small

Just right



Too big

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Package Validations

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Packaging Tests

Evaluated through all intended processes

- ✓ Sterilization
- ✓ Handling
- ✓ Distribution
- ✓ Storage
- ✓ Include all materials – IFU, labeling

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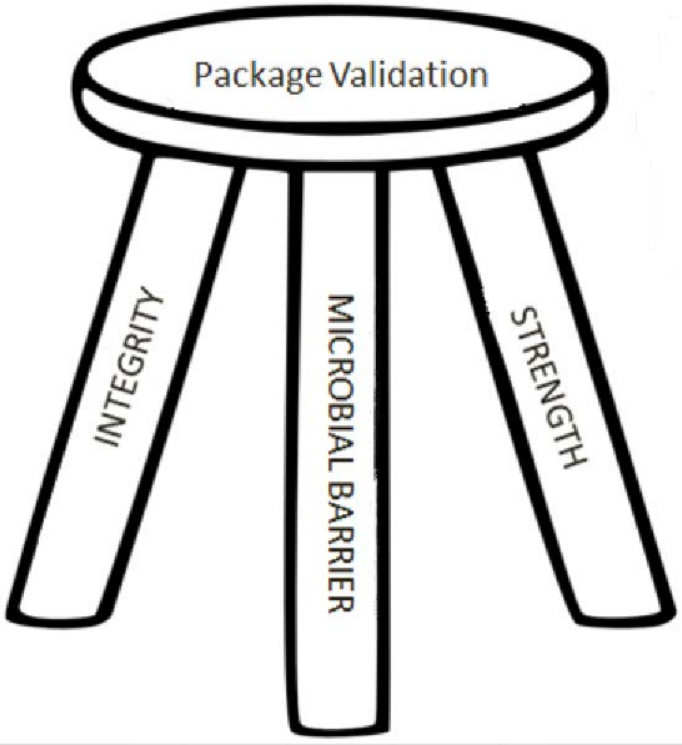
Basic Packaging Validation Plan

- You must demonstrate
  - Overall effectiveness of the packaging system
  - The sterile barrier system (SBS) effectiveness using 3 properties
  - Through the expected use by date



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Packaging Test Summary

Strength	Integrity	Microbial Barrier
Seal Peel	Visual Inspection	F1608
Burst Test	Dye Migration	Microbial challenge
Creep Test	Dye Immersion	F2638
	Bubble Emission	Gurley Nonporous
	Mass Extraction	

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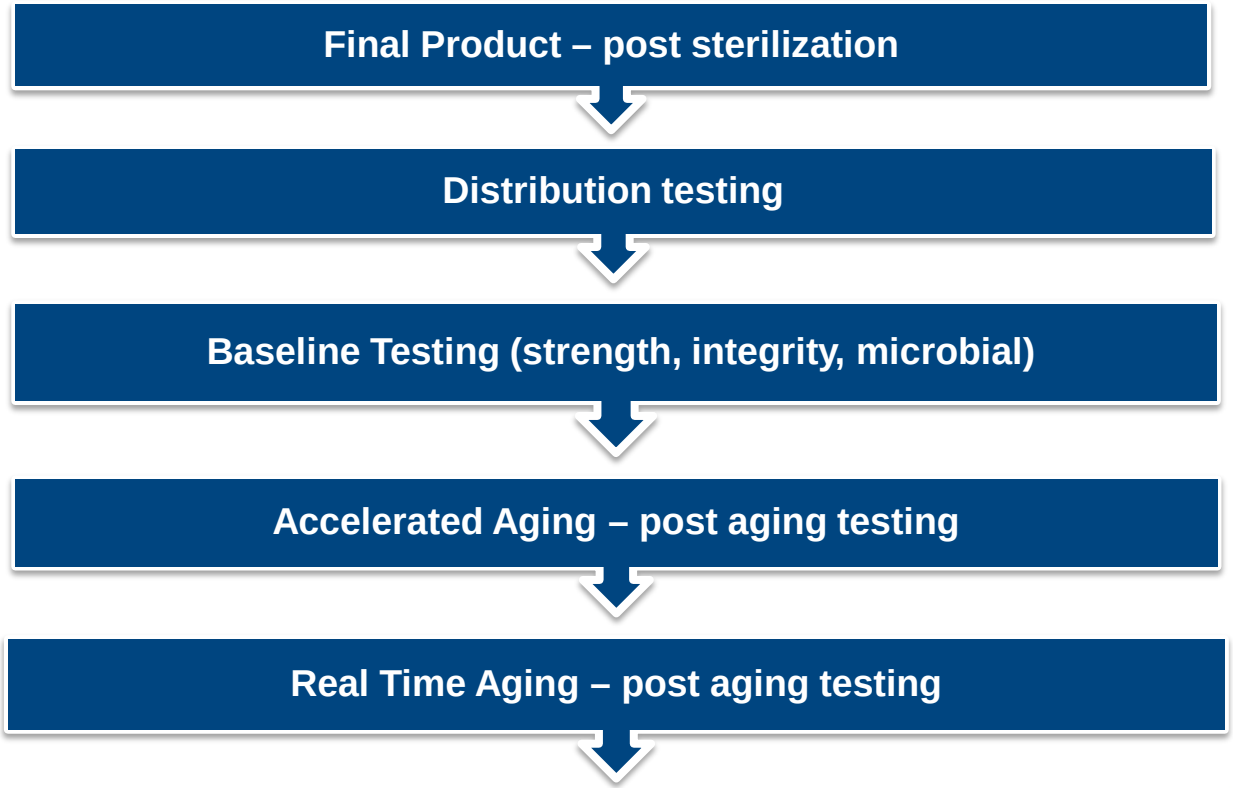
Basic Packaging Validation Plan



