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MEDICAL DEVICE PACKAGING VALIDATION GUIDE

A step by step handbook on Package Validation per ISO 11607

ISO 17025 ACCREDITED LABORATORY
ACCREDITED Certificate No. 3545.01
ista CERTIFIED LABORATORY ST 2081

INTRODUCTION

The most crucial aspect of any medical device packaging design is to assure that the products derived thereof maintains the sterility of any terminally sterilized medical devices that may form its content. This sterility must be maintained from the initial packaging until the point of use. In testing to verify if packaged medical devices meet the required condition that they remain sterile until the point of use, the ISO 11607 standard, widely accepted in the industry, is often used. The standard outlines the requirements and test methods for materials, preformed sterile barrier systems, sterile barrier systems and packaging systems.

1. **Scope**

   The ISO 11607 standard is the most important and most widely acceptable standard for testing and validating medical device packaging. There are two parts to this standard: Part 1 and part 2. While part 1 deals with "Requirements for Materials, Sterile Barrier Systems and Packaging Systems", Part 2 entails the "Validation Requirements for Forming, Sealing and Assembly Processes".

   As stated earlier, and repeated here for emphasis, the ISO 11607 is the most important test validation standard applicable to medical packaging. Its reach extends far and wide in the medical packaging testing and validation field: It is widely accepted in the health care and related industries, health care facilities, and in scenarios in which medical devices are placed in sterile barrier systems and sterilized.

   The main intent of this guide is to provide an important tool that may be used to increase the chance of an expedited and successful test outcome for medical device packaging and validation, tested according to the ISO 11607 standard. Followed carefully, the steps and suggestions outlined in this guide, and based mostly on a careful time management regime, may help reduce the time to market latencies and other similar mitigating factors.

2. **Normative Sources**

   In putting together this guide, the standards listed below, were of paramount importance. In addition, the sources given in the index section of the guide were also useful.

   - ISO 11607-1:2006
   - ISO 11607-2: 2006
   - ISO/IEC 17025:2005
   - ASTM D4169-14
   - ASTM F1980-07
   - ASTM F1929-12
   - ASTM F2096-11
   - ASTM F88-09
   - ISTA Procedures 1A, 2A, 3A

Table 1: Standards of Importance for Validation	
ISO 11607-1	Requirements For Materials, Sterile Barrier Systems And Packaging Systems
ISO 11607-2	Validation Requirements For Forming, Sealing And Assembly Processes

The purpose of this guide is to help startup companies learn from the successful methods practiced over the years by leaders in the field of medical device packaging design and testing.
Numerous players in the medical device packaging design and testing field have suffered serious setbacks in delivering their product to market because of packaging design failures that led to noncompliant test results, implying a packaging that cannot guarantee the integrity of its content, in terms of sterility, etc.
Whether such failures occur during the product distribution phase, as a result of environmental factors, or due to internal packaging issues, the end result is always the same-a non-compliant packaging for which

sterility has been compromised. All of this due chiefly to flaws in the packaging design phase and/or device design features.

To help avoid a non-compliant test outcome, and in the process increase the chance of a successful product launch, it is crucial that the package testing/validation team get involved at the earliest possible product design stages, conduct a discussion on how the package should appear, perform a market analysis on currently deployed packaging schemes and subsequently use the gathered data and any useful inferences derived thereof in the product design, with final stage packaging and validation testing in mind.
Experience has shown for example that when there are sharp edges on the product knobs, switches and handles should be avoided and any product, especially one that is required to be sealed in pouches or need to maintain its sterility, must be design with its radius on outer edges. When a step such as just described is followed, bad product designs and the costs associated with these whether in terms of time or money, can be avoided.

STEP 1 – VALIDATION OF PACKAGING PROCESSES AS PER ISO 11607-2 STANDARD

There are a number of factors that the medical packaging designer must take into consideration before releasing and subjecting the final product to the hostile conditions that occur during product transportation and distribution or in the environment at large. In order to obtain a package that complies with the required standards at any phase of the product life cycle, the right sterile barrier should be selected, the right seal must be ensured, and the sterile barrier must be properly secured in the external packaging. Taking these steps as given, lead to a dramatic improvement in nearly every scenario, of the chance of meeting the stated design goals.

