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Standard Guide for Design and Evaluation of Primary Packaging for Medical Products[1]

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1. Scope

1.1 This guide provides directions for the design and evaluation of primary packages for medical products. The package materials must be selected appropriately for manufacturing process, end use, and the product being packaged.

1.2 This guide provides a compendium of test methods. Specific individual test methods must be selected based on the pertinent characteristics of the specific product to be packaged and the purpose for testing, research and development, or compliance. Not all test methods will be applicable.

1.3 This guide does not address acceptability criteria, which need to be determined jointly by the package producer and the medical products manufacturer.

1.4 This guide does not assess the product to be packaged; the sterilization method to be used; or package performance through sterilization, distribution, and handling.

2. Referenced Documents

2.1 *ASTM Standards:*

D 374 Test Methods for Thickness of Solid Electrical Insulation[2]

D 589 Test Method for Opacity of Paper (15 % Diffuse Illuminant A, 89 % Reflectance Backing and Paper Backing)[3]

D 645/D 645M Test Method for Thickness of Paper and Paperboard[3]

D 726 Test Methods for Resistance of Nonporous Paper to Passage of Air[3]

D 882 Test Methods for Tensile Properties of Thin Plastic Sheeting[4]

D 1003 Test Method for Haze and Luminous Transmittance of Transparent Plastics (Gardner)[4]

D 1709 Test Methods for Impact Resistance of Plastic Film by Free-Falling Dart Method[4]

D 1777 Test Method for Thickness of Textile Materials[5]

D 1894 Test Method for Static and Kinetic Coefficients of Friction of Plastic Film and Sheeting[4]

D 1922 Test Method for Propagation Tear Resistance of Plastic Film and Thin Sheeting by Pendulum Method[4]

D 1938 Test Method for Tear Propagation Resistance of Plastic Film and Thin Sheeting by a Single Tear Method[4]

D 2019 Test Method for Dirt in Paper and Paperboard[3]

D 2457 Test Method for Specular Gloss of Plastic Film and Solid Plastics[6]

D 3078 Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission[3]

D 3335 Test Method for Low Concentrations of Lead, Cadmium, and Cobalt in Paint by Atomic Absorption Spectroscopy[7]

D 3420 Test Method for Dynamic Ball Burst Pendulum Impact Resistance of Plastic Film[6]

D 3718 Test Method for Low Concentrations of Chromium in Paint by Atomic Absorption Spectroscopy[7]

D 3776 Test Methods for Mass per Unit Area (Weight) of Woven Fabric[8]

D 3985 Test Method for Oxygen Gas Transmission Rate Through Plastic Film and Sheeting Using a Columetric Sensor[3]

D 4279 Test Methods for Water Vapor Transmission of Shipping Containers—Constant and Cycle Methods[3]

D 4321 Test Method for Package Yield of Plastic Film[6]

D 4754 Test Method for Two-Sided Liquid Extraction of Plastic Materials Using FDA Migration Cell[9]

D 5264 Practice for Abrasion Resistance of Printed Materials by the Sutherland Rub Tester[3]

F 88 Test Method for Seal Strength of Flexible Barrier Materials[3]

F 151 Test Method for Residual Solvents in Flexible Barrier Materials[3]

[1] This guide is under the jurisdiction of ASTM Committee F02 on Flexible Barrier Materials and is the direct responsibility of Subcommittee F02.60 on Medical Packaging.

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[2] *Annual Book of ASTM Standards*, Vol 10.01.

[3] *Annual Book of ASTM Standards*, Vol 15.09.

[4] *Annual Book of ASTM Standards*, Vol 08.01.

[5] *Annual Book of ASTM Standards*, Vol 07.01.

[6] *Annual Book of ASTM Standards*, Vol 08.02.

[7] *Annual Book of ASTM Standards*, Vol 06.01.

[8] *Annual Book of ASTM Standards*, Vol 07.02.

[9] *Annual Book of ASTM Standards*, Vol 08.03.

