



A WHITE PAPER

## PACKAGE VALIDATION REQUIREMENTS FOR MEDICAL DEVICES AND COMBINATORY PRODUCTS

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### INTRODUCTION

FDA concerns regarding terminally sterilized medical products are based on years of data that implicates failures in primary packaging. The majority of failures occur because of inadequate package validation programs. This paper provides insight on the general requirements in a microbiological and physical testing program. We discuss how combination products pose a unique set of challenges to the package validation engineer. For example, one key issue involves the requirement for a pharmaceutical or biologic component to meet ICH guidelines for stability in a flexible pouch under nominal conditions of storage and shipment.

Unfortunately, medical device package testing is not standardized in terms of shelf life requirements and microbiological procedures. Physical testing is probably the best indicator of adequate sealing parameters. However, these tests do not give technicians the ability to extrapolate to real world microbiological ingress limits. This paper discusses some of the options.

### THE CHALLENGES OF MEDICAL DEVICE PACKAGING VALIDATION

All medical device materials and drug products have a finite life span. Materials such as plastics, adhesives, polymers, and films degrade with time. Most medical devices have a primary and a secondary packaging system. Both packaging systems require validation programs. Historically, medical devices have been tested for degradation (forced degradation studies) by heating in a hot air oven at 55°-60°C from weeks to months. This procedure, generally called accelerated aging, is based on the following formula (Q 10 coefficient): a 10°C rise in temperature doubles the chemical reaction rate. Extrapolating the rate to time gives one a set point that can be used to indicate aging at real time at room temperature. After treatment, the devices are tested for various material characteristics. These characteristics can be as subtle as ASTM D2240 durometer, form, fit, and function, or they can be as intensive as polymeric testing. The testing of plastics can require infrared scans, gel permeation chromatography (GPC), and GC/MS testing for leachates. Typically, the validation program will cull out tertiary testing based on a suitable product risk analysis.

Combinatory products require strict adherence to ICH guidelines for stability of the drug/biologic throughout the shelf life of the product. For products that have a delivery system (such as needle-less injection systems), storage and shipping parameters are critical to maintaining required potency. For other products that have a drug coating or scaffolding application, the validation program requires a unique perspective into both medical device shelf life studies and ability of the drug/biologic formulation to maintain stability throughout all phases of the manufacturing and sterilization process. Formulation issues are very important prior to FDA filings, and these considerations will be a major portion of the final regulatory filing. This paper does not address formulation.

Medical device packaging validations are performed with baseline products that have not been subjected to normal warehouse storage. Non-sterile samples are required for initial fingerprint seal analysis. These samples reveal data changes with sterilization. All sterile samples sent in for secondary phase measurements allow one to determine changes during accelerated or real-time aging studies. Transportation samples are taken from both real-time and aged products.

Packaging testing guidelines are listed in ISO 11607. This document describes the available ASTM packaging tests. It also brings together many other key aspects of packaging validation (i.e. material qualification, validation of seal process, whole package seal integrity). However, it does fall short in not speaking to a definitive validation regimen for all to follow. Physical tests that are performed may include burst, creep, creep to fail, peel, and leak. Our packaging validation specialists can help you decide on test selection based on your packaging materials.

A robust packaging validation program should include transportation simulation testing with concomitant sterility testing. Some device manufacturers bracket the potential storage and shipment temperatures and conditions (such as air cargo) during their initial studies.

## THE PACKAGING VALIDATION PROCESS

**Select appropriate package material and design, qualify equipment, validate sealing process, produce test samples**

**Perform burst test, peel strength creep test on both sterile and non-sterile: non-accelerated aged product**

**Place an appropriate number of samples into accelerated aging for the required period.**

**After aging, the packaging is tested for physical testing. Device samples are tested for material problems and whether or not they meet product specifications.**

**A portion of the accelerated samples are culled for transportation simulation tests: ISTA /ASTM shipping tests.**

**Packaging samples are tested for physical parameters as above. A visual exam is performed to look for holes caused by vibration testing. Device samples are tested for specification requirements.**

Table 1: Standardized test methods commonly used in the U.S. for satisfying ANSI/AAMI/ISO 11607 requirements (excerpted from AAMI TIR 22)

Test	ISO	ASTM	TAPPI
Accelerated Aging		F 1980-07	
Air Permeance	5636-2:1984 5636-3:1992 5636-5:2003	D 737-04	
Basis Weight	536:1995	D3776-07	T410 om-08
Biocompatibility	10993-1:2003		
Burst Strength	2758:2001	F1140-07	
Cleanliness		T 437-0M-96	
Chlorides	9197:1998		T256 cm-07
Coat Weight	F 2217-02		
Conditioning	187:1990 2233:2000	D4332-01	
Dimensions	F2203-02		
Drapability	9073-9:1995 2493:1992		
Extraction Resistance		F34-02 (2007)	
Flexural durability		F392-93 (2004)	
Gas sensing		F2228-02 (2007)	
Gas transmission		D1434-82 (2003)	
Integrity		F1929-98 (2004)	

