
CHAPTER 23

STERILE MEDICAL DEVICE PACKAGE DEVELOPMENT

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23.1 REGULATORY HISTORY	23.2	23.6 PACKAGE PROCESS	
23.2 FUNCTIONS OF A PACKAGE	23.5	VALIDATION	23.19
23.3 PACKAGE TYPES	23.6	23.7 SHELF LIFE STUDIES	23.25
23.4 PACKAGING MATERIALS	23.9	23.7 FINAL PACKAGE VALIDATION	23.30
23.5 COMMON TESTING METHODS	23.13	REFERENCES	23.33

This chapter provides an overview of the process of designing and developing a package system for a medical device. A comprehensive discussion of this subject is beyond the scope of this chapter; however, numerous references are provided for further detail and study of the subject. The information provided in this chapter is a compilation from the references cited as well as from the experiences of the author in developing package systems for medical devices.

Introduction

Implementation of a standard for the process of designing and developing a package for terminally sterilized medical devices is essential to the overall endeavor of marketing a sterile device in the international and domestic communities. It is incumbent upon the medical device manufacturer to ensure that a safe, reliable, and fully functional device arrives at the point of end use. This assurance is complicated by the fact that the package must maintain its barrier integrity throughout its intended shelf life and through the rigors of manufacture and shipping and handling. The total product development effort must include the packaging design process and encompasses the package design, manufacturing process, sterilization process, and distribution environment effects. The intended sterilization method and the intended use, shelf life, transport, and storage all influence the package design and choice of packaging materials.

The issue of developing a package system seems uncomplicated and elementary. In actuality, the package process is complicated by the fact that device packages must allow effective sterilization of their contents by a wide array of methods; therefore the materials must be compatible with the sterilization method. Consequently, the package must provide a consistent and continuous barrier to environmental microorganisms and bacteria so as to maintain product sterility. The package must be designed to prevent product damage and loss of functionality from the dynamic hazards of shock and vibration inherent in the distribution environment. In addition, the manufacturer must have documented evidence that the performance of the package system is not adversely affected over time. The interactions of the materials and product, combined with the processes required to bring the product to its end use, influence the package design and manufacturing of the finished product.

23.1

23.2 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

The importance of packaging to the implementation of a medical device is illustrated in a speech by George Brdlik in 1982 that is no less true today. Brdlik stated:

Packaging is too often neglected as an important characteristic of a medical device. When sterile medical devices are involved, deficient packaging can cause the following problems:

- Increased risk of patient infection if product sterility is compromised by defective seals, pinholes fragile packaging materials, or packaging which shreds, delaminates, or tears upon opening.
- Hampering of a surgical procedure because of difficulties in product identification or aseptic transfer, or if a product selected for use must be replaced because the package is either initially defective or damaged upon opening.
- Increased hospital costs due to discarded products or excessive storage space requirements
- Increased manufacturing costs for refund/replacement of damaged products and recall of products with potentially compromised sterility or integrity.

In essence, poor packaging can transform the best, safest, and most economical medical device into an inferior, unsafe, and expensive product.

This chapter will provide a systematic and standard approach to developing a comprehensive package system that meets regulatory hurdles and ensures a high degree of confidence that the sterile medical device product will meet its performance specifications at the point of end use. These elements include:

- Selection of materials
- Design of the package
- Process validation
- Final package design validation

All of these elements must be combined to produce a package system that meets regulatory, industry, and consumer's requirements.

23.1 REGULATORY HISTORY

The regulatory burden for validating the manufacturing process and package system has become significant and considerable. It was started in 1938 with the amended Food and Drug Act of 1906 in which medical devices were first regulated, and then progressed to the Quality System Regulation (QSR), which specifies the requirements for components, device master record, and environmental controls, to name a few.

It is appropriate to present a brief history of how the medical device industry became regulated and how eventually the FDA recognized the importance of the package as an integral part, and in fact a component, of the medical device. As mentioned earlier, the Food and Drug Administration began regulating medical devices in 1938. At that time, the Federal Food, Drug, and Cosmetic Act extended the FDA's legal authority to control foods and drugs and bestowed the agency with new legal powers over cosmetics and medical devices. However, the act was limited in scope in that the regulatory actions could only be taken after a device was introduced into interstate commerce, and only after the device was found to be adulterated or misbranded. Surprisingly, the burden was on the government to provide evidence of violation of the act. In addition, the 1938 act could not prevent the introduction and marketing of "quack" medical devices. However, there was also an explosion of legitimate and sophisticated new devices using postwar biotechnology. These devices not only presented huge potential benefits to patient healthcare, but also caused an increased risk for harm. It became apparent that additional legal controls were necessary in order to harness the potential good from the new technologies.

A government committee studied the best approach to new comprehensive device legislation, and, as a result, in 1976 a new law amended the 1938 Act and provided the FDA with significant additional authority concerning the regulation of medical devices. The amendments included classification of all devices with graded regulatory requirements, medical device manufacturer registration, device listing, premarket approval (PMA), investigational device exemption (IDE), good manufacturing practices (GMP), records and reporting requirements; pre-emption of state and local regulations, and performance standards. Two years later, in 1978, the FDA published the GMP regulations that provided a series of requirements that prescribed the facilities, methods, and controls to be used in the manufacture, packaging, and storage of medical devices. The law has since been modified, with the most substantive action occurring in 1990 with the passage of the Safe Medical Devices Act (SMDA). It broadly expanded FDA's enforcement powers by authorizing the levying of civil penalties and creating a series of postapproval controls for monitoring the performance of medical devices.

Over the past 18 years, the FDA has significantly changed the way medical devices are regulated. The issuance of guidance documents effectively circumvented rulemaking and public comment. Publishing FDA's interpretation of the GMP effectively causes the manufacturer to comply with that interpretation. Legally, guidances are not binding on the public, whereas certain rules are. But for all practical purposes, there is little difference between the two. For example, two of these guidance documents are

- Guideline on General Principles of Process Validation—1987
- Preproduction Quality Assurance Planning: Recommendations for Medical Device Manufacturers

FDA issues dozens of guidances each year on specific products and processes. The last significant piece of legislation for medical devices came with the signing of the Food and Drug Administration Modernization Act of 1997 (FDAMA). This legislation essentially changed FDA's approach to standards-based enforcement and adds a system to recognize national and international standards in product reviews. The FDA will publish the recognized standards in the *Federal Register*, and these standards will then serve as guidance, enabling companies to use them to satisfy premarket submission requirements through a declaration of conformity. The list of recognized standards is provided in the FDA guidance document entitled "Guidance for Recognition and Use of Consensus Standards: Availability." This legislative change enables companies to submit a one-page 510(k) that simply states that the device complies with a stated list of recognized standards.

Significant legislation affecting medical devices and packaging includes:

- 1938—Federal Food, Drug, and Cosmetic Act enacted
- 1976—Medical Device Amendments (MDA) passed
- 1978—GMP Regulations published in *Federal Register*
- 1990—Safe Medical Device Act (SMDA) enacted
- 1997—Food and Drug Administration Modernization Act (FDAMA) passed

So, medical device manufacturers are subject to the provisions of the FDAMA and the GMP when doing business in the United States. The regulations are published in 21CFR (Code of Federal Regulations), part 820. The section dealing specifically with the requirements for packaging is contained in section 820.130. FDA approves products for use through the investigational device exemption (IDE), premarket application (PMA), and 510(k) processes. There may be additional regulatory burdens when the device is being marketed outside the United States. Some of these regulations are discussed in Sec. 23.1.1.