F 372 Test Method for Water Vapor Transmission Rate of Flexible Barrier Materials Using an Infrared Detection Technique[3]
F 392 Test Method for Flex Durability of Flexible Barrier Materials[3]
F 748 Practice for Selecting Generic Biological Test Methods for Materials and Devices[10]
F 813 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices[10]
F 895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity[10]
F 904 Test Method for Comparison of Bond Strength or Ply Adhesion of Similar Laminates Made from Flexible Barrier Materials[3]
F 1140 Test Methods for Failure Resistance of Unrestrained and Nonrigid Packages for Medical Applications[3]
F 1249 Test Method for Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor[3]
F 1306 Test Method for Slow Rate Penetration Resistance of Flexible Barrier Films and Laminates[3]
F 1327 Terminology Relating to Barrier Materials for Medical Packaging[3]
F 1443 Practice for Using 0.008-in. (0.203-mm) Aperature Reflectometers as Test Instruments for Measuring Visual Image Quality of Business Copy Images[3]
F 1608 Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)[3]
F 1884 Test Method for Determining Residual Solvents in Packaging Materials[3]
F 1886 Test Method for Determining Integrity of Seals for Medical Packaging by Visual Inspection[3]
F 1929 Test Method for Detecting Seal Leaks in Porous Packaging by Dye Penetration[3]
F 1980 Guide for Accelerated Aging of Sterile Medical Device Packages[3]
F 2054 Test Method for Burst Testing of Flexible Package Seals using Internal Air Pressurization with Restraining Plates[3]
F 2096 Test Method for Detecting Gross Leaks in Porous Medical Packaging by Internal Pressurization (Bubble Test)[3]

2.2 *EN/ISO Standards:*[11]

EN 868/1 Annex C Gurley, Schopper, Dye Penetration
ISO 5636/5
ISO 11607 Annex A Gurley

2.3 *Military Specification:*[12]

Mil Spec 36954C Bacterial Filtration Efficiency

2.4 *FPA Standard:*[13]

FPA/SPMC 009 Standard Test Method for Coating/Adhesive Weight Determination

2.5 *TAPPI Standards:*[14]

TAPPI T 404 Tensile Breaking Strength and Elongation of Paper and Paperboard
TAPPI T 437 Dirt in Paper and Paperboard
TAPPI T 460 Air Resistance of Paper (Gurley Method)
TAPPI T 494 Tensile Breaking Properties of Paper and Paperboard (Using Constant Rate of Elongation Apparatus)
TAPPI T 536 Resistance of Paper to Passage of Air (High Pressure Gurley Method)

3. Terminology

3.1 *Definitions of Terms Specific to This Standard:*

3.1.1 *barrier requirements*, *n*—the need to promote or inhibit moisture, gas, or light, or a combination thereof, while maintaining necessary levels of sterility.

3.1.2 *durability requirements*, *n*—material properties relevant to the ability of the package to protect the product.

3.1.3 *integrity and seal requirements*, *n*—the ability of the package to prevent inadvertent escape of contents or entrance of outside substances while preserving intended opening for use features.

3.1.4 *printing requirements*, *n*—the printed ink properties needed to ensure physical and chemical resistance to degradation.

3.1.5 *processing requirements*, *n*—the material characteristics needed to ensure the consistent and reliable production of the package.

3.1.6 *safety requirements*, *n*—safeguard product against contamination and deleterious health effects.

3.1.7 *visibility and appearance requirements*, *n*—the desired package aesthetics needed to permit or inhibit viewing of the product or to enhance product presentation.

3.2 For other terms used in this guide see Terminology F 1327.

4. Significance and Use

4.1 This Design and Evaluation guide describes seven categories for evaluating medical packages and packaging materials. These include safety, barrier properties, durability, package and seal integrity, visibility and appearance, processing, and printing ink properties.