Internal pressure		F2096-04	
Microbial Barrier		F1608-00 (2004)	
Odor		T483 cm-02	
Oxygen Gas Transmission		D-3985-05	
Performance testing	4180-1:1980	D4169-08	
pH	6588-1:2005 6588-2:2005		T509 om-06 T435 om-06
Porosity (Air resistance)		D726-94 (2003)	T460 om-06
Pressure leak	F2338-07		
Printing and coating		F2250-03 (2008) F2252-03 (2008)	
Puncture		D1709-04 F1306-90 (2008) D3420-08	
Seal Strength		F88-07a F1140-07 F2054-07	
Sulfates 9198:2001		T255 cm-07	
Tear resistance	1974:1990 D1938-06	D1922-06a	
Tensile Properties	1924-2:1994	D882-02	
Thickness/Density	534:2005 F2251-03 (2008)	D645m-97 (2007)	T411 om-05
Vacuum leak	D3078-02 (2008)		
Visual Inspection		F1886-98 (2004)	
Water Resistance	811:1981	D779-03	
Water Vapor Transmission		F372-99 (2003)	
Wet burst in wet Condition	3689:1983		
Wet Tensile Strength		D829-97 (2002)	
Wet tensile properties	3781:1983		

Combinatory products require a second-tier approach to package validation. Appropriate pre-validation questions may contain concerns over API potency, biologic activity, medical device polymer and drug/biologics interactions, and ICH stability issues. These issues are addressed in my white paper: *Combinatory Products: Navigating Two FDA Quality Systems*. This paper can be downloaded at [www.microtestlabs.com/combovalidationpaper](http://www.microtestlabs.com/combovalidationpaper).

Drug/ biologic interactions with polymers can be an issue with respect to emitted dose and stability. Some medical device polymers may cause changes to small and large molecules. These changes, such as emitted dose variabilities during product use, can be critical to product launch. The testing regimen must flush out the variables for stability and concentrate on the criticality of the studies and assays in terms of experimental design (DOE) and robust method development studies. Some of these issues become prominent during production scale up.

Cell therapy products such as xenografts, allografts, and stem cell products create unusual challenges for the package validation engineer. The FDA offers very little guidance on these issues. Cells must be able to withstand shipment and storage during a finite, defined period. Evaluation of cell lines and tissue implants during a stability program is required prior to FDA submission. Stalwart evaluations encompass generic and novel studies that lend regulatory credibility to both the study data and labeling claims.

## POINTS TO CONSIDER DURING PACKAGE VALIDATION STUDIES FOR CELL THERAPY PRODUCTS:

- Bacterial /fungal/ mycoplasma sterility testing (USP sterility and FDA mycoplasma test)
- Viral sterility test (FDA virus assay)
- Particulate test (USP)
- Cytotoxicity (USP)
- Container integrity testing (MBD immersion test)
- pH analysis
- Buffering capacity (container) USP
- Leachate testing (container) GC/MS analysis

## SUMMARY

In closing, medical device stability package validation programs should be designed to encompass the overt product storage and shipment conditions. Performing accelerated aging studies does little to address liability during shipment and storage. In the future, the FDA may require one to perform similar ICH-type stability studies. In the 1991 FDA guidance document “Shelf life of Medical Devices” by Geoffrey Clark, much needed guidance was posited. But today, new guidance documents are needed to address combination products and move the medical device industry closer to ICH compliance.

The necessity to develop a robust packaging validation regimen cannot be overstated. A comprehensive regulatory approach to validation during early product development can save many weeks of redevelopment and testing activities. Ideally, as the FDA and global community move toward harmonization, a guideline for combinatory products will emerge that provides a path forward for validation specialists.

## About Microtest

Microtest is a leader in testing services and contract manufacturing for medical devices, pharmaceuticals, and biotechnology. The company was founded in 1984. Its expertise and flexible processes enhance product safety and security, speed time to market, and minimize supply chain disruption. Microtest’s unique single-source capability to provide testing and manufacturing solutions allows the company to support a full pharmaceutical or medical device product release. Facilities in Agawam, Massachusetts, U.S.A. include state-of-the-art aseptic manufacturing areas; analytical chemistry, microbiological, and virological laboratories; Class 100 cleanrooms; onsite steam and ethylene oxide sterilization, plus depyrogenation capabilities; purified water systems; and voice/data systems.

## About the Author

Steven Richter, Ph.D, is President and Chief Scientific Officer of Microtest Laboratories, Inc. Dr. Richter founded Microtest in 1984 after a distinguished career at the U.S. Food & Drug Administration. Under his leadership, Microtest has provided the medical device, pharmaceutical, and biotechnology industries with premier testing and manufacturing support.

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