STERILE BARRIER – For the medical packaging design to meet its intended goal, that is, arriving in tact and in the expected condition to the end user, it is of crucial importance that the proper sterile barrier be selected for the application. This aspect of medical device packaging is clearly spelt out in the ISO 11607-2 standards and includes the following: I. Pouch, reel or bag sealing; II. Sterilization sheets folding and wrapping; III. Filling and closing of reusable sterilization containers.
Packaging failures can occur due to sterile barrier pinholes (a breach of the sterile barrier of the device). Decades of experience has taught this writer that pinholes are often the cause of bubble leak test failures.

Mention should now be made of off the shelf pouches. While the use of these may lead to a time savings ranging typically between two to three weeks, nevertheless, care must be taken to ensure that the process is properly carried out. There is the need for example to select a pouch of the correct specifications, one made of the right material and of the proper size, if such is not the case, compliance is less likely. Additionally , there is the necessity for the following actions to be properly conducted: Selecting the pouches/ reels, packing the medical devices, sealing pouches/reels, conducting visual inspection of the seal seam, protective packaging using see through wrap, labeling and final protective packaging after sterilization.

I. Selecting The Pouches/ Reels
   It is advisable to select a pouch length/width that is the same as the shelf carton length/width. There must not be any restriction to the insertion of the medical device into the pouch/reel.
II. Packing The Medical Devices
   The Medical device should be inserted such that user can hold the gripping end on the peel side. Protection must be fitted to any pointy instruments before being placed into pouches or reels
III. Sealing Pouches/Reels
   The pouches or reels should be placed (flat and gusset) evenly and free of folds while feeding it into the heat sealer.

IV. Conducting Visual Inspection of the Seal Seam
Each seal must spread along the total width and length of the seal lines without any folds or air pockets.

V. Labeling
The label must be done in the following manner: it can only be outside the seal seam surrounding the device.

VI. Final Protective Packaging after Sterilization.
To ensure damage free transportation and storage, the package must be protected during transportation, as well as during any extended storage period. In both scenarios there is a requirement for proper documentation.

Failures are very costly and become a drain to a company's financial and time resources. In order to help prevent these failures and their negative consequences from materializing, it is suggested that the steps just discussed and elaborated upon, as well those in the following sections of the guide be stringently followed. What now follows is a number of quick facts checks that may help in this regard.

Suggestions that may help in mistake avoidance:

- It is advisable to avoid kinking, folding or creasing the pouches to get them into the shelf carton.
- Always use the right gauge of the material based on the product gross weight.
- Always make the pouch fit nice and snug to the device.
- For high profile devices, consider a gusseted pouch to avoid folds on the width of the pouch when removing and inserting the pouch into and out of the box.

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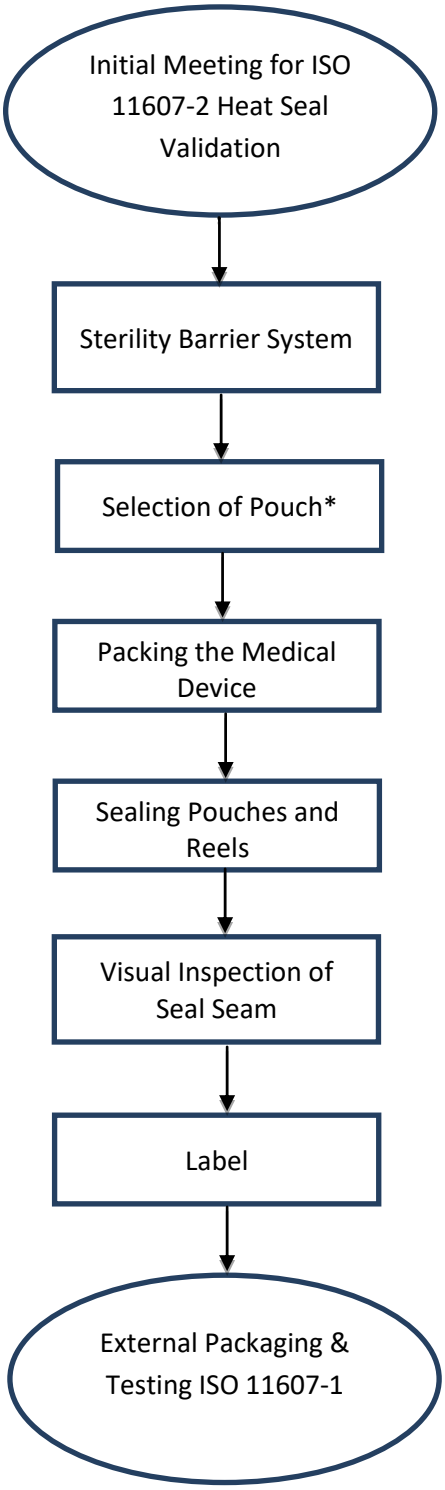
VALIDATION OF PACKAGING PROCESSES AS PER ISO 11607-2