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Test Methods

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Test Method Key Points

- Any test method used needs to be validated for use in your facility and/or with your equipment:
  - Repeatability – variation within a lab
  - Reproducibility – variation from lab to lab
  - Sensitivity – measure of the limits of the test method
- Precision and bias statements that can be found in the standards can help assess any variability found in validation results.
- Some test methods are actually processes that prepare materials for evaluation by test methods.

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Distribution Simulation

Distribution Testing simulates physical hazards a package encounters throughout the shipping and distribution environment.

These hazards include:

- Temperature
- Humidity
- Altitude
- Shock
- Vibration
- Compression

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Distribution Hazards

Boxes are manually moved from conveyer belts and transported by hand, forklift or hand truck within the warehouse.

- Drop
- Impact
- Compression (side)

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Distribution Hazards

Boxes are transferred to smaller trucks for delivery.

- Vibration (loose load)
- Impact (concentrated)

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Distribution Simulation

Standards most commonly used are:

- ASTM D4169, DC 13 (AL I or AL II)
- ISTA 3A
- D7386
- ISTA 2A

They all designed to simulate the vibration environment in a controlled, lab setting

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Distribution Simulation

How to select the right cycle?

- Distribution Cycle: the sequential listing of the test schedules employed to simulate the hazard elements expected to occur for a specific routing from production to composition (most fall into DC13 encompassing both air and truck.

- Assurance level: the level of intensity based on the probability of occurring in a typical distribution cycle
  - Assurance level 1: high test level, low probability of occurrence
  - Assurance level 2: most common approach
  - Assurance level 3: low test level, high probability of occurrence

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Distribution Simulation

Climatic Stressing - In accordance with ASTM and/or ISTA Standards, the following is a list of climatic stresses that the package will be subjected to:

ASTM D4332:

- Extreme cold (winter); -30°C (uncontrolled RH)
- Desert (hot/dry); 60°C/15 % RH
- Tropical (warm/wet); 40°C/90% RH

ISTA varies slightly but it is similar

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Distribution Simulation

Drop

- Free fall
- Hazard impact
- Rotational

- Incline impact
- Horizontal impact
- Vertical impact

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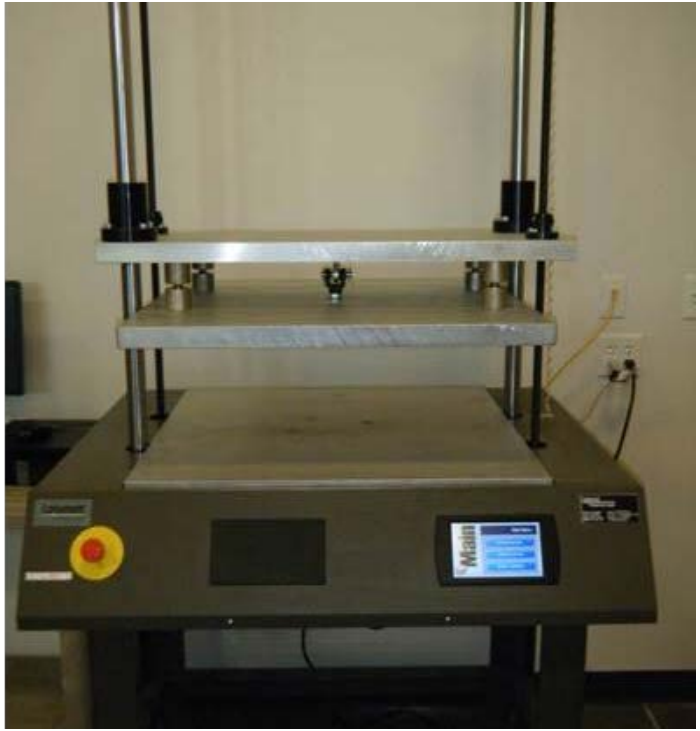
Distribution Simulation

Compression test

- Static (Dead Load) Machine
  - Apply and release
  - Apply and hold
- Dynamic Load Under Vibration



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Mechanical Shaker

- Fixed Displacement
- Rotary
- Vertical linear

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Vibration Table

- Variable Displacement
- Random
- Vertical
- Multi-axis

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Strength Tests

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Seal Peel Test

Seal Peel Test - ASTM F88

Determines the strength of the seal at a specific place on the package

Measure a one inch segment of the package along one of the seals • Cut the package so that there are 3 inches of material on each side of the seal	2 Seals • Manufacturer's • MDM Seal • Testing both seals makes for easy acceptance criteria!	Porous or Non-porous Seal test only

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Seal Peel Test

How do you establish the minimum seal strength value?