4.2 The intent of this Design and Evaluation guide is to evaluate all seven categories and select those that are applicable. Once the product has been characterized and the sterilization methodology has been defined, there are numerous sets of requirements for any specific package. This Design and Evaluation guide provides an avenue for assessing these requirements and choosing test methods for both evaluating the package design and monitoring package compliance.

4.3 Product characterization shall include mass or weight, geometry (length and width, height and shape) and product composition.

4.4 All seven categories must be considered for applicability.

[10] *Annual Book of ASTM Standards*, Vol 13.01.

[11] Available from International Organization for Standardization (ISO) 1 rue de Varembé, P.O. Box 56, CH-1211, Geneva 20, Switzerland.

[12] Available from Standardization Documents Order Desk, Bldg. 4 Section D, 700 Robbins Ave., Philadelphia, PA 19111-5094, Attn: NPOPS.

[13] Available from the Flexible Packaging Association, 971 Corporate Blvd., Suite 403, Linthicum, MD 21090.

[14] Available from the Technical Association of the Pulp and Paper Industry, P.O. Box 105113, Atlanta, GAA 30348.

Safety	Chemical Properties	Extractables: ASTM D-4754 Toxicity: ASTM F-748; ASTM F-813 e1; ASTM F-895 Retained Solvents: ASTM F-1884; ASTM F-151 Heavy Metals: ASTM D-3335; ASTM D-3718
	Particulate	Visual Inspection: ASTM D-2019; TAPPI T-437
Barrier	Porous	Porosity: ASTM D-726; TAPPI T-460; TAPPI T-536 Microbial Barrier: ASTM F-1608; Mil Spec 36954C
	Non-porous	Impermeability: ISO-5636-5; EN 868-1, Annex C; ISO 11607, Annex A Oxygen Transmission: ASTM D-3985 Light Transmission: ASTM F-1443 Water Vapor Transmission: ASTM D-4279; ASTM F-372; ASTM F-1249
Durability		Puncture Resistance: ASTM D-1709; ASTM F-1306; ASTM D-3420 Tear Resistance: ASTM D-1922; ASTM D-1938 Thickness: ASTM D-1777; ASTM D-374; ASTM D-645 Tensile: ASTM D-882; TAPPI T-494; TAPPI T-404 Flexural Durability: ASTM F-392 Basis Weight: ASTM D-4321; ASTM D-3776 Bond Strength: ASTM F-904 Accelerated Aging: ASTM F-1980 Abrasion Resistance: To be developed
Package Integrity & Seal Strength	Package Integrity	Seal Integrity: ASTM F-1929; ASTM F-1886 Package Integrity: ASTM D-3078
	Seal Strength	Tensile Peel: ASTM F-88 Package Burst: ASTM F-1140 Restrained Burst: ASTM F-2054
Visibility and Appearance		Haze: ASTM D-1003 Gloss: ASTM D-2457 Opacity: ASTM D-589
Processing		Dimensional Measurements: To be developed Friction: ASTM D-1894 Sealability: To be developed Coat Weight: SPMC 009
Printed Ink		Rub Testing: ASTM D-5264 Anchorage: To be developed Chemical Resistance: To be developed

FIG. 1 Summary of Test Methods for Medical Packaging Design and Evaluation

4.5 The Summary of Test Methods for Medical Packaging Design and Evaluation (Fig. 1) provides a compact graphical presentation of the test methods referenced in this guide.

4.6 *Test Description and Applicability* (see Table 1):

4.6.1 Table 1 lists the test methods commonly used to evaluate medical packaging. The test methods are used in two phases.

4.6.1.1 *Package Design: Characterization of the Materials and Evaluation of the Resultant Package*—This is referred to as "R&D Evaluation" in Table 1. Testing during this phase is characterized by the generation of quantitative data on the performance of the component materials and the package assembly. These test methods are lengthy, making them inappropriate for the manufacturing environment where rapid response is required for process control. Often, they are expensive and require specialized equipment not readily available at a medical packaging or device manufacturing facility.