*Time for planning / completion may vary from 6-8 weeks depending upon the pouch size/type.

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STEP 2 – PACKAGE DESIGN

The packaging design process can be divided into two phases, phase I and phase II:

- Phase I – Internal Packaging Design: The objective of this phase is to keep the product organized, secured, sterilized and ready to use by a physician.
- Phase II – External/tertiary packaging: In this phase, there is the requirement of a master shipping container that is designed to survive the distribution environment, keeping the internal packaging free of any distribution or environmentally induced stress.

Phase 1 - Internal Packaging: This is a highly important aspect of the packaging design. It determines how the product will ultimately appear to the end user and should therefore be as pleasing ascetically as possible, while maintaining functionality. The internal packaging design phase can be divided into three sections:

1. **PRODUCT PROTECTION** – This section entails the Securing and protecting of the product by means of a backing card or a thermo-forming tray.
2. **STERILE BARRIER** – This section involves the Selecting of the pouch of the right size and material thickness, so that the product fits slug to the backing card or thermo-forming tray.
3. **SHELF CARTON** – This section deals with developing an internal shelf box.

1. **PRODUCT PROTECTION** – It is essential to secure the medical device on to a backing card or a thermo-forming tray so that it can survive transit conditions. Here are a few common examples of the materials used to accomplish this task:

   SBS Chip Board: The SBS board is coated on both sides and provides a dust free environment. This material is readily available and lead times are shorter. Chip board provides a platform that can be easily die-cut to secure the product in place by creating locking taps and folds. Chip board can also be used for shelf carton. Steel rule dies are considered low cost compared to molded parts, a fact that has led to many start-up companies selecting this method of packaging.

   Medical Grade HDPE: It comes in various thicknesses and the material is a lot more rigid than chip board. HDPE provides a good platform for medical devices that have handles and are long in length. When designing a backing card with HDPE, ensure to put radius in all edges so they don't create pin holes in pouches. Steel rule dies are considered low cost compared to molded parts resulting in many start-up companies selecting this method of packaging.

   Thermoform Trays: Thermoform trays are a highly effective way to package a product. They allow creating pockets for the product's safety and tabs in securing the product during distribution testing. However, the process is expensive and very lengthy. Tooling can cost anywhere from $3,000 - $15,000.

   Closed Cell Foam: Numerous medical devices (small /large, including hearing devices with accessories) can be packed in closed cell foam (dust particle-free), with customer's choice of color and size, that may render the product very appealing.

2. **STERILE BARRIER** – As discussed above in Step 1 under: "Validation of Packaging Processes as per ISO 11607-2 Standards", it is recommended not to compromise the sterile barrier of the materials used. It is a good practice to follow the standards for creating a good packaging design, that is, one that can withstand the various stresses and conditions the overall package would experience.

3. **SHELF BOX**: There are two types of material frequently used in this particular aspect: the SBS chipboard (0.024" thick - commonly used) and the E-flute corrugated box. Frequently, SBS backing card designers recommend the box be constructed with the same materials that works well with light weight devices. In addition it should have a clean look. On the other hand, E-flute corrugated boxes provide a stronger structure to protect the device packaged in the sterile barrier material and has an additional compression strength to the outside shipper box. E-flute corrugated boxes come in #1 white for a cleaner look as well as in Kraft (non-bleached material).

Phase 2 – Tertiary/External Packaging: External packaging should be designed to protect the internal product and packaging. Based on the number of internal boxes per master shipper, gross weight should be considered in selecting the right bursting strength of the corrugated box.