- ✓ Establish your design inputs (regulatory, marketing, sales)
- ✓ Work with your packaging supplier
- ✓ Validation (low, nominal, high)

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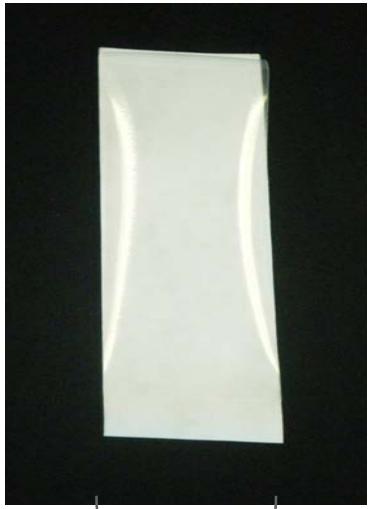
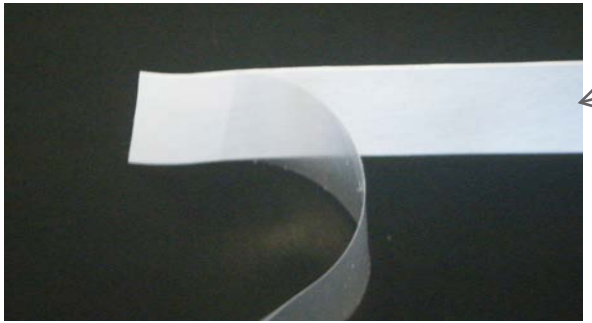
Seal Peel Test



1” across

Identifying the material in each grip is critical as it can have an affect on the results.



Most rigid material in mobile grips

Most flexible in stationary grips

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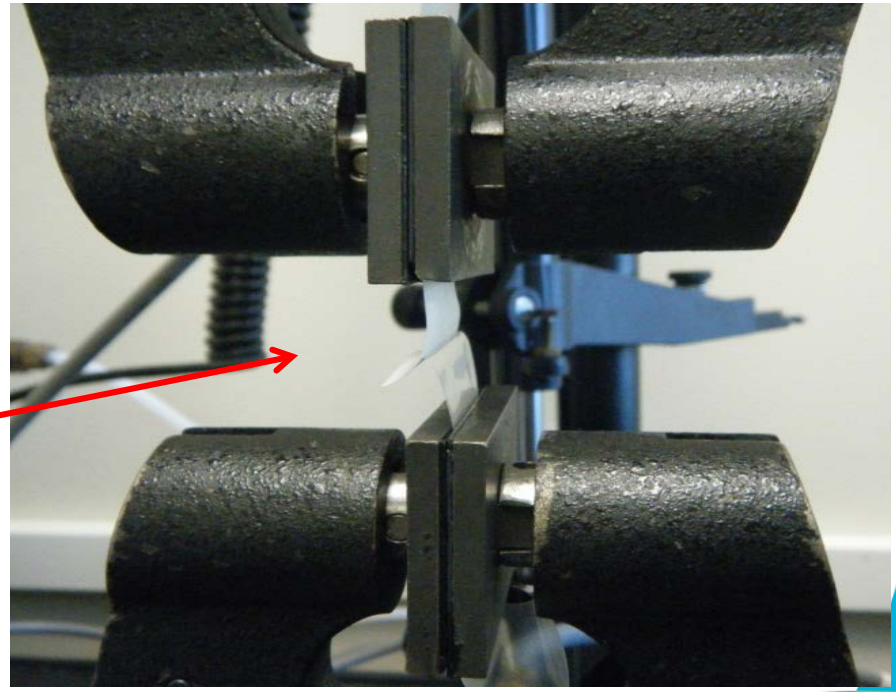
Seal Peel Test

90° Unsupported

Usually provides the most conservative value (lowest)

Tail is free floating during the pull



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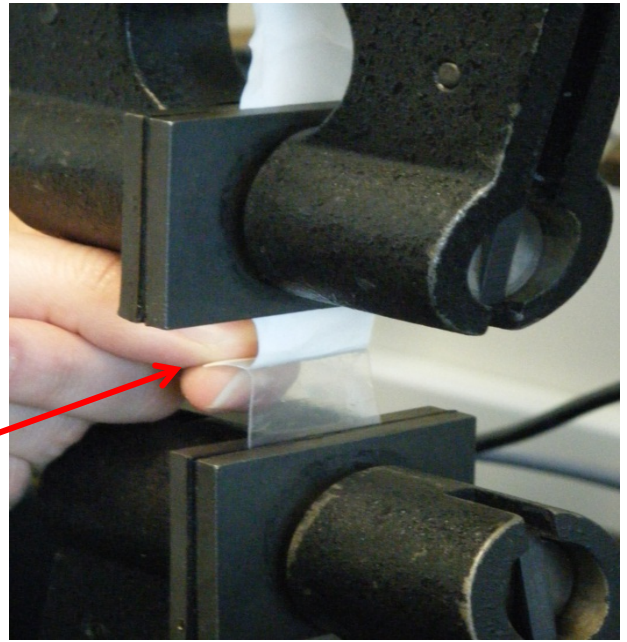
Seal Peel Test

