European Union (EU) Package Testing

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Who are Anecto?

ANECTO
Trusted Test Experts

Innovation Ireland

www.anecto.com
Your Best Route to Europe
Accreditations & Certification & Membership

ISO17025:2005 Test Laboratory Accreditation
50 + International standards accredited

ISO9001:2008 Quality Management System

ISTA (International Safe Transit Association)

ASTM International Organisation Member
Votes on Committee D10 and F02 Standards

ISO11607 Irish Committee - Expert Member

Continuously adding new equipment and processes
Services Provided by Anecto

- Reliability and Environmental Testing
- Validation of electronic equipment
- Process equipment validation
- Transportation / Package Testing
  - Package Design Consultancy
  - Test Process Analysis & Design Consultancy
- Package Integrity Testing (Including Visual Inspection)
- Catheter Burst testing
- Corrosion Testing on needles and stainless steel tubing
- High and Low Pressure testing
- Cold Chain / Temperature Mapping
- Design Support, Test Development (electronic)
- HALT & HASS
- Warranty, Repair & Support
- Dangerous Goods Package Testing
Product Specific Testing

- Mechanical Performance
  - Tensile and Micro Tensile
  - Kink Resistance
  - Torque
  - Fatigue

- Fluid Dynamics
  - High Pressure Injection Capability
  - Static and Dynamic Catheter Burst testing
  - Micro Flow and Leak Testing

- Catheter Dynamic Performance
  - Catheter Push, Track, Cross and Wire Movement

- Balloon Testing
  - Burst, Fatigue, Compliance, Inflation / Deflation, Balloon Wrapped Profile

- Dimensional Analysis
  - Length / Diameter, Lumen ID, Luers
  - Deployment Accuracy, Foreshortening, ‘dog-boning’, Unsupported Area

Your Best Route to Europe
Failures seen in packaging performance testing and required conformance to the EU/ISO11607-1:2006 standard.
Packaging – Often The Poor Relation

- Left until the end
- Seen as a necessary evil
- Sometimes there is Little or No Budget
- Not Seen as Value Add
- Conflict between marketing and manufacturing

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Your Best Route to Europe
Risks!

• Every processes or product has associated risks
  – Process
  – Packaging
  – Handling
  – Transportation / Distribution
  – Storage
  – Integrity
  – Altitude
  – Global Distribution location

• Risk factors must be assessed to determine when and why failures may occur
Testing Questions

From your Risk assessment you will be able to determine

• How much testing should be done?
• What tests are needed?
  – Transportation Testing
  – Integrity Testing
  – Seal Strength testing
  – Stability studies
• How many samples are needed?
• Is Accelerated and Real time Ageing needed?
### ISO 11607:2006 List of Tests