Corrugated materials come in 200 and 275-pound bursting strength single wall, as well as 275 and 350-pound bursting strength double wall. For special applications a 500-pound bursting strength and triple wall corrugated is also available.

Here are some key points on how to select the outer shipping box:

1. Select the right bursting strength for the gross weight of the product:
   - 0-19 lbs. #200 C
   - 20-29 lbs. #275 single wall
   - 30-59 lbs. #275 double wall

2. Stock boxes or U-line boxes: Boxes with a bursting strength of #200 are adequate for use if the product is light and the void space do not have to be filled by paper or bubble wrap. If the savings after using extra packaging material plus labor is taken into account, and if suitability is considered as part of packaging and calculated, then this process would be found not to be worthy of the savings. Outer and inner packaging should work as one unit; otherwise it can be damaged during distribution testing.

3. A #200 verses #275 outer shipping container: For a #200 single wall RSC (regular slotted container), enjoys the advantage of cost and availability. The disadvantage is that all #200 boxes must go through a concentrated impact test with an increased chance of failure, since the #200 provide less compression and impact resistance. A #275 single wall RSC provides greater compression value and impact resistance but it's a custom item that requires running a quantity of 250 units to be cost effective.

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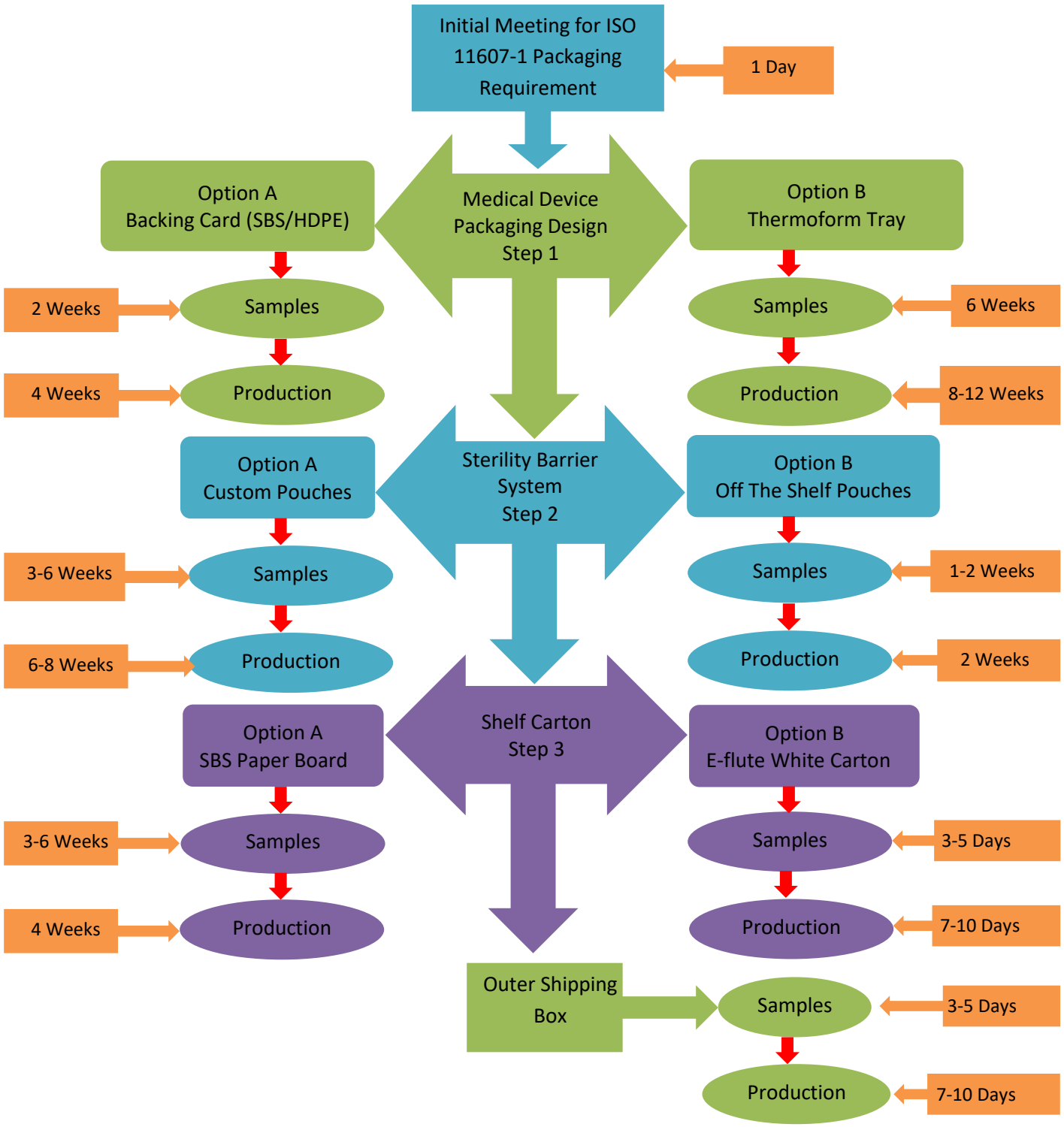
PACKAGING DESIGN TIME CHART OF MEDICAL DEVICE PER ISO 11607-1