23.1.1 International Regulations

International regulations play a significant role in the marketing and use of medical devices. The European Union "Council Directive concerning medical devices" is the international equivalent of the

23.4 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

FDA regulations. The directive (93/42/EEC), also known as the Medical Device Directive (MDD), as published in the EEC in 1993, lists the essential requirements for devices and packages, and all medical devices sold on the European free market must meet the specifics of this directive, which overrides all national regulations. The “Essential Requirements” section for medical devices and packages are found in Annex I of the MDD. General requirements for ensuring that the characteristics of the medical device are not altered or adversely affected during their intended use as a result of transport and storage are found in Sec. 5. More specific requirements for infection and microbial contamination as it relates to packaging is found in Sec. 8. It is incumbent upon the medical device manufacturer to conform to all of the sections of the “Essential Requirements,” not just the packaging requirements.

ISO 11607. An ISO standard approved in 1997 by the international community has become essential to the development and validation of a package system for a terminally sterilized medical device. The ISO 11607 standard, entitled *Packaging for terminally sterilized medical devices*, provides the guidance for selecting materials (Clause 4), designing and validating the manufacturing process (Clause 5), and validating the final package design (Clause 6). Compliance with this standard and other European standards ensures compliance with the packaging provisions of the MDD, “Essential Requirements.” The FDA has recognized this standard for product reviews in its 1997 *Guidance for Recognition and Use of Consensus Standards: Availability*. This standard specifies the basic attributes that materials must have for use in packaging for terminally sterile medical devices. In addition, it provides the producer or manufacturer the guidance to conduct a formal qualification and validation of the packaging operations. There must be a documented process validation program that demonstrates the efficacy and reproducibility of all sterilization and packaging processes, to ensure the package integrity at the point of end use.

Finally, the ISO standard provides a series of recommended tests and criteria to evaluate the performance of the complete package under all of the stresses and hazards inherent in the packaging and distribution process. These tests include the following types:

- Internal pressure
- Dye penetration
- Gas sensing
- Vacuum leak
- Seal strength
- Transportation simulation
- Accelerated aging
- Microbial barrier

EN 868 Part 1. This European standard, entitled *Packaging Materials and Systems for Medical Devices Which Are to Be Sterilized: General Requirements and Test Methods*, provides detailed guidance on meeting the requirements of the MDD. It includes more detail on the selection and validation of packaging materials than does Clause 4 of the ISO 11607 standard. However, there are some differences, and both standards must be considered in evaluating the packaging system for compliance to the FDA and MDD regulations.

Standards within the EN 868 series fall into two distinct categories—horizontal and vertical. EN 868 Part 1 is a horizontal standard, since it specifies the requirements for a broad range of packaging materials, types, and designs. The requirements of Part 1 are essentially the same as ISO 11607, Clause 4; however, the ISO document includes requirements for package forming and final package validation. Vertical standards within the 868 Series include detailed requirements for individual materials or specific package types or medical device products. These standards are designated Parts 2 through 10. They specify limits for material properties for:

- Sterilization wraps (Part 2)
- Paper for use in the manufacture of paper bags, pouches, and reels (Parts 3, 4, 5)

- Paper for the manufacture of packs for medical use for sterilization by ethylene oxide (ETO) or irradiation (Part 6)
- Adhesive-coated paper for the manufacture of heat-sealable packs for medical use for sterilization by ETO or irradiation (Part 7)
- Reusable sterilization containers for steam sterilization conforming to EN 285 (Part 8)
- Uncoated nonwoven polyolefin materials for use in the manufacture of heat-sealable pouches, reels, and lids (Part 9)
- Adhesive-coated nonwoven polyolefin materials for use in the manufacture of heat-sealable pouches, reels, and lids (Part 10).

The “Essential Requirements” of the MDD can be effectively met by complying with the requirements of the ISO 11607 and EN 868, Part 1 standards.

CE Mark. A CE Mark can be affixed to the medical device when all of the essential requirements of the MDD and other directives, as appropriate, are met. The declaration of conformity that contains the documented evidence that all requirements have been met achieves this.

23.2 FUNCTIONS OF A PACKAGE

The first step in designing and developing a package system for a medical device is the selection of materials appropriate for and compatible with the device. Packages are intended to contain the product. However, for medical devices, there are other functions the package serves; it provides protection, identification, processability, ease of use, and special applications. A basic knowledge of the product’s use, dimensions, shape, and special characteristics (sharp edges, points, fragility, etc.); distribution environment, application, and barrier requirements are essential to selecting appropriate materials and designing the final package.

23.2.1 Protection

Protection of the device by the package may be provided in several different ways. Obviously, the sterile medical device must be protected from the bacteria and microorganisms natural to the environment. The package must provide a protective barrier from the environment but must also allow the product to be terminally sterilized, be opened easily by medical professionals, and maintain integrity until the point of end use. Materials must allow for the most efficient and effective sterilization method but not be degraded by that method. The package must also provide protection to the product from the rigors of the distribution and handling environment. In addition, there cannot be any damage to the package itself from shock or impacts associated with handling in shipment, or loss of seal integrity. Materials should be resistant to impacts and abrasion. The package must be designed so as to prevent sharp objects from piercing the materials or damaging seals, by eliminating movement of the device inside the package. In some applications, the product may be so fragile that the package must have cushioning characteristics that prevent excess shock energy from being transmitted to the device. Protection of the device over an extended shelf life is another function of the package design requiring material stability over time.

In summary, the protective features a package for a sterile medical device the package must have are

- *Sterilizability:* provide the ability to terminally sterilize the device by one or more methods without degrading the material.
- *Stability:* provide a barrier throughout the intended shelf life of the product.

23.6 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

- *Environmental resistance:* provide a barrier to moisture, air, bacteria, oxygen, light.
- *Physical:* provide dynamic protection; resist impacts and abrasion, provide structural support.

The materials most commonly used for medical device packages today incorporate the characteristics required for a protective package.

23.2.2 Identification

Packages must not only provide protection to the product, but they must also communicate what the product is, instructions, warnings and safety information, and other pertinent information such as; lot number, sterilization method, and expiration date. Space must be provided on the package for conveying this information either by printing directly on the package or by applying a label. Often, there must be adequate space for the information in two or more languages. The information must be legible at the point of end use; therefore abrasion, water, and the sterilization process must not damage the printing and labels.

23.2.3 Processability

By *processability* we mean the ability of the packaging material along with its product to be processed through a series of manufacturing operations that includes mechanical stresses in filling and sealing, chemical or physical actions during sterilization, stresses of shipping and handling, and the environmental effects of aging before the product is finally used. This processability requirement is clearly stated in 21 CFR Part 820.130, "Device Packaging":

The device package and any shipping container for a device shall be designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling and distribution.