<table>
<thead>
<tr>
<th>Test Standard</th>
<th>Description</th>
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<tbody>
<tr>
<td>Accelerated aging</td>
<td>ASTM F1980, EN 868-8</td>
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<tr>
<td>Air permeance</td>
<td>ISO 5636-2, ISO 5636-3, ISO 5636-5, EN 868-2, ASTM D 737</td>
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<td>Basis weight</td>
<td>ISO 536, ASTM D4321, ASTM D3776</td>
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<td>Biocompatibility</td>
<td>ISO 10993-1</td>
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<tr>
<td>Burst strength</td>
<td>ISO 2758</td>
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<tr>
<td>Cleanliness</td>
<td>TAPPI T 437-OM-96</td>
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<tr>
<td>Chlorides</td>
<td>ISO 9197</td>
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<td>Coat weight</td>
<td>ASTM F 2217</td>
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<tr>
<td>Conditioning</td>
<td>ISO 187, ASTM D4332, ISO 2233</td>
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<tr>
<td>Dimensions</td>
<td>ASTM F2203</td>
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<tr>
<td>Drapability</td>
<td>ISO 9073-9, ISO 2493, DIN 53121</td>
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<td>Flexural durability</td>
<td>ASTM F392</td>
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<td>Gas sensing</td>
<td>ASTM F2228</td>
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<td>Integrity</td>
<td>ASTM F1929, ASTM F2227</td>
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<tr>
<td>Internal pressure</td>
<td>ASTM F2096</td>
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<tr>
<td>Low-tension surface liquid resistance</td>
<td>IST 80-8</td>
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<tr>
<td>Microbial barrier</td>
<td>ASTM F1608, DIN 58953-6, BS 6256, ASTM F2101, SS 876 0019</td>
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<td>Peel-open characteristic</td>
<td>EN 868-5</td>
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<tr>
<td>Performance testing</td>
<td>ASTM D4169, ISTA 1,2, and 3, ISO 4180-1, EN 868-8</td>
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<td>pH</td>
<td>ISO 6588-1, ISO 6588-2</td>
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<td>Pressure leak</td>
<td>ASTM F2338</td>
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<tr>
<td>Printing and coating</td>
<td>ASTM F2250, ASTM F2252</td>
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<tr>
<td>Puncture</td>
<td>ASTM D1709, ASTM F1306, ASTM D3420</td>
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<tr>
<td>Seal strength</td>
<td>ASTM F88, ASTM F1140, ASTM F2054, EN 868-5</td>
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<tr>
<td>Static electricity</td>
<td>BS 6524</td>
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<tr>
<td>Sulfates</td>
<td>ISO 9198</td>
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<tr>
<td>Tear resistance</td>
<td>ASTM D1922, ASTM D1938, ISO 1974</td>
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<tr>
<td>Tensile properties</td>
<td>ISO 1924-2, ASTM D882</td>
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<tr>
<td>Thickness / Density</td>
<td>ISO 534, ASTM D645, ASTM F2251</td>
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<td>Vacuum leak</td>
<td>ASTM D3078, EN 868-8</td>
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<td>Visual inspection</td>
<td>ASTM F1886, EN 868-8</td>
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<td>Water resistance</td>
<td>ISO 811, EDANA 170-1, ASTM D779, EN 20535</td>
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<td>Wet burst in wet condition</td>
<td>ISO 3689</td>
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<tr>
<td>Wet tensile properties</td>
<td>ISO 3781</td>
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</table>

71 test standards covering 34 types of test

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How Much Testing?

- **DQ** → **IQ** → **OQ** → **PQ**
  - 3 separate lots required for PQ
  - Package Integrity Tests
  - Physical Strength Tests
  - Test Report

- **Production Packages**
  - Sterilisation
  - Distribution Simulation

- **Accelerated Ageing Testing**
  - 1 year Accelerated Ageing
  - 3 year Accelerated Ageing
  - Package Integrity Tests
  - Physical Strength Tests

- **Real Time Ageing Testing**
  - 1 year Real Time Ageing
  - 3 year Real Time Ageing
  - Package Integrity Tests
  - Physical Strength Tests

- **T0 Base Line Testing**
  - Package Integrity Tests
  - Physical Strength Tests

- **T0 Test Report**
  - 1 yr Accel Ageing Test Report
  - 3 yr Accel Ageing Test Report

- **3 separate lots required for PQ**

- **www.anecto.com**
Where do you look for failures?

DQ → IQ → OQ → PQ → Production Packages

Package Integrity Tests → Physical Strength Tests → Test Report

T0 Base Line Testing → T0 Test Report

Accelerated Ageing Testing → Distribution Simulation

1 year Accelerated Ageing → Package Integrity Tests → Physical Strength Tests → Distribution Simulation → 1 yr Accel Ageing Reports

2 year Accelerated Ageing

3 year Accelerated Ageing

1 year Real Time Ageing → Package Integrity Tests → Physical Strength Tests → Distribution Simulation → 1 yr Real Time Ageing Reports

2 year Real Time Ageing

3 year Real Time Ageing

Distribution Simulation → Package Integrity Tests → Physical Strength Tests → Distribution Simulation → Test Report

Package Integrity Tests → Physical Strength Tests → Test Report

Your Best Route to Europe
What Causes Packaging Failures?