By using the above chart to plan sample testing requirement of 29 (plus three additional packaging units recommended not required), it can take four to six month for the overall process which is only the initial phase of Packaging design and getting ready for Packaging validation testing.

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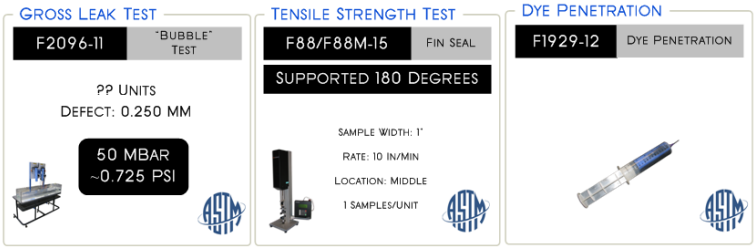
STEP 3 – TESTING STAGE

PHASE I – ISO 11607-2 STANDARD HEAT SEAL PROCESS VALIDATION (INCLUDES STERILIZATION OF TEST ARTICLES):

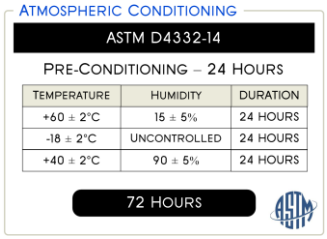
Once the desired pouch is selected, a pouch validation test is required on 29 pouches in order to get a 90 % Reliability and 95% Confidence Interval with zero failures. To validate for 95% Reliability and Confidence, zero failure needs to be obtained for 59 pouches. Most turnkey facilities have a method of conducting pouch validation for setting in-house seal temperature, and such a method can be used to obtain the data used in the validation report. To assure the quality of the in-house seal, it is often desirable to let instead an independent test laboratory to conduct the test.

The Bubble, Dye penetration (ink) and Tensile Strength tests are conducted to check the seal integrity of the pouch, while, the Gross leak test is for its part conducted to verify if the seal is consistent and without leaks. If leaks are detected, then the ink test is performed to draw a conclusion and the Tensile strength test is conducted to assure that the pouch meets the minimum seal strength required

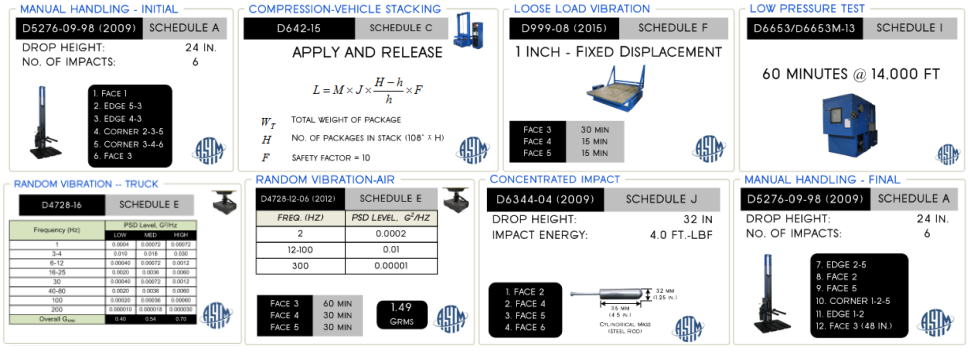


PHASE II – PACKAGE VALIDATION TESTING (INCLUDES STERILIZATION, DISTRIBUTION SIMULATION AND AGING –AA + RTA):
Section one of the testing is distribution simulation required as listed in ASTM D4169-16.