90° Supported

Tail is manually held with slight pressure during the pull



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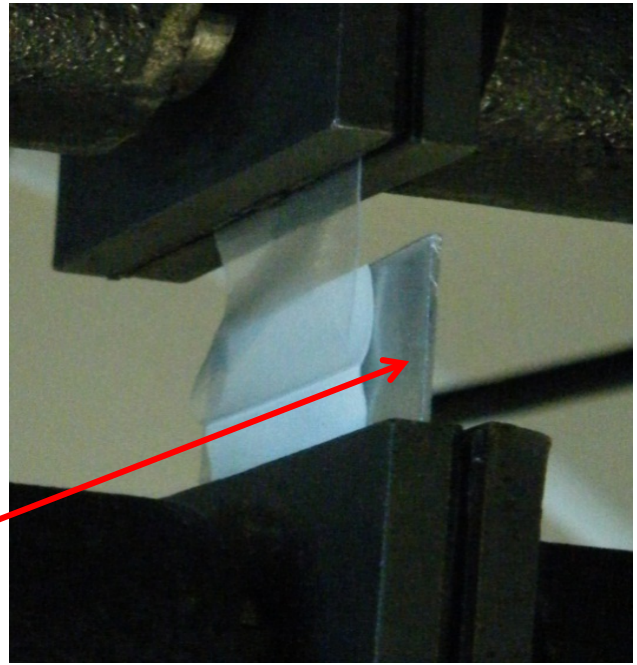
Seal Peel Test

180° Supported

Provides values significantly higher than with tail in 90 ° position. Plate is placed in the stationary grip.

Tail is held with a backing plate during the pull



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Seal Peel Test – Failure issues

Over sealed as a result of too high temperatures causing melting/bending of materials and voids in the seals.

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Seal Peel Test – Failure issues

Example of Delamination

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Burst / Creep Test

Burst Test - ASTM F1140

Determines package seal strength

Test system pressure is pre-set to a point above the known burst point Perform by pressurizing the package until it bursts	Results include the burst pressure data and a description where the seal failure occurred. • This provides a better idea of where the stress points are located	Whole package Porous or non-porous

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Burst Test

Burst values of a pouch are dependent on several factors:

- ✓ Pouch Size – larger pouches give lower values
- ✓ Pouch configuration
- ✓ Material type – porous versus nonporous
- ✓ Equipment and airflow rate – sensitivity (response to pressure drop)
- ✓ Restraining plates

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Integrity Tests

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Visual Inspection - ASTM F1886

Visual Inspection is a process of methodically and purposefully examining a package for a specific range of defects and recording observations.

- ✓ Packages are checked for a list of common defects
- ✓ Analysts should be properly trained
- ✓ There should be adequate lighting
- ✓ Inspections should take 1-5 minutes a sample
- ✓ Observations are documented with writing and pictures

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Unsealed Areas

Example of open seal

Package misalignment

Equipment malfunction

Defects within the material or foreign body in the seal

Seal rupture

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Nonhomogeneous or Undersealed

Nonhomogeneous seals can occur with improper sealing parameters. For example: insufficient heat, pressure, or too short of dwell time.