• Have you asked the relevant questions on the purpose of your packaging?
  – What are you packaging?
  – What is the value of the product?
  – What type of packaging is required (shelf or display)?
  – Where is the product being sold?
  – What standards must the packaging meet?
  – What is the marketing plan for the product?

Are there any other considerations?
Why Failures Occur?

– Device requirements not defined!
– Packaging Material Selection not defined!
– Sealing Parameters not defined!
– Labelling requirements not defined!
– Sterilisation requirements not defined!
– Packaging equipment capabilities not defined!
– Distribution and storage requirements not defined!
– Expiry Date not defined!
Why Products Fail?

Stress Exceeds Strength $\Rightarrow$ Failure

![Desired State Diagram]

Statistical Distribution of the High Temperature Stress Level in the Field

Statistical Distribution of a High Temperature Stress Level at which Product will Fail

HIGH TEMPERATURE STRESS LEVEL (C)
Why Products Fail?

**Possible State**

- **Probability of Occurrence of a High Temperature Stress Level in the Field**
- **Statistical Distribution of the High Temperature Stress Level in the Field**
- **Overlap means Possible Failure**

- **Statistical Distribution of a High Temperature Stress Level at which Product will Fail**
- **Probability of Occurrence of a High Temperature Stress Level at which Product will Fail**

**Stress Exceeds Strength => Failure**
Examples of Failure
Sample Size Failure

• What is the correct sample size?
  – How do you calculate your sample size for your product?
  – How many for Transportation test, Ageing, Integrity, Strength?
  – What is your acceptable pass / fail rate 0, 1, 2, 3……?

• Failure Due to small Sample Size
  – Reject by regulatory body due to a sample size as follows
    • 1 Partially filled shipper for transportation testing
      – Normal filled shipper 20 units only 14 units in the shipper
    • 7 pouches for strength testing
    • 5 pouches used for integrity testing
    • 2 returned to customer for functional testing
Heat Sealing Process

Evaluating your sealing process

Process Failure
(x% Spottiness)

Low alarm limit
Low Spec limit

Nominal Settings for Temperature Pressure and Time

Upper Spec limit
Upper alarm limit

Process Failure
(x% Transparent)

Spotty Seals

Optimum Range

Glazed Tyvek

100% seal Transfer (no spots, no glazing)
Visual Inspection Attribute Qualification

Have you set your Accept / Reject level for your sealing process

Visual Characteristic Rating Scale

- 5 – Acceptable- Package meets highest visual requirements
- 2 to 4 – Acceptable- Package meets seal requirements
- 1 – Rejectable- Package seal does not meet minimum requirements

Define Acceptance Criteria
Visual Inspection Criteria for Packaging

What To Look For

- Non-uniform seal width
- Wrinkles or visible bubbles through the width of seal
- Foreign particles (dirt or debris) in the seal area
- Channels in the sealed area

(If applicable) Transparent areas in the Tyvek indicate that the material has over-sealed (melted through)

- Non-uniform seal width
- Wrinkles or visible bubbles through the width of the seal
- Foreign particles (dirt or debris) in the seal area
- Sealed tray (Lid side)
- Channels in the seal area

(If applicable) Transparent areas in the seal indicate that the Tyvek has over-sealed (melted through)
Visual Inspection Failures

What To Look For

- Fibre in seal
- Sealed area less than 2mm
- Seal creep
- Over Sealed in closing seal
- Channel in seal
- Puncture in surface of pouch
Visual Inspection Failures
Labelling Failures