Distribution Simulation – Climate Conditioning
ASTM D4332-14- Below is a typical atmospheric profile used by medical device companies (time required for conditioning is 3.5 days):



Distribution Testing: A majority of medical device companies follow ASTM D4169-14, distribution cycle 13.



VISUAL INSPECTION ASTM F1886/F1886M-13:

Visual inspection should be conducted to examine if there is any damage to the outer shipping container. Any excessive damage to the internal container may compromise the look and feel any new device should convey to the user. The pouch requires careful examination especially in the areas where it is folded prior to insertion into the inner box (retail box). This is a common area for pin holes caused by shock and vibration forces during the distribution.

Time required for Visual Inspection is 4-6 hours (based on 32 test articles).

Once the conditioning, distribution and visual inspection are complete, a gross leak test on the pouch is conducted to verify how well the packaged product has served and if the pouch has maintained its sterile properties. The Gross Leak (bubble) and Tensile Strength Tests, stipulated in ASTM D-4169-14, are used for this purpose.

GROSS LEAK TEST ASTM F2096-11 (Whole package integrity test)

This test is briefly conducted as follows: A known defect of 0.025µm is created in the pouch; the pouch is inflated with an external air source and immersed under water until the known defect shows a constant blow of bubble caused by air leaking from the pouch. During that time period, inspection of all seals is conducted to assure the integrity of the seals. For more details of this test, refer to ASTM F2096-11.
An examination of the pressured pouch underwater will show air bubbles that are not constant but such is not a definitive proof of a potential leak. To confirm or deny a leak, a dye penetration test is required per ASTM F1929-12.

Time required for Gross Leak Testing is 4-6 hours (based on 32 test articles).

DYE PENETRATION TEST* ASTM F1929-12

This test is used to detect and locate a leak equal to or greater than the channel formed by a 50µm wire on package edge seals between a transparent material and a porous sheet material. During the test, the package is visually inspected after applying a dye solution through the leaks to be tested. Complete details of the test can be found in ASTM F1929-12.

Time required for Dye Penetration Testing is 4-8 hours (based on 32 test articles).
*If required

TENSILE STRENGTH TEST – ASTM F88/F88M-15

To assure that environment and transit conditions did not have any effect on seal integrity, samples are removed from all four sides of the pouch for tensile value. They can also be compared with an original base line testing results to assure the required tensile values are maintained.

Time required for Tensile Strength Testing is 8 hours (based on 32 test articles).

AGING:

There are two types of aging: Real Time Aging and Accelerated Aging. Real time aging is accomplished by storing the product under ambient conditions. Accelerated aging is achieved by subjecting the product to a heightened temperature for a pre-determined amount of time as obtained by using the accelerated aging formula and aging factor.

Accelerated aging time can be different depending on the selection of ambient temperature and aging factor, The information below provides an overview of the accelerated aging formula and process. For greater detail please refer to ASTM F1980-11.
A typical profile for accelerated aging is for one year at 55C uncontrolled humidity for 40 days (equivalent to 1-year real time aging with assumed ambient of 23C).

ACCELERATED AGING – ASTM F1980-15
Test specimens are placed in an environmental chamber at an accelerated rate to simulate aging. The accelerated aging methods are based on ASTM F1980-11 and the assumption that for every 10˚C (18˚F) above ambient temperature, the aging rate is doubled.

Simulated Real Time Aging was determined by the following formula:

Accelerated Aging Time (AAT) = SRTA / AAF

Where:
AAF (Accelerated Aging Factor) = $Q_{10}^{[(T_{AA}-T_{RT})/10}$
Q_{10} = *2,*
T_{AA} = *Accelerated Aging Temperature (°C),*
T_{RT} = *Room Temperature (˚C) = assumed ambient temperature (chosen by client)*
SRTA = Simulated Real Time Aging

The accelerated aging test time depends on the selection of temperature and can be anywhere from 30-70 days. Typical temperatures used for accelerated aging are between 40˚C and 60˚C.