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Narrow Seals

Tray misalignment

Internal creep due to tray warp

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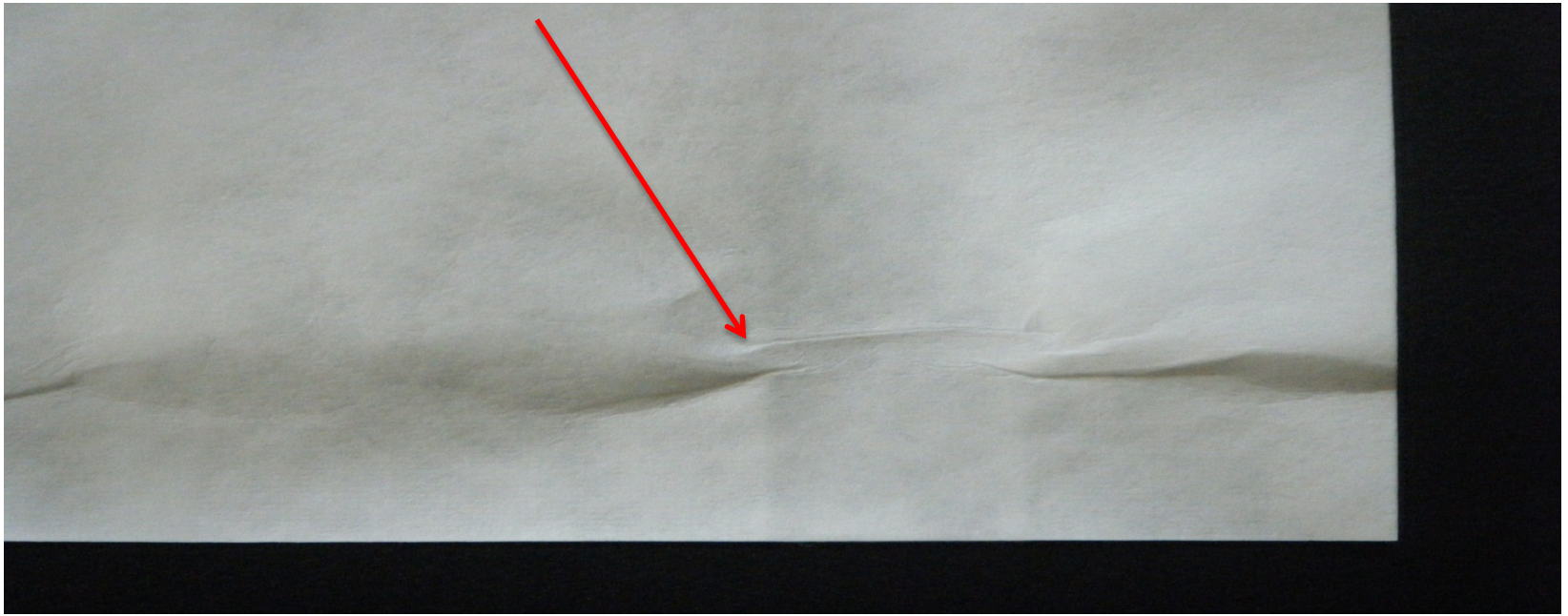
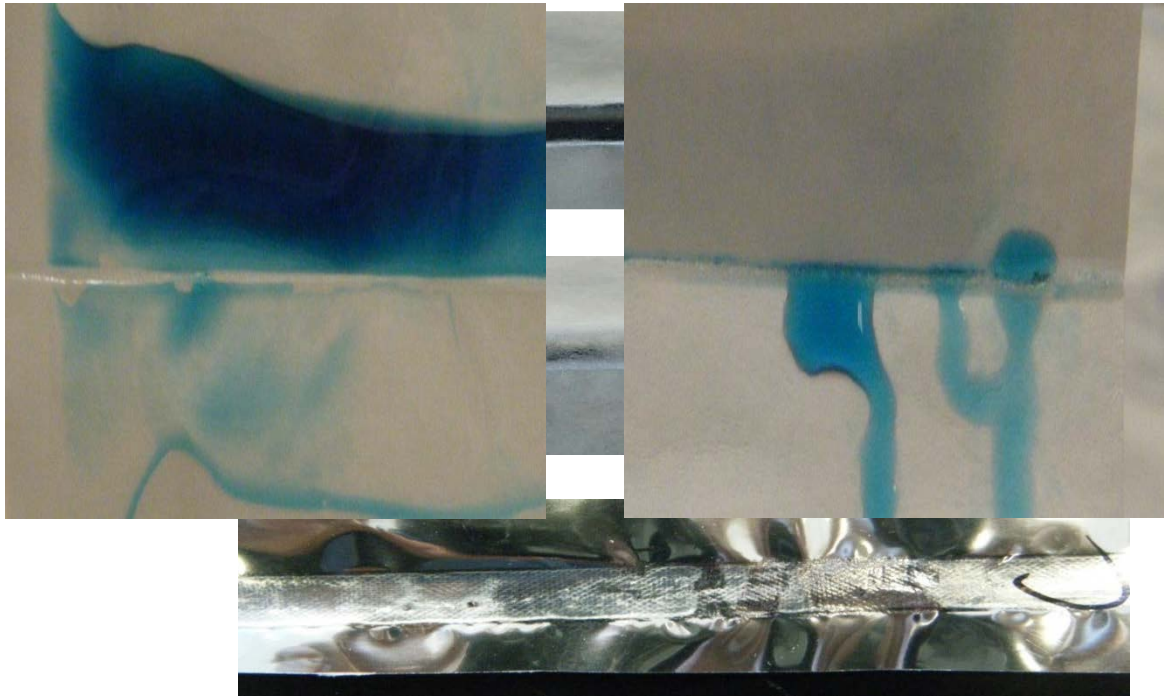
Channels

Channel through seal



Oversealed



Dye leak through seal

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Dye Migration Test

Dye Migration Test - ASTM F1929 Porous

Determines the integrity of the package seal

Involves injecting dye into the package

- Placing the weight of the solution against each portion of the seal for a specific length of time
- Dye migrating through the seal is a failure