4.6.1.2 *Package Compliance: Routine Monitoring of Adherence to Specifications*—This is referred to as "Compliance Testing" in Table 1. Testing during this phase must be rapid, inexpensive, and readily implemented in a manufacturing environment. The objective is not to develop design data, but to ensure that the design specifications are being met. These test methods do not necessarily make direct measurements of critical values, but detect variations in material, process, or product that are indicative of all critical characteristics.

4.6.2 It is important to note that no individual test method is entirely predictive of final package performance. Filled packages must be evaluated under conditions of use.

TABLE 1 Test Description and Applicability Table

Test	Test Method	Description	Applicability
		Safety Requirements	
		Chemical Properties	
Extractibles Useage R&D evaluation	ASTM D 4754	This test method covers the use of the FDA migration cell in the extraction of components and permits quantitation of individual migrants from plastic materials by suitable extracting liquids, including liquid foods and food-stimulating solvents. This test method provides a two-sided, liquid extraction test for plastic materials that can be formed into film, sheet, or disks.	This test method has been applied to a variety of migrant/polymer systems in contact with numerous foods and food simulants. Though most of the migrants examined were radiolabeled, the use of the FDA cell has been validated for migration studies of unlabeled styrene from polystyrene. This test method has been shown to yield reproducible results under the conditions for migration tests requested by the FDA. However, if the data is to be submitted to the FDA, it is suggested that their guidelines by consulted. Because it employs two-sided extraction, this test method may not be suitable for multilayered plastics intended for single-sided food contact use. The size of the FDA migration cell as described may preclude its use in determining total nonvolatile extractives in some cases.
Toxity Useage R&D evaluation	ASTM F 748	This practice recommends generic biological test methods for materials and devices according to end-use applications. Tests include those performed on materials, end products, and extracts. Rationale and comments on current state of the art are included for all test procedures described. Biological evaluation of materials and devices, and related subjects such as pyrogen testing and batch testing of production lots are also discussed.	The biocompatibility of materials used in single-component or multicomponent medical devices for human use depends to a large degree on the particular nature of the end-use application. It is not possible to specify a set of biocompatibility test methods which will be necessary and sufficient to establish biocompatibility for all materials and applications. While chemical testing for extractable additives and residual monomers or residues from processing aids is necessary for most implant materials, such testing is not included as a part of this practice. The reader is cautioned that the area of materials biocompatibility testing is a rapidly evolving field, and improved methods are evolving rapidly, so this practice is by necessity only a guideline. These test protocols are intended to apply to materials and medical devices for human application.
Toxity Useage R&D evaluation	ASTM F 813	This practice describes a reference method of direct contact cell culture testing that may be used in evaluating the cytotoxic potential of materials for use in the construction of medical materials and devices. This practice may be used either directly to evaluate materials or as a reference against which other cytotoxicity test methods may be compared.	This practice tends to be used less frequently due to the risk of inducing a response from mechanical damage due to direct placement of the sample onto the cell layer. This practice may be suitable for products which have leachates that are not able to diffuse through agar and are not too heavy.