- **Labelling system failures**
  - Torn or illegible
  - Not compatible with
    - the materials,
    - sterile barrier system or
    - medical device
  - adversely affect the sterilisation process due to size and location
  - Peels off or fades during the sterilisation process
  - Incorrect ink / printer ribbon used print rubs off
  - Glues damage the packaging material
  - colour change making the label illegible.
Typical Label Failures

- Human readable text worn away
- Barcode rubbed away
Sterilisation Compatibility for Various Materials

<table>
<thead>
<tr>
<th></th>
<th>Paper</th>
<th>Tyvek</th>
<th>Film</th>
<th>Foil</th>
<th>Plastic</th>
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<tbody>
<tr>
<td>EtO</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Electron Beam</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Gamma Radiation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Steam*</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Low Temp Oxidation</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Sterilisation method must be Compatible with the labelling

- Package must retain adequate permeability if it is to be sterilised using EtO, Steam or Oxidation / Plasma type processes
- Package Must not transfer anything to the device

* Under controlled conditions - industrial at 121°C max for 20 minutes
Steam Sterilisation Failure
Transportation Test Failure

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Atmospheric Conditions

- What is the glass transitioning point (Tg) of my product and packaging?
- Will the packaging survive a world wide conditioning sequence?
  - Failure Modes
    - Changes in Physical Properties
    - Insulation Degradation
    - Seals / Glue Joints
Atmospheric failures
Shock / Drop

Damage to Product & Packaging

- Cosmetic & Functional Failures

• If You Can Lift It, You Can Drop
Effects of Drop

- Product protruding through shipper
- Shipper split along manufacturers joint even after packing tape was applied by customer
- Corner damage and Packaging tape broken
- Packaging Tape broken
Effects of Drop

X40 magnification

X400 magnification

X40 magnification

X100 magnification
Effects of Vibration

Corner of IFU punctured Pouch

Puncture from internal product

Internal product causing indentations

After top loaded vibration test

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Effect of Compression / Stack Test

Box incorrectly manufactured resulted in corner being pushed in when assembled

Result after Compression / Stack test
Effect of Compression / Stack Test

Product Punctured foil pouch under compression 200X magnification

Product on Pallet arriving for test

Shipper box after test

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Effects of Altitude

- Shipper split along joint due to internal product packaging expanding during altitude test
- Packaging Tape broken due to internal product packaging expanding during altitude test
- Product spilling out of shipper after altitude test

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Effects of Concentrated Impact Test

Hole Through shipper after test
Pass / Fail ?

Indentation on shipper after test
Pass / Fail ?

Indentation on Pouch after test
Transportation Testing Case Study

Medical device company asked Anecto to validate their new packaging prior to submission of 510K.
  – Shippers passed Transportation test
  – Product failed visual inspection and further product failed bubble leak testing.

Failure analysis
  • The product was heavy and had come out of its snap fit and damaged the seals of the tray
  • The product in the tray had sharp edges and had damaged the Tyvek
  • Internal supports in the shipper were damaged

Root Cause and Analysis
The cardboard supports in the shipper had given way and allowed the product boxes to move excessively giving the product sufficient momentum to damage the seals and the Tyvek
Package Design Fault

Image showing top view of box after transportation testing

Image showing close-up view of corner of box after transportation testing

Package integrity test failed due to excessive movement of heavy product inside its tray package which resulted in perforations of the Tyvek
Medical device company asked Anecto to validate their new packaging prior to submission of 510K.

- Shippers passed Transportation test
- Product failed visual inspection and further product failed bubble leak testing.

**Failure analysis**

There were transparent areas in the surface of the Tyvek and a number of impact holes in some of the pouches

**Root Cause and Analysis**

There were 40 Tyvek and clear film pouched products in the shipper.

- These were layered either clear film to Tyvek or Tyvek to Tyvek

When the product was vibrated the pouches rubbed off each other.