23.2.4 Ease of Use

Parallel with the increase in the use of disposable medical devices is the requirement for easy-to-open packages for the sterile field. The package has to be designed such that the materials are strong enough to withstand the rigors of processing but can be opened without tearing or excessive stress on the package or product.

23.2.5 Special Applications

In some cases the package may serve as a tool in the procedure. The obvious application is as a delivery mechanism for the product to the sterile field; for example, heart valve holders for aseptic transfer to the surgery site. However, even more complex applications may be designed into the package to aid in the procedure.

23.3 PACKAGE TYPES

The form the package takes is fundamentally dependent upon the characteristics of the device such as size, shape, profile, weight, physical state, irregularities, density, application of the device, and other considerations.

The medical device industry uses a limited variety of types but many different materials in each form. Over the past 20 years, the industry has standardized on the following basic medical device package types.

23.3.1 Thermoform Trays (Semirigid)

Thermoform trays are made from a variety of plastics by molding them to the desired shape through the thermoforming process. Trays are particularly suited for devices with irregular shapes and high profiles, since the tray can be designed to accommodate these device characteristics. Trays are ideal for procedure kits that contain several devices, as they can be molded with special flanges, undercuts, and snap fits or ridges for securing the components. Semirigid trays are self-supporting.

In designing a tray for a medical device, several criteria must be considered in the selection of the material:

- Tensile strength
- Stiffness
- Impact resistance
- Clarity
- Ease of forming and cutting
- Heat stability
- Compatibility with sterilization processes
- Cost, on a yield basis, versus performance
- Product compatibility
- Ability to be sealed with lidding material

In using a tray for a sterile medical device, in order to perform the most basic protection function, the tray must be sealed to prevent loss of sterility. This is accomplished by using a lidding material that is sealed around the flange area of the tray. Until the advent of Tyvek™ into the market, it was difficult to provide lidding material that would provide a means for terminal sterilization using the common sterilization methods of the day. However, Tyvek has allowed widespread use of thermoform trays for many applications.

23.3.2 Flexible Formed Pouches

This type of package is one in which a flexible material is drawn by the thermoform process into a flexible “tray.” The package essentially is a formed pouch that allows containment of high profile devices. These packages are generally not self-supporting.

Characteristics of the formed flexible packages are:

- Relatively low cost, suitable to high-volume, low-cost devices
- May be made to be heat sealable
- Ease of forming
- Available for form-fill-seal operations
- Suited to relatively simple tray configurations
- Can conform to product
- Good visibility of product
- Cannot be preformed
- Offer little structural protection

23.8 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

- Limited variety of materials available
- Relatively lower heat resistance

Like the semirigid tray, this package type must also be sealed using a lidding material or top web. The top web material must be designed with the particular barrier properties needed to be compatible with bottom web material and the chosen sterilization process. The selection of the top web material must therefore be based on the following three factors:

- *Type of device.* Environmental or product barrier requirements
- *Method of sterilization.* Gas, radiation, steam,
- *Method of dispensing.* Peel, cut, tear, puncture

23.3.3 Flexible Nonformed Pouches

The most common package in this category, and probably for most single-use medical devices, is the two-web peel pouch. The package form is very common for a variety of medical devices including gloves, catheters, tubing, adhesive bandages, dressings, sutures, and other low-profile and lightweight products. This flat pouch design is suitable for high-volume, low-cost devices, as it provides the basic protection for devices (e.g., sterile barrier, sterilizable by one or more methods, efficient manufacturing, easily opened for dispensing). The most popular form of flat pouch is known as the *chevron* pouch. It gets its name from the peak-shaped end of the package where the initial peeling of the seal begins. This design provides ease of peeling as the peel forces are distributed angularly along the seal line rather than across the entire seal end. Other forms of the flat pouch can be achieved by forming seals across the corner of the package, leaving a tab to initiate the peel.

The typical peel pouch used for devices is made from two separate web materials that are heat sealable or adhesive coated. Since these packages usually contain sterile disposable devices that are terminally sterilized inside the primary package, a porous material is required for one of the webs. Either paper or Tyvek is used as one of the web materials along with a plastic film such as a laminated polyester and polyethylene.

Some of the benefits of the peel pouch are

- Relatively low cost
- Suitable for small-run or high-volume uses
- Can be fabricated from a wide variety of materials
- Can be prefabricated or formed in-line
- Provides a sterile delivery capability
- Product visibility
- Easy opening
- Printable with product information and instructions

Some of the disadvantages are

- Not useful for high-profile devices
- Low dynamic protection capabilities
- Not suitable for irregularly shaped devices
- Not suitable for kits or multicomponent devices

Another type of peelable pouch is known as the *header* bag. This package is essentially a two-web pouch in which a portion of one web is a peelable Tyvek or paper vent. The header bag provides high permeability, ease of opening, and convenient product dispensing. An advantage of this package type is that a basic flexible bag can contain a high-profile device.

23.4 PACKAGING MATERIALS

This part provides a basic overview of some of the more common packaging materials used for medical device packages. Since entire books are published describing the chemical characteristics, applications, and performance properties of packaging materials, it is beyond the scope of this chapter to provide all of the necessary information for the selection of materials for the specific medical device. Consult the references for additional information.

23.4.1 Primary Materials

Tyvek. Tyvek, a spun-bonded olefin, is used in almost every major form of sterile package including peelable pouches, header bags, and lid stock of thermoform trays and kits. Tyvek is a fibrous web material composed entirely of extremely fine, continuous strands of high-density polyethylene. This material has exceptional characteristics that distinguish it from other materials. It has superior dry and wet strength, chemical inertness, and dimension stability. Its excellent puncture and tear resistance and toughness allow for a wide range of applications for medical devices, particularly irregularly shaped and bulky products. This material has an unusual fiber structure that allows for rapid gas and vapor transmission but at the same time provides a barrier to the passage of microorganisms. Tyvek is used most often with ethylene oxide (ETO) sterilization methods because of its unique combination of properties of high porosity and microbial impermeability. Tyvek provides several other attributes useful to package integrity and aesthetics:

- *Water repellency.* Repels water but is porous to moisture vapor.
- *Chemical resistance.* Resists usual agents of age degradation (e.g., moisture, oxidation, rot, mildew, and many organic chemicals).
- *Radiation stability.* Unaffected by common levels of radiation used for sterilization.
- *Low-temperature stability.* Retains strength and flexibility at subzero temperatures.
- *High-temperature stability.* Can be used in steam sterilization methods.
- *Aesthetic qualities.* Bright, white, clean appearance for printing.

Since Tyvek does not readily adhere to other plastics, except other polyolefins, through the application of heat and pressure, it has been made a more versatile packaging material by applying coatings that enable it to bond with a wide variety of plastics. There are several grades of Tyvek used for medical packaging applications including 1059B, 1073B, and 2FS.

Paper. For many years, paper was the only choice for package types until the introduction of Tyvek as a medical packaging material. However, paper still plays a significant role in the medical device industry. Over the years before the introduction of Tyvek, paper materials compiled a significant performance record of product protection and patient safety. Although Tyvek has taken a majority share of the medical device package market, the industry is finding ways to utilize paper in combination with plastics and foils to provide the needed performance characteristics with favorable economics.