Seal only test

Porous and Non-porous

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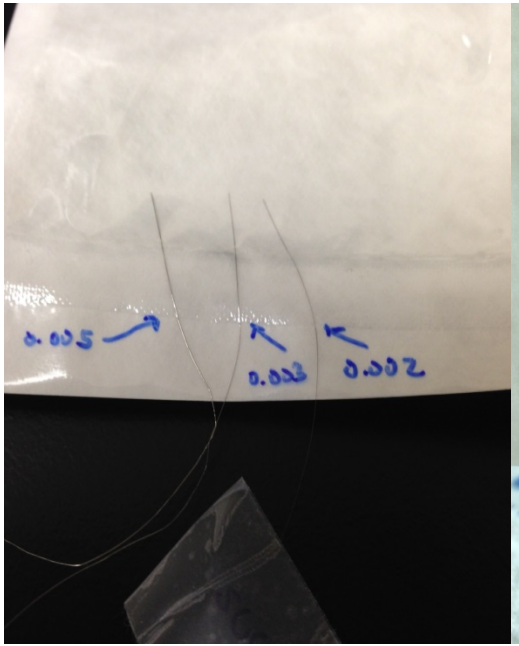
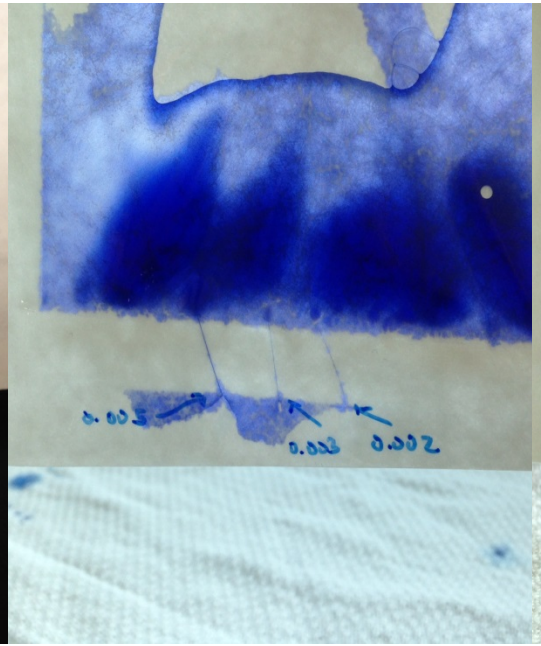
Dye Migration Test - Porous





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Dye Migration Test - Porous

Injection Method A	Placing weight of the solution against the seal for ≤ 5 sec Examine package for evidence of seal failure
Edge Dip Method B	Remove any excess material beyond seal Edge of seal touches solution for ≤ 5 sec
Eye Dropper Method C	Peel open package to expose testing seal Lay a bead of solution across seal for ≤ 5 sec

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Dye Migration - Nonporous

ASTM F3039 Detecting leaks in Nonporous Packaging or Flexible Barrier Materials:

- ✓ Injection method with a different solution, higher concentration of surfactant
- ✓ Standard updated to include a roller method and changed the surface tension

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Dye Migration Questions

What do you do with a double pouch system?

- ✓ Cut into interior without damaging the seals
- ✓ Edge dip outer pouch

Can it be used for whole package integrity?

- ✓ No due to the nature of the test – porous material will wick first
- ✓ Designed to detect channels through the seals only

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Bubble Emission Test

Bubble Emission Test - ASTM F2096

Determines the integrity of the package and the seal

Inflate the package under water to a set pressure and look for escaping bubbles	Whole package test Porous or Non-Porous

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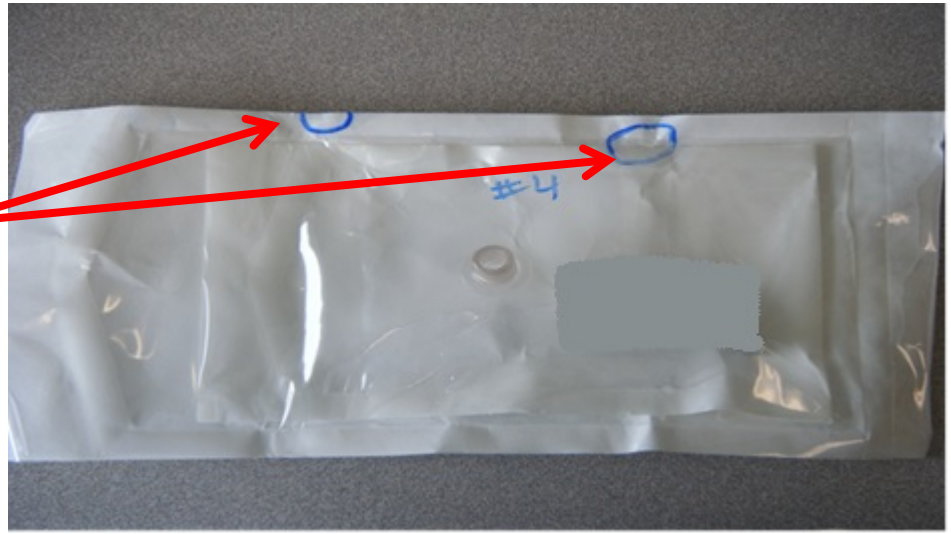
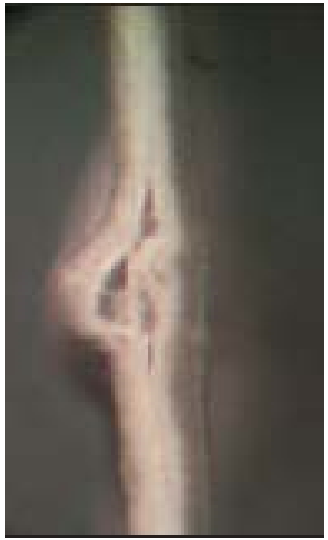
Bubble Emission – Failure Issue