- A hard edge on the product rubbed against the Tyvek causing a week spot
- When the shipper was dropped the hard edge punctured the weakened Tyvek area
Transportation Testing Case Study

Medical device manufacturer updated their display boxes to improve the look of their shelf product but had complaints from outlets due to scuffing / scratching on the new display boxes.

Standard ISTA 2A Vibration test

Vibration test on product inspected and packed in Anecto

Passed all standard tests with no scuffing on new or old box

Repeat of ISTA 2A vibration test on standard packaging straight from factory floor

Failed boxes scuffed on new boxes only

Repeat of ISTA 2A vibration test with the addition of standard packaging / process dust from the factory warehouse

Failed boxes scuffed on new boxes only
Failure analysis
Analysis of the board used on the new box showed that the external lacquer that had been used on the old box had not been applied to the new box allowing the ink to scuff.

Costs
Cost to Supplier approx €10,000 for boxes that were rejected, including cost of testing plus cost of down time..........

Conclusion
If the company had carried out specification testing on a sample of the new box before going into production the problem would have been discovered at an early stage.
Integrity and Strength Test Failure
Peel Test Fixture Methods

In Europe $90^\circ$ with 15mm samples are most commonly used.
Sealing Inconsistencies

- “Suppliers” seal? vs. “In-house” seal?
  - If in-house seal is not set up properly, welding of the pouch material may occur at the seal.
Which is the failure

All samples were taken from the same seal location?...

All samples were taken from Tyvek and clear film pouches from the same process and lot.
Evidence of Failure

- Dye Test: ASTM F1929, EN868
  - Challenges heat seal for evidence of channels or inclusions that create a torturous path
Subjective Failures (False Positive?)

- Sheet Separation of Tyvek (Delamination)
- Bulk Density Reduction
  - Follow-up with a Dye Test for validation
Sheet Separation (Delamination)

- Sheet Separation
- Bulk Density Reduction

At bend, thickness compression causes core densification of inner layers.

Inter-laminar tension is created (Red Arrows) – Shear strength goes down in the presence of inter-laminar tension.

Due to radius, inner bonded side bulges to take up distance.

Geometry is regular and constrained far away from bend – No in-plane slippage.

Is It A Real Failure
Package Integrity Case Study

Customer requested as part of their product / packaging process validation that Anecto carry out bubble leak test as part of a suit of tests including Dye Penetration test and Peal Test prior to submission to FDA.

Standard Inspection Test ASTM F1886  
Passed

Standard Bubble Leak Test ASTM F2096  
5 pouches Failed

Failure analysis

The 5 pouches failed due to holes / cuts in the surface of the clear film. The Pouches had gone through the manufacturers standard process. All machines were checked with no issues found.

A sample of product was re-run and the product tested again.
Package Integrity Case Study

Re-test results

3 of the 12 pouches failed again for the same failure

Root Cause and Analysis

There was an extra bench added to the inspection area. When the bench was assembled 2 of the screws that were used were too long and came through the top surface less than half a millimeter.

When the pouches were moved along the bench

Conclusion

If you change anything in your process you need to validate that it will not have an impact on your product or its sterility.
Cold Chain Failure
Typical Cold Chain Conditioning
How long will it Last

Temperature (°C)

Hot spots in packaging

Time
What will be discovered

Hot spots in packaging
Product Ownership

The most expensive product is the one that is rejected by the customer or stops working after a short period of time

- Recall / retrofit often leads to loss of reputation
- Scraping of damaged Product / Packaging
- Customer satisfaction
- Loss to competition

You must remember the name on the package is your company name
Testing is Global

• Testing is globally the same provided
  – You are all using the same international standard
  – Your equipment meets the requirement of the standard
  – Your test people understand the standard
  – Your people are sufficiently trained

The products may vary along with the documentation

• 75% of the Top Global Medical Device Companies worldwide use our services in Europe
Do You have the Correct Packaging

This box had travelled less than 80km and only contained 2000 empty sterile plastic vials!!!

One test is worth a thousand expert opinions