The significant features of paper materials that enable it to continue as a feasible packaging material alternative are:

- Cost
- Disposability
- Sterilization
- Combination with other materials
- Versatility

23.10 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

- Peelability
- Range of grades

Some of the limitations of paper as a medical device packaging material are:

Strength—low tear and puncture resistance
 Dimensional stability
 Moisture sensitivity
 Aging—limited under certain environmental conditions

Paper can be used as lidding material for semirigid and flexible trays, and for peelable pouches. Adhesive coatings are required to allow sealing.

Films, Laminates, and Coextrusions. Many films are used in medical device packaging applications. Both flexible formed and nonformed pouches, as well as bags, use films for their manufacture. These materials offer a high degree of versatility and are available in a countless variety of forms in monofilms, laminations, and coextrusions. The specific material to be used for a medical device is dependent upon the performance properties required for the device application. For example:

- Sterilization method (e.g., the material must tolerate high temperature)
- Protection requirements (e.g., high puncture resistance)
- Peel requirements (e.g., easily peelable)
- Package style (e.g., formable versus nonformable pouch)
- Barrier properties (e.g., moisture or oxygen barrier)
- Packaging process (e.g., in-line sealing versus form-fill-seal)
- Packaging aesthetics (e.g., visibility of product)

The flexible materials used for medical device packages include a plastic film that is usually a lamination or extrusion-coated material. The material most commonly used for flexible packaging applications is oriented polyester (e.g., Mylar™), which is used as a base for properties such as dimensional stability, heat resistance, and strength with an adhesively laminated seal layer such as low-density polyethylene, which provides the film structure with heat scalability. The variety of film combinations is virtually unlimited and the performance properties of the film can be customized to meet the requirements of the package specifications and the medical device. Other examples of film constructions are

- Polyester/Pe/EVA
- Polyester/Surlyn
- Polyester/nylon/Pe
- Polyester/nylon/PP
- Polyester/PVDV/Pe
- Metallized polyester/Pe
- Polyester/foil/Pe
- Polyester/foil/Polyester/Surlyn
- Oriented PP/Pe
- Polycarbonate/Pe/EVA

The thermoplastic films used in flexible applications are suited only for sealing to themselves or to chemically related materials. The sealing of like materials produces fused bonds that may not be peelable and thus applicable for single use medical devices. To overcome the limitations of sealing like materials, adhesives specifically tailored for seal-peel functionality are applied to the film surface allowing films to remain unaltered and to retain their performance characteristics. Uncoated or

coextruded materials for medical device packages are limited in their application because they allow only a narrow sealing range, provide limited scalability on high-speed equipment, allowing sealing of only chemically similar materials, and commonly overseal to paper and Tyvek materials. On the other hand, materials coated with an adhesive provide versatility and greater benefits such as a wider sealing range, easy and consistent scalability to porous materials such as Tyvek and paper, barrier properties, lower cost, and versatility in adhesive properties dependent upon the application (e.g., pouch or tray application).

Foils. Foil laminate materials are used in applications where high moisture, gas, and light barriers are essential. Foil can be used in all forms of packaging and for both medical devices and pharmaceuticals. The lamination of the foil with plastic films is required to provide scalability. Foil materials are being used for lidding of thermoform tray packages where high moisture and gas barriers are required and where the sterilization method allows it (e.g., gamma, e-beam, steam, etc.).

Wet devices such as dressings, solutions, sponges, swabs, and other saturated products requiring a high moisture barrier are particularly suited to foil packages. Foil laminations with high-density polyethylene or polypropylene are common constructions for these package types. For solutions, a form-fill-seal application would be ideal, as the pouch is formed and filled in a multiphase operation on a single machine.

The trend in medical device packaging over the past 10 years has been to flexible packages, as they are less costly, more resistant to shipping damage, easier to handle, and produce less packaging waste. A foil-laminated package offers many benefits such as strength, high environmental barrier, peelability, easy opening, temperature resistance, opacity for light-sensitive products, sterilizer resistance, ease of formability, compatibility with many products, and tamper evidence.

Thermoformable Plastics. Thermoformed plastics are among the most widely used package materials because of aesthetic appeal, medical device applications, and versatility for customized designs to fit contours of medical devices or several components of procedure kits. The selection of a material for a specific medical device is dependent upon several factors such as barrier requirements, sterilization method, and cost. There are many thermoformable plastics; however, not all have the ideal properties that lend themselves to medical device packaging applications. For example, an acrylic-based plastic has very low structural flexibility, low impact resistance, and poor clarity, but has a very high radiation resistance. The polyethylene terephthalate (PET) plastics have excellent clarity, structural flexibility, impact resistance, scalability, and radiation resistance, but only marginal water vapor barrier and heat resistance. So each material has its favorable and unfavorable properties, and the material that most closely fits the desired packaging application must be selected. The most common packaging materials for thermoform tray applications are discussed in some detail.

Polyethylene Terephthalate (PET). The generic material called PET or polyethylene terephthalate is probably the most widely used material for medical packaging applications because of its favorable characteristics, as mentioned previously. This material forms easily in thermoforming operations and provides good barrier performance and scalability with various lidding materials. The material imparts excellent clarity, flexibility, and radiation resistance—all important characteristics for packaging medical devices. It is produced in forms for injection or blow molding of rigid containers such as bottles and jars, and in sheet form for thermoforming trays, and blisters. When PET is coextruded with other materials such as glycol to make PETG, the barrier performance characteristics of the material are improved. PETG is not heat sealable, so the lidding stock must be adhesive coated to facilitate a functional seal for the package.

Polycarbonate (PC). Polycarbonate is used for high-performance package applications where high strength and toughness are required because of the size, density, or shape of the product. In some applications PC is used because of its superior clarity and the aesthetic appeal of the product. PC has the most impact resistant of all the plastics but has only average moisture and gas barrier properties. The cost of PC is somewhat prohibitive in a high-volume product application. However, for low-volume, high-priced devices such as pacemakers, defibrillators, and other implantable

23.12 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

devices, it is an excellent material for thermoform trays. Most of the common sterilization methods such as autoclave, steam, ethylene oxide, gamma, and e-beam can be used on packages made from polycarbonate. Typically, PC film for thermoform applications is coextruded with a polyolefin heatseal layer.

Polyvinyl Chloride (PVC) and Polyvinylidene Chloride (PVdC). The material known as PVC or polyvinyl chloride is one vinyl-based polymer used commonly in packaging applications. Another material in the same family is polyvinylidene chloride or PVdC. These materials differ from polyethylene in having a chlorine atom that replaces one hydrogen atom in its chemical structure. This is important, since it is this chlorine atom that has caused the material to lose favor for packaging applications because of environmental concerns. The environmental concern is that when incinerated, the material generates a hydrogen chloride gas. Several European countries have banned the use of vinyl-based materials. The criticism is controversial. The perceived environmental threat has caused many PVC applications to be replaced by PET. PVC is used most frequently in packaging application for blow-molded bottles, blisters, and thermoform trays. PVC is tough and clear and has excellent barrier properties as well as high impact resistance.