Folds





Can result in sheet separation of the material leading to false failures

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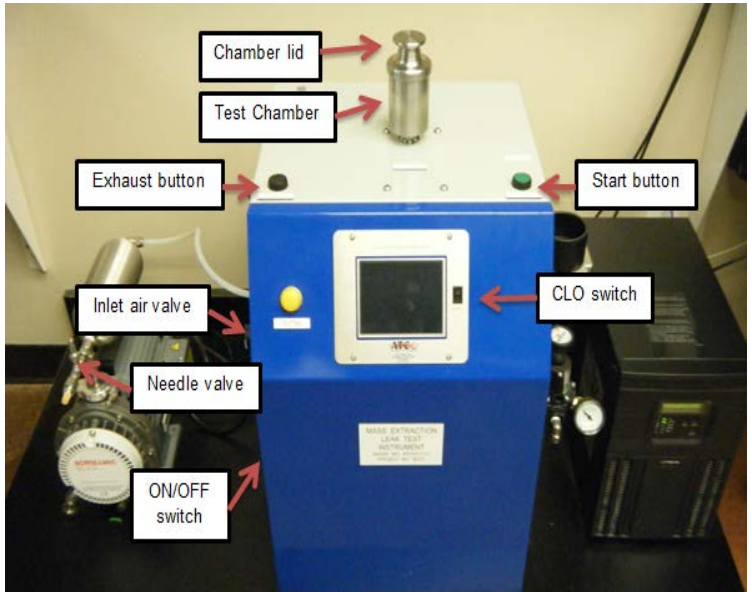
Mass Extraction –ASTM F3287

- ✓ The samples are placed into a fitted chamber with inserts to reduced free space.
- ✓ A vacuum is pulled and the sample is evaluated for leaks.
- ✓ Defects 2 µm to 5 µm
- ✓ Rigid Containers



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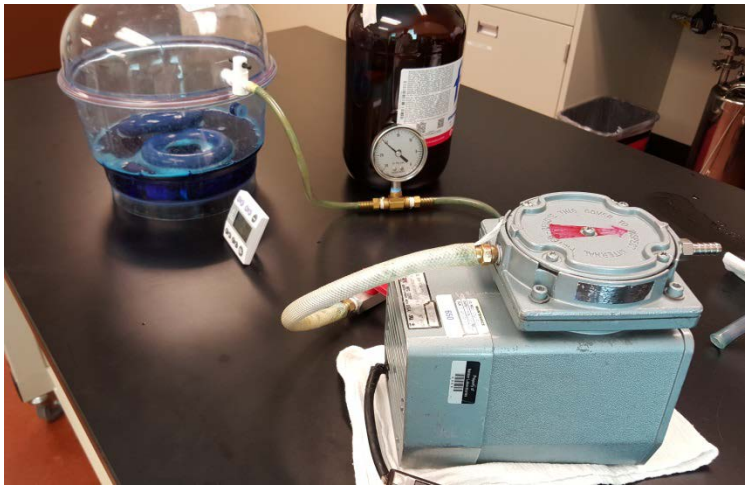
Dye Immersion

- ✓ Samples immersed in dye and placed under vacuum
- ✓ Vacuum is released, samples are removed and washed
- ✓ Contents are examined visually or using a UV-Vis for the presence of dye



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MICROBIAL TESTS

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Microbial Ranking Test

Microbial Ranking Test - ASTM F1608

Determines the Log Reduction Value (LRV) of porous material

A 47mm disc is tested. *Bacillus* spores are drawn through the material. The number that pass through are used to calculate an LRV.	Standard says to test a minimum of 2	Material only Porous only

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Microbial Aerosol Challenge

Microbial Aerosol Challenge

Determines the integrity of the whole package

Packages are placed in an aerosol chamber and exposed to a specific organism (*Bacillus*). The contents are tested for the presence/absence of the indicator organism after exposure.	Whole package Porous or Non-porous *Novel packaging systems