Test	Test Method	Description	Applicability
Toxicity Usage R&D evaluation	ASTM F 895	The agar diffusion assay is an indirect contact test in which the test material is placed onto an agar layer that protects the cells. This test method is commonly used to evaluate the response of small samples that have at least one flat surface such as elastomeric closures.	This is one of a series of reference test methods for the assessment of cytotoxic potential, employing different techniques. Assessment of cytotoxicity is one of several tests employed in determining the biological response to a material, as recommended in Practice F 748. This test method is appropriate for materials in a variety of shapes and for materials that are not necessarily sterile. This test method would be appropriate in situations where the amount of material is limited. For example, small devices or powders could be placed on the agar and the presence of a zone of inhibition of cell growth could be examined. While the agar layer can act as a cushion to protect the cells from the specimen, there may be materials which are sufficiently heavy to compress the agar and prevent diffusion or to cause mechanical damage to the cells. This test method is not appropriate for leachables that are not water soluble because they may not diffuse through agar or agarose and thus not be detected. This test method would not be appropriate for these materials. The L 929 cell line was chosen because it has a significant history of use in assays of this type. This is not intended to imply that its use is preferred; only that the L 929 is an established cell line, well characterized and readily available, that has demonstrated reproducible results in several laboratories.
Retained solvents Useage R&D evaluation Compliance testing	ASTM F 1884	This test method covers determination of the amount of residual solvents released from within a packaging material contained in a sealed vial under a given set of time and temperature conditions and is a recommended alternative for Test Method F 151. This test method covers a procedure for quantifying volatile compounds whose identity has been established, and are retained in packaging materials.	This test method does not address the determination of total retained solvents in a packaging material. Techniques such as multiple headspace extraction can be employed to this end. For purposes of verifying the identity of or identifying unknown volatile compounds, the analyst is encouraged to incorporate techniques such as gas chromatography/mass spectroscopy, gas chromatography/infrared spectroscopy, or other suitable techniques in conjunction with this test method. This is an off-line head space analysis. It is sensitive to technique and sampling equipment resulting in large variations (~25 %) between laboratories. It is a simplified version of Test Method F 151 providing about the same level of accuracy. This method differs from Test Method F 151 in that it specifies certain conditions. Test Method F 1884, for example, specifies a pre-heat condition of 90°C for 20 min. Test Method F 151 defines a procedure for determining optimum heating time and temperature conditions for the preheat. Because solvents will escape from surface wraps on a roll of film, this test should be performed immediately after manufacturing to provide an indication of solvent levels in the inner wraps of the roll of film.
Retained solvents Useage R&D evaluation Compliance testing	ASTM F 151	This test method provides an index for comparing the level of solvents retained in flexible barrier materials of the same construction, which result from casting, coating, printing, or laminating operations. This test method does not yield absolute quantitative measurements of solvents retained in flexible barrier materials.	This method is essentially identical to Test Method F 1884 except for a complicated determination of the optimum heating time and temperature for the films in the head space container. There is no improvement in the interlaboratory variation. All other comments under Test Method F 1884 apply equally to Test Method F 151.
Heavy metals Useage R&D evaluation	ASTM D 3335	This test method covers the determination of lead contents between 0.01 and 5 %, cadmium contents between 50 and 150 ppm (mg/kg), and cobalt contents between 50 and 2000 ppm (mg/kg) present in the nonvolatile portion of liquid coating or contained in dried films by means of atomic absorption.	Higher levels of all three elements can be determined by this test method, provided that appropriate dilutions and adjustments in specimen size and reagent quantities are made. This test method is not applicable to the determination of lead in samples containing antimony pigments (low recoveries are obtained). If lead is present in the sample to be analyzed in the form of an organic lead compound at a concentration greater than 0.1 %, small losses of lead may occur, resulting in slightly poorer precision.
Heavy metals Useage R&D evaluation	ASTM D 3718	This test method covers the determination of the content of chromium (including chromium oxide) in the range from 0.005 to 1.0 % present in the solids of liquid coatings or in dried films obtained from previously coated substrates by means of atomic absorption.	Higher concentrations of chromium can be determined by this test method provided that appropriate dilutions and adjustments in specimen size and reagent quantities are made.