Polystyrene (PS). Polystyrene (PS) is one of the most versatile, easily fabricated, and costeffective plastic used in the packaging industry. It can be molded, extruded, and foamed. It is probably best known for its use as cushioning materials for electronic products. There are two types of polystyrene available for packaging applications: general purpose and high impact (HIPS). It is the high-impact type that is used for medical device packaging applications. High-impact polystyrene contains a small amount of rubberlike polybutadiene blended in to overcome the brittleness of the general-purpose material. This makes the HIPS tougher but less clear, usually translucent or opaque. The material may be acceptable for applications where visibility of the device is not required. The advantages of the material are its cost, heat resistance, and ease of formability. However, it may be susceptible to impact damage during shipping and handling. Another styrene-based material is styrene butadiene copolymer (SBC) and is commonly processed into containers, sheet, and film. It is used extensively in medical packaging applications because of its ability to be sterilized by both gamma irradiation and ethylene oxide.

The styrene materials are commonly recycled in communities where economics or legislation is favorable. However, where these materials are incinerated, PS, like PVC, causes unacceptable gaseous emissions and thus have come under intense environmental pressure and outright banning in some communities.

Other Materials and Properties. There is a host of other materials used in thermoform packaging applications. Some are specifically engineered for high barrier applications while others are resistant to high temperature. Although these materials have their greater use for medical device components, some materials are finding use for various types of packages such as tubes, blown containers, molded closures, and in some cases thermoform sheet material. Table 23.1 shows barrier and mechanical strength properties for the most common thermoformable plastics.

23.4.2 Secondary Materials

Secondary packaging is often used with primary packages to provide several functions in the overall distribution system for a medical device. Secondary packages are defined as containers that enclose one or more primary packages. One function the secondary package provides is the communication of information about the device. Protection of the device through the rigors of distribution and handling is another function a secondary package provides. In addition, the secondary package allows for storage of primary packages in a neat and orderly manner before use.

Paperboard Cartons. The most common form of secondary package used for primary medical device packages is the paperboard carton. This package is used for all types of primary packages including the semirigid tray, flexible formed pouch, chevron pouch, and header bag. It is used most often when the primary package requires some additional protection and as a “shelf box” for storage at the point of end use. A paperboard carton is usually inserted into a shipping container (i.e., shipper) that

TABLE 23.1 Barrier and Mechanical Strength Properties

Plastic	WVTR, nmol/m · s	Oxygen, nmol/m · GPa	Tensile strength, psi	Elongation, %	Impact strength, kg/cm	Tear strength, g/0.001 in
PET	0.45	6–8	25,000–30,000	120–140	25–30	13–80
Polycarbonate	2.8	N.A.	10,000	92–115	100	16–25
PVdC	0.005–0.05	0.02–0.03	8,000	60–100	5–15	4–6
HDPE	0.095	200–400	3,000–7,500	10–500	1–3	15–300
LDPE	0.35	500–700	1,000–3,500	225–600	4–6	50–300
PVC	0.55	10–40	2,000–16,000	5–500	12–20	Varies
PP	0.16	300–500	9,000–25,000	60–100	5–15	4–6
Polystyrene	1.8	500–800	N.A.	N.A.	N.A.	N.A.

Source: Diana Tweede and Ron Goddard, *Packaging Materials*, Pira International, Leatherhead, Surrey, U.K.

provides more substantial protection for transport. Many paperboard cartons may be consolidated into a single shipper.

Materials used to fabricate paperboard cartons may also be variously known as boxboard, cartonboard, chipboard, containerboard, and solid fiberboard. They are made in the same manner as paper and allow semirigid formability as well as surface strength and printability. Solid bleached boxboard is the highest quality, as it is made from the purest virgin bleached chemical pulp. This grade of paperboard is most often used for medical devices for its aesthetic good looks and excellent printability for graphics and product information. Various styles of paperboard carton are available to suit a particular product or primary package type or application.

Corrugated Fiberboard Boxes. A corrugated fiberboard box is used to transport the medical device through the distribution environment and to its ultimate user. This package may be known as the shipping container, shipper, shipping box, transport package, or other name that denotes its purpose as the final package to be offered for shipment. This package may contain only primary package types, or single or multiple secondary packages containing primary packages. In this case the package system may be considered to have a primary, secondary, and tertiary package. Most shippers are made from a material known as *corrugated fiberboard*. The paper-based material consists of a corrugated medium sandwiched between two kraft paper faces. It is characterized by the thickness and spacing of the medium (fluting), the weight of the facing layers, and the quality of the paper used. Most medical devices are transported in a grade and style of shipper known as a single wall, C flute, or regular slotted container (RSC).

23.5 COMMON TESTING METHODS

This section details some of the testing methods used and accepted within the medical device industry for characterizing the performance of the package. These methods will be used to validate the packaging processes and to establish performance specifications for continuous monitoring of quality.

23.5.1 Introduction

The package for a medical device plays a key role in safely delivering specialized treatment to the patient for which the device was designed and developed. It must ensure the efficacy of the device

23.14 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

from the point of manufacture to the point of final use. Most single-use terminally sterilized medical devices must be delivered with a very high confidence that the device has remained in a sterile condition throughout its storage, handling, and transport environment. In addition, packaging may have a direct function in the application of the treatment, as it may act as a fixture or dispenser for the physician. Thus mechanical damage to the package may not be tolerated. The design and development of the packaging system has come under closer and closer scrutiny by both the international and domestic regulatory agencies. This scrutiny has placed a great deal of emphasis on standardizing the package development process. Some standardization of the packaging process has come in the form of the international standard entitled ISO 11607, "Packaging for terminally sterilized medical devices." This section will specifically discuss the current consensus (ASTM) and industry test methods available for evaluating the integrity and strength of packages.

23.5.2 Package Integrity Versus Package Strength

First, there seems to be some confusion within the medical device industry regarding the strength of a package versus the integrity of a package. Package strength concerns the force required to separate two components of the package. It could be the force to separate two flexible components of a pouch, or a flexible lid and a thermoform tray. These forces may be measured in pounds per inch width, as in the seal/peel test, or in pounds per square inch, as in the burst test method. Alone, these tests of package strength values do not necessarily prove the integrity of the entire package. For example, since the seal/peel test per ASTM F-88 evaluates only a 1-inch segment of the package, there may be other areas of the package that are not sealed adequately to prevent contamination of the product. In fact, the seal width that was actually measured may be within the strength specification but may have a channel leak that could breach the package and negate integrity.

Likewise, the ASTM F-1140 burst test method as referenced by ISO 11607 also has its pitfalls. This method evaluates the whole package by applying pressure to all areas of the package, however the pressure is not applied equally at all points as a result of package irregularities and distortions. This can lead to a relatively high degree of variability between tests. Further, the burst test may not detect breaches in the package, such as pinholes and channel leaks, even though the burst test values have met the performance specification.