See the chart on the next page for an overview of all the steps detailed in this guide.

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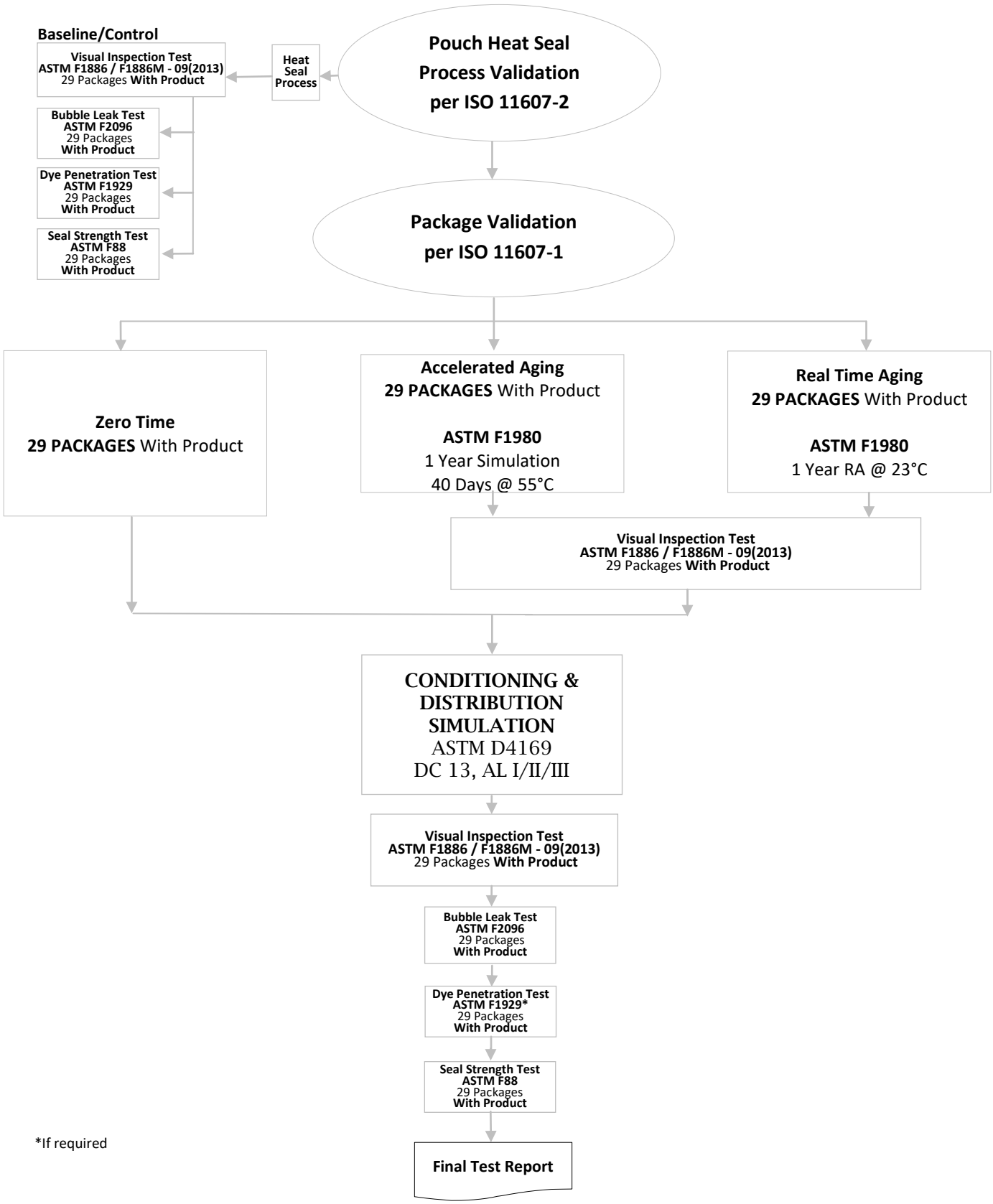
Package Validation Testing Flowchart



*If required

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