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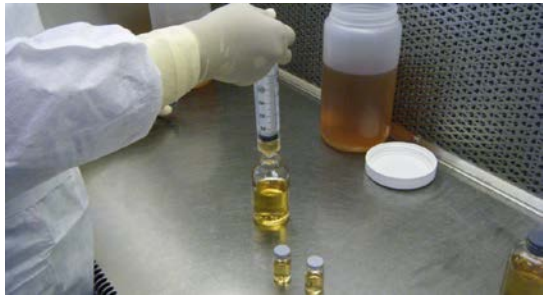
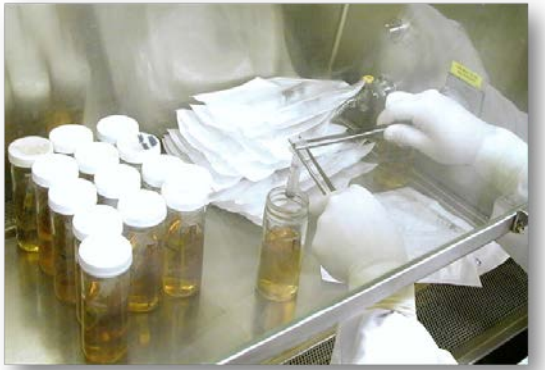
Microbial Aerosol Challenge





- Indicator testing
  - Immersion
  - Flush
  - Media fill

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Aerosol Filtration for Measuring the Performance of Porous Packaging Materials- ASTM F2638

- ✓ Measures aerosol filtration performance of porous materials by counting particles as they pass through the membrane
- ✓ Uses 1.0 µm latex spheres
- ✓ Uses realistic environmental flow rates
- ✓ Results in the max penetration of material

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Accelerated Aging

Accelerated Aging - ASTM F1980

Purpose/Theory		
Demonstrate the package is not affected by aging to the expected shelf life	Does **not** replace real time aging	Based on the observations of Arrhenius

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Accelerated Aging

Q_{10} = 2; 25ºC ambient

ºF	ºC	1yr	2 yrs	3 yrs	4 yrs	5 yrs
77.0	25.0	52.0	104.0	156.0	208.0	260.0
86.0	30.0	36.8	73.5	110.3	147.1	183.9
95.0	35.0	26.0	48.5	72.8	97.0	121.3
104.0	40.0	18.4	36.8	55.2	73.5	91.9
113.0	45.0	13.0	26.0	39.0	52.0	65.0
122.0	50.0	9.2	18.4	27.6	36.8	46.0
131.0	55.0	6.5	13.0	19.5	26.0	32.5
140.0	60.0	4.6	9.2	13.8	18.4	23.0
149.0	65.0	3.3	6.5	9.8	13.0	16.3

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Accelerated Aging

Justify test conditions and duration	With or Without Product
• Ambient temperature • FDA recommends 25°C • Aging temperature • Relative humidity • < 10-15°C T_g for all polymers–*Caution!*	• The presence of a device can stress a package and affect performance. Use of simulants is not uncommon.

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Worst Case - Device

"When similar medical devices use the same packaging system, a rationale for establishing similarities and identifying the worst case shall be documented." – ISO 11607

- Medical Device (heavy, light, sharp)
- Material (porous, nonporous)
- Sterilization (single, multiple)
- Distribution, storage, handling

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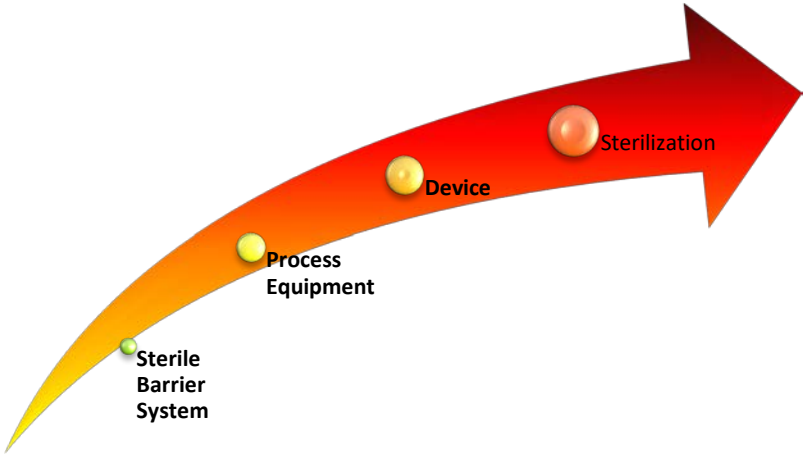
Re-validation

Changes to:



Re-validation

- Some changes are so minor that revalidation is not required – but a record of the justification for not revalidating is required
- Periodically a review should take place to determine if many small changes in total now require revalidation

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Packaging Test Summary

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Seal Peel	Visual Inspection	F1608
Burst Test	Dye Migration	Microbial challenge
Creep Test	Dye Immersion	F2638
	Bubble Emission	Gurley Nonporous
	Mass Extraction	

Non-Porous
Porous
Either material
Container closure

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THAT'S A WRAP

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