Even though the package strength specifications are confirmed, the package integrity is not necessarily proved. Package integrity is defined by ISO 11607 as *unimpaired physical condition of a final package*. Seal integrity is defined as *condition of the seal, which ensures that it presents a microbial barrier to at least the same extent as the rest of the packaging*. Neither definition refers to the *strength* of the seal. Package integrity is independent of package strength, although a strong package seal is a convincing indicator of a safe package. Further, if the entire seal area is proved to be homogeneous and continuous, then one could say that the package seals provide integrity. However, this says nothing about the package surfaces that may have pinholes or leaks not detected by seal strength tests. Other mechanical tests may be appropriate for determining package seal homogeneity.

Seal strength is important in the overall scheme of developing the package process, but the seal strength performance specification is used most effectively to monitor the process, not to determine ultimate acceptance. Seal strength is also an important determinant for establishing package process parameters. In fact, the ISO 11607 standard requires that the *seal strength shall be determined at the upper and lower limits of the defined critical sealing process variables and shall be demonstrated to be suitable for the intended purpose*. To restate, seal strength is an important performance attribute for the package and provides suitable guidance in establishing statistical process control limits, but is not the absolute determinant of the acceptability of the package for its intended use. Package integrity at the point of final use is the principal acceptance criterion for a sterile medical device package. However, both performance attributes are essential to the package design and development process.

23.5.3 Determining Package Strength

The performance specification of the package may be based on the seal and burst test values of packages produced from a specific validated production line. These tests are performed using standardized test methods developed by American Society for Testing and Materials (ASTM). The seal strength test procedure is described in ASTM F-88, "Seal Strength of Flexible Barrier Materials." This test covers the measurement of the strength of a seal of a given width at a specific point of the package. It does not measure the seal continuity. Other methods such as the 180° peel test may be used to determine the seal continuity or peeling characteristics. The seal strength test is performed by cutting a 1-in-wide strip from the seal of the package. The strip is placed in the tensile test machine by clamping each leg of the sample in the grips, aligning the specimen so that the seal is perpendicular to the direction of pull. The seal is pulled apart at a rate of 10 to 12 in/min. The peak force required to pull the seal completely apart is recorded. It would be appropriate to perform the test at several points of the package, including the manufacturer's seals (seals produced by the vendor of the package), and the production seals (seals produced by the manufacturer of the product). Typical seal strength values lie in the range between 1 and 4 pounds. The optimum seal strength varies according to the type of package being tested and its specific applications.

The burst test procedure is described in ASTM Standard D-1140, "Failure Resistance of Unrestrained and Nonrigid Packages for Medical Applications." This method covers the determination of the ability of package materials or seals to withstand internal pressurization. Since packages may be produced from substandard materials or with inadequate seals, or both, package integrity may be compromised during production, distribution, or storage. Burst testing may provide a rapid means of evaluating overall package quality during production, and overall package integrity after dynamic events associated with shipping and handling.

Two methods of burst testing are provided in the standard: the open-package test and the closed-package test. The open-package test is performed in a fixture that clamps the open end but provides a means for pressurizing the package. The pressure is increased in the package at a rate greater than the permeability of the porous package component, until a failure occurs. The type and location of the failure is recorded as well as the maximum pressure at which failure occurred. The open-package test is most useful as a quality assurance procedure on incoming materials to ensure that the supplier of the material is meeting pre-established specifications for seal strength.

The closed-package test is performed on production samples as an internal quality assurance procedure. This method is performed by inserting the pressure source through a component of the package and then increasing the pressure until a failure occurs. The pressure at failure and location and type of failure are recorded. Burst test values typically fall in the range between 0.5 and 3 psi. No correlation has been made between the burst test value and seal strength values. A recent study has shown that unrestrained pressure testing may lead to inconsistencies in test results while more consistent test results are achieved by restraining the test specimen between parallel plates (Hackett, 1996).

23.5.4 Determining Package Integrity

One category of package integrity test methods has been available for over 10 years and involves microbial challenge and product sterility. As you will read later in this chapter, these are not the only means of determining package integrity and these methods are coming under tighter examination, as alternate test procedures are developed. In fact, the FDA has recognized ISO 11607 as a consensus standard, which states, "The manufacturer shall demonstrate the integrity of the package by testing the package. This can be accomplished by physical tests." Examples of physical tests as described in the ISO 11607 standard include: internal pressure test, dye penetration test, gas sensing test, vacuum leak test. All of these methods have their advantages and disadvantages.

Microbial Challenge/Product Sterility Test Methods. There are really two types of microbial barrier test: those performed on materials and those performed on whole packages. Microbial barrier tests on

23.16 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

materials are performed by packaging manufacturers to ensure that their materials are impervious to microorganisms while allowing sterilant gases to permeate for product sterilization purposes. These tests are typically performed using ASTM F-1608, "Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)." Microbial barrier testing of materials is significantly less controversial than microbial testing of whole packages, since this methodology lends itself to some level of standardization and control. Determining the microbial barrier characteristics of materials is very different from the methods required for a whole package. A whole package is significantly more complex than a single material.

Aerosol Challenge. At the risk of oversimplifying the procedural demands of microbial testing, here is a summary of how a microbial challenge/product sterility test is performed. There are two types of whole-package microbial barrier tests currently in use.

One method takes a sterile finished primary package containing an actual device and fixtures it into a vacuum chamber. The chamber is loaded using a specific configuration and then performance is qualified to establish a homogeneous distribution of the indicator organism prior to the actual test runs. After the performance qualification, the test packages are subjected to a microbial challenge of a high concentration of bacteria, which is nebulized into an aerosol and circulated in the chamber for a specified period of time. Next, the outer surfaces of the package are decontaminated and the product is aseptically extracted from the package. The product may even need to be manipulated further at this point to facilitate the sterility test. The product sterility test determines if any of the indicator micro-organisms were able to breach the package and contaminate the product.

Although this method would appear to be the best at determining package integrity since it is a direct indicator of product sterility or nonsterility, it has several deficiencies:

1. It is very expensive to perform the test using an adequate sample size while providing statistical significance.
2. It is prone to false positive results due to the high precision necessary for lab technicians to aseptically handle and manipulate packages and products.
3. Each package type, configuration, and size must be prequalified in the chamber.
4. Several well known studies by HIMA and member companies have indicated that it may not even detect obvious breaches in the package integrity (Jones et al., 1995).
5. There is no standardized method to ensure the reliability and repeatability of the test.

Dust/Talc Challenge. The other whole-package microbial method involves a similar concept of challenging the package with a high concentration of micro-organisms and then performing a product sterility test. This method uses talc or dust mixed with a specific micro-organism. The package is exposed to the dust by shaking in a chamber. Similarly, the outer package surfaces are decontaminated prior to product removal and sterility testing. Likewise, this method has deficiencies similar to the aerosol method.

The microbial methods are still in use to evaluate package integrity essentially because the regulatory agencies are still asking manufacturers for data using these methods, or medical device manufacturers have always evaluated their packages for integrity and they are hesitant to change their protocols. However, there are alternative methods.

Physical Test Methods. Some of the physical test methods have been available for many years as published ASTM standards. Recently, industry has taken a closer look at the validity and effectiveness of these methods and has developed new methods for evaluating package integrity.