Test	Test Method	Description	Applicability
		Particulate	
Visual inspection Useage Compliance testing	TAPPI T 437	This test method is suited for the visual estimation of dirt in paper or paperboard in terms of equivalent black area. Dirt in paper or paperboard is defined as any foreign matter embedded in the sheet, which, when examined by reflected, not transmitted, light has a contrasting color to the rest of the surface and has an equivalent black area of 0.04 mm^2 or over.	This test method can be used to size characteristics other than dirt. Frequently used for estimation of gels, fisheyes, ink splashes, and other visual defects.
Visual inspection Useage Compliance testing	ASTM D 2019	This test method is intended for the numerical estimation of dirt in paper or paperboard in terms of equivalent black area. This test method is satisfactory only for the estimation of visual characteristics and it may be entirely inadequate when nonvisual effects such as grittiness of dirt are of importance. This is ASTM's version of TAPPI T 437. It refers to the TAPPI Dirt Estimation Chart.	This test method can be used to size characteristics other than dirt. Frequently used for estimation of gels, fisheyes, ink splashes, and other visual defects.
		Barrier Requirements	
		Porous	
Porosity Useage R&D evaluation Compliance testing	ASTM D 726	This test method is applicable in papers that permit the passage of up to 25 mL of air/0.785 $in.^2$ in 15 s.	This test method cannot be used in those cases where the paper cannot be clamped securely against surface and edge leakage, such as, crepe or corrugated papers. For testing porous and semiporous paper, refer to TAPPI T 460, and T 536, respectively. Since the three test methods (D 726, T 460, and T 436) do not give the same results, it is recommended that a specific method be agreed upon in specifications covering paper between the seller and the purchaser, and that the test method be chosen to conform to the principle range.
Porosity Useage R&D evaluation Compliance testing	TAPPI T 460	This test method references the use of a Gurley densometer that measures the amount of time required for a certain volume of air (100 cm^3) to pass through a test specimen of a given area. The air pressure is generated by a gravity-loaded cylinder that captures an air volume within a chamber using a liquid seal. The pressurized volume of air is directed to the clamping gasket ring, which holds the test specimen. Air that passes through an area of the test specimen of 6.4 cm^2(1 $in.^2$) escapes to atmosphere through the holes in the downstream clamping plate.	The pressure differential used in this test method is 1.22 kPa. The recommended range of time measured is from 5 to 1800 sec/100-mL cylinder displacement. For more impermeable materials the time requirements become so excessive that other techniques are preferable. Since this test method measures air passage through the specimen, as well as, leakage across the surface, it is unsuitable for rough-surfaced materials that can not be securely clamped in the mechanism and may allow significant surface and edge leakage. For measurement of materials at higher pressure (3 kPa) refer to TAPPI T 536. To measure materials at pressures up to 9.85 kPa, TAPPI T 547 references the use of a Sheffield tester which measures the amount of air passing through a material of a given area over a specific time period.
Porosity Useage R&D evaluation Compliance testing	TAPPI T 536	This test method measures the amount of time required for a certain volume of air to pass through a test specimen of a given size. This test method measures at a higher pressure differential (3 kPa) and is recommended for papers that require 10 or more seconds for 10 mL of air to pass through.	This test method cannot be used in those cases where the paper cannot be clamped securely against surface and edge leakage, such as, crepe or corrugated papers. Since the three test methods (D 726, T 460, and T 536) do not give the same results, it is recommended that a specific test method be agreed upon in specifications covering paper between the seller and the purchaser, and that the test method be chosen to conform to the principle range.
Microbial barrier Useage R&D evaluation	ASTM F 1608	This test method is used to determine the passage of airborne bacteria through porous materials intended for use in packaging sterile medical devices. This test method is designed to test materials under conditions that result in the detectable passage of bacterial spores through the test material.	A round-robin study was conducted with eleven laboratories participating. Each laboratory tested duplicate samples of six commercially available porous materials to determine the LRV. Materials tested under the standard conditions described in this test method returned average values that range from LRV 1.7 to 4.3. Results of this round-robin study indicate that caution should be used when comparing test data and ranking materials, especially when a small number of sample replicates are used. In addition, further collaborative work should be conducted before this test method would be considered adequate for purposes of setting performance standards.
Microbial barrier Useage R&D evaluation	Mil Spec 36954C	This test method is performed at high flow rates. The challenge particles are microbial clusters with a mean diameter of 3 µm. Removal of challenge particles is therefore almost entirely by impaction.	Test methods based on this specification are intended to evaluate materials for use in surgical masks. This test method is not applicable for materials intended for low flow rate, barrier applications such as medical packaging where particulate removal is almost exclusively a diffusion mechanism.