Visual Inspection. ISO 11607 handles visual inspection for package integrity in Sec. 6.2, which is very detailed in the requirements and procedures. ASTM Subcommittee F2.60 on Medical Packaging recently published standard F-1886-98. "Standard Test Method for Determining Integrity of Seals for Medical Packaging by Visual Inspection," to help further detail a method for visual inspection. This standard describes a method to visually detect channel defects in package seals down to a width of 0.003 in with a 60 to 100 percent probability, depending upon the package type and size of the channel. It provides attribute data (accept/reject) for package integrity of finished, unopened packages.

It is generally not effective in detecting pinholes and minute tears in package substrates. In addition, visual inspection cannot be used for packages with two opaque substrates, as transparency of the seal surfaces is essential to the inspection. Its most applicable attribute is for monitoring package quality in production to detect any significant changes in heat-sealing process parameters, which may provide the first indication that the process is out of control. Additional testing using more sensitive methods for leak detection of packages under suspicion of having defects may be warranted to confirm whether the channel or void is in fact an unsealed area. Visual inspection is not considered to be the only means by which the manufacturer should evaluate for package integrity.

Internal Pressure Test. ISO 11607 describes the internal pressure test as applying an internal pressure to the sterile package while it is submerged in water and noting any escaping air bubbles. A Flexible Packaging Association (FPA) committee, Sterilization Packaging Manufacturers Council (SPMC), has published several standards for testing packaging. One of those standards, FPA/SPMC Standard 005-96, "Standard Test Method for Detection of Leaks in Heat Seal Packages-Internal Pressurization Method," details the internal pressure test method.

The advantages of using this method for determining package integrity are that it is very easy to perform the test. In addition, it is inexpensive to test a large sample size and obtain statistical significance in the test sample set. The equipment costs are low, since all that is required is a pressure source and a water bath.

This method has not been validated by round robin testing, and no precision and bias statement has been made as to its repeatability and reproducibility. Nor is its sensitivity for detecting leak size known. However, independent verification has proved its usefulness in detecting gross leaks in packages. Gross leaks in packages occur most often as a result of handling and distribution hazards that cause tears, gouges, and punctures. Package validations most often fail as a result of the rigors of shipping and distribution. This test is sufficiently sensitive to detect those types of defects caused by the hazards of distribution. Leaks in seals and in material surfaces can be detected using this method.

The method can be used for both porous and nonporous packaging materials. For packages with porous materials, the porous material substrate is sealed using a label or coating to reduce the porosity of the material. This facilitates the pressurization of the package and reduces the interpretation of what constitutes a leak and where a leak is occurring in the package. The porous material is not evaluated for leakage, as the coating may mask or block leaks. However, pinholes, tears, gouges, and channel leaks are readily apparent under an internal pressure that does not begin the separate the seals.

Validation of the method for the package under investigation must be performed to determine the proper internal pressure, and to evaluate the ability to detect channel and pinhole leaks over the permeation of air through the porous substrate.

Vacuum Leak Test. The vacuum leak test is similar in concept to the internal pressure leak test in that the result is a pass/fail for the detection of bubbles emanating from the package while submersed in a water bath. The method is described in ASTM D3078, "Standard Test Method for Leaks in Heat-Sealed Flexible Packages." The pressure differential is obtained by evacuating the chamber, causing the package to expand.

The difficulty in using this method for porous packages is that the pressure differential may not reach a point at which air passes through a channel or material leak before air passes readily through the porous material. Lowering the porosity of the material by coating it with a lacquer or other means could reduce this problem. This test is more suitable for nonporous packages that will expand under vacuum and create an internal pressure adequate to force air through leaks.

Dye Penetration Test. The ASTM F2 Committee has recently approved a dye penetration test method. The new standard, designated F-1929, "Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration," finally provides a standardized method for conducting leak testing of package seals using a low-surface-tension solution and dye indicator. The basis of the test is that, when the test solution comes in contact with a channel or breach in the package seal, it will flow through the channel by capillary action. The leak will be indicated by a blue streak visible in the seal and/or a profuse and consistent flow of the dye through the channel.

This test method is generally considered to be more sensitive than the whole-package microbial challenge methods discussed earlier in this chapter. It is reported in a study on Tyvek-to-plastic

23.18 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

pouches that seal defects down to 0.0015 in were readily detected with a blue dye solution (Nolan, 1996). The published test standard has verified by round robin testing that the smallest channel that can be reliably detected is on the order of 0.002 in. In fact, the detection rate for breathable pouches and trays with breathable lids was found to be 98 to 99 percent. It was discovered during the testing that significant reductions in test performance can be observed when indicator dyes other than toluidine blue were used. Also, the round robin results are specific for the wetting agent (Triton X-100) used for the solution.

The most effective application for the dye penetration test method is for detecting breaches in the seals of transparent packages, since seal defects must be observed easily. It is possible to use this method for opaque packages; however, observation of the seal leak must be made at the seal's outside edge and the exact location of the leak may be difficult to ascertain. One characteristic of this test methodology is that it is difficult to use for detecting leaks in the surfaces of package components. That is, pinholes, gouges, or abrasions of the materials cannot be detected, since the dye cannot be easily contacted with all of the package surfaces. So, although the dye penetration test is a sensitive leak indicator for seals, it is not a good whole-package integrity test. Other means must be used to detect material leaks, such as the bubble emission leak test. Other characteristics of this test method must be considered before incorporating it into a package validation protocol. The method is difficult to use for packages having a paper component, as the dye solution can destroy the material in a very short time—maybe even faster than the dye would travel through a channel. Other porous packages may allow the dye solution to wick through, causing difficulty in distinguishing a true leak from the permeation or wicking of the solution through the material. Since the dye solution is injected into the package, the method is destructive to the package and, in many instances, also to the product.

Gas Sensing Test Method. Up until now, there has never been a cost-effective means of performing this type of test. The introduction of a new technology that allows a trace gas (helium) to permeate through the porous component of a package has made nondestructive package integrity testing possible. The test is performed by first placing the test package into a specially designed housing.

This system is ideal for thermoformed trays with porous lids and flexible pouches with one porous side. The test has been shown to detect leaks as small as 0.002 in. Guidant and Medtronic have demonstrated the reliability of detecting leaks in blind tests and have quantified 100 percent of the purposely manufactured leaks in thermoformed trays (Hackett, 1996). In addition, there were no false positive readings in any of the unaltered packages.

The test method will be suitable for testing packages for package validation in which the package system is being designed and developed. In the short term, it is thought that this test methodology could replace the whole-package microbial challenge test methods, as it provides greater reliability, reduces the risks of false positives, and is similar in cost. In the long term, since the test housing is designed and manufactured for the package, this test methodology could be incorporated into a quality assurance program to validate the integrity of each and every package being manufactured. An ongoing 100 percent inspection or lot-to-lot sampling program would ensure the efficacy of the package process. The risk of a nonsterile package finding its way into the operating room would be virtually eliminated.

23.5.5 Conclusion

Package seal strength does not necessarily equate to package integrity. These two attributes of a finished medical device package are separate considerations in proving the efficacy of the package. Industry has developed methods for seal strength testing that are used to validate the package process. Although package seal strength is an important performance attribute, the ultimate acceptance of the package is based on its complete integrity. There are several means available for evaluating the integrity of sterile medical device packages. The application of a particular integrity test depends upon many factors, including the type of package, materials of construction, size, desired sensitivity, and objective of the test.

23.6 PACKAGE PROCESS VALIDATION

This section provides an overview of the package manufacturing and the elements that must be considered for validating the process.

23.6.1 Introduction

The product engineering team has developed an exciting new medical device that will improve the quality of life for many patients. The product has been tested and retested. Regulatory questions concerning the product have been defined and answered. Clinical trials to show that the product performs as intended have been completed. The manufacturing process has proved to be consistent and is fully documented. However, the challenge of bringing the device to the market is just beginning. Many more questions must be answered before the product can be safely distributed and used by the patient's caregiver. The most basic one is "How will I get the product to the caregiver in the condition required for safe and proper use?" The most basic answer is "By designing a package system that will combine with the device to create a total product that performs efficiently, safely, and effectively in the hands of the user.

At first glance, the issue of developing a package system seems uncomplicated and elementary. After all, what could be difficult about placing the device into a thermoform tray, covering it with a Tyvek lid, inserting it into a paperboard carton, and consolidating the cartons into a shipping unit? In actuality, the process of designing and developing a package for terminally sterilized medical devices is complex and complicated. This is because of all of the interactions of various processes, equipment, materials, and environments that combine to influence the package design and manufacture of the finished product.

For example, the product engineering team has developed the product as a disposable sterile device that must remain sterile at the point of end use. Therefore, the microbial barrier properties of the packaging materials, along with the suitability of forming and sealing, are crucial for assuring package integrity and product safety. So, the product and package materials must be compatible with the chosen sterilization process. In addition, the product will need to survive the rigors of transportation with its intrinsic hazards of shock, vibration, and environmental conditions. Finally, the manufacturer must have documented evidence that the performance of the package is not adversely affected over time.

Unfortunately, the product engineering team was unaware that there are regulations within the FDA and International community that require a formal package system qualification process and a documented validation program demonstrating the efficacy and reproducibility of all sterilization and packaging processes (i.e., forming, sealing, capping, cutting, and handling). At this point, the engineering staff has realized that the package design and development process should have been an integral part of the product development program and should not have been left to the very end of the development process. Serious delays in distribution of the product have resulted, since the package validation process requires significant time and effort to complete. The engineering team now turns to the Regulatory Affairs (RA) department for help in identifying the regulatory requirements for packaging.

Investigation by the Regulatory Affairs (RA) Department for the requirements imposed on packaging reveals an array of documents on the subject. Foremost is the Quality Systems Regulation (QSR), found in Title 21 CFR, Part 820. The requirements for components, device master records, and environmental controls that affect the selection and use of packaging appear throughout the QSR. However, the specific requirements for packaging are in Sec. 820.130. Further investigation discloses two international documents regulating the design and development of packaging include the International Standards Organization (ISO) 11607 "Packaging for terminally sterilized medical devices" and European Norm (EN) 868-1, "Packaging materials systems for medical devices which

23.20 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

are to be sterilized—Part 1: General requirements and test methods.” Both of these documents provide an outline of general requirements and test methods for validating the complete package system. RA has reviewed the two international documents and has found that they are very similar, but with a few significant differences. “What standard do we follow?” becomes the next basic question to answer.

FDA has helped answer this question by acknowledging the importance of international consensus standards. The FDA stated in the FDA Modernization Act of 1997: *Guidance for the Recognition and Use of Consensus Standards*:

...conformance with applicable consensus standards can provide a reasonable assurance of safety and/or effectiveness. Therefore, information submitted on conformance with such standards will have a direct bearing on determination of safety and effectiveness made during the review of IDE's and PMA's. Furthermore, if a premarket submission contains a declaration of conformity to recognized consensus standards, this will in most cases, eliminate the need to review actual test data for those aspects of the device addressed by the standard.

Consequently, FDA has recognized the ISO 11607 standard as the consensus standard for manufacturing and quality control of packaging processes, materials, product package and design, and sterilization processes. Confusion about the existence of two packaging standards to conform to is a concern for medical device companies. However, conformance to the EN 868-1 standard will become a moot issue as the ISO 11607 standard undergoes a revision by the ISO TC 198 Working Group 7 to harmonize the differences. So now we know what needs to be accomplished in regards to packaging, right? We just need to perform a package process validation. That's simply a matter of following the ISO 11607 standard. Yes, but unfortunately it's not a cookbook recipe to success.

23.6.2 What Is Process Validation (PV)?

The FDA defines validation as “establishing by objective evidence that the process, under anticipated conditions, including worst case conditions, consistently produces a product which meets all predetermined requirements (and specifications)” Likewise, the ISO 11607 standard, “Packaging for terminally sterilized medical devices,” defines validation as a “documented procedure for obtaining and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications.” What these definitions are really saying in a practical sense is that a process validation must address:

1. The requirements or application of the package
2. The interaction of people and equipment used in the manufacture of the package
3. The consistency with which a package can be made
4. The effects of processing (e.g., sterilization) on the performance of the package
5. The storage and handling of the package

A manufacturer must become intimately involved with how the product is packaged and how to maintain consistency and uniformity. It must have proof that a process performs as it was intended.

The process validation (PV) consists of a series of qualifications of the processes making up the complete package system. These processes include the installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). Each facet of the packaging system must be challenged and qualified in order to claim validation of the entire system.

ISO 11607 addresses the package system validation in three phases, or clauses. Clause 4 specifies the basic attributes required for a wide range of materials as they combine and interact with various medical devices, packaging designs, sterilization methods, and distribution modes. Clause 5 defines the framework of activities to qualify the processes used to make and assemble the final package

configuration. Clause 6 is intended to assist in the selection of tests and to provide criteria that can be used to evaluate the performance of the final package.

23.6.3 Why Is Package Validation Important?

The primary objective of a package process validation should be to provide the medical device manufacturer with a high degree of assurance that the product will reach the user in a condition suitable for optimum functionality and for its intended purpose.

The specific benefits of the package process validation include not only reducing the manufacturer's risk of product malfunction or the potential of a nonsterile operating condition but also improved customer satisfaction, improved manufacturing efficiencies, reduced costs, reduced development time, and compliance with regulatory requirements. The "Guideline on General Principles of Process Validation" provides valuable understanding of quality systems requirements and may be relied upon with the assurance of its acceptability to FDA.

23.6.4 The Total Validation Process

Prior to beginning any work on a validation, it is essential to write a protocol. The protocol provides a blueprint stating how testing is to be conducted, including the purpose, scope, responsibilities, test parameters, production equipment and settings, and the acceptance criteria for the test. Validation requires careful planning and preparation and it begins with a well-conceived and -written protocol. As was mentioned earlier, the validation process consists of a series of qualifications of unique processes that make up the complete package process system. This total package process system includes the final package design, the materials chosen for the package, and the ability to sterilize the product inside its package. The design of the package and its dynamic interactions with the product, the machinery used to assemble the package, the setup and maintenance of the machine, and consistency of production are other important considerations. If one of these processes is not right, the entire system breaks down and the manufacturer is at risk of malfeasance.

23.6.5 Package Forming and Sealing

While working with a packaging vendor, the package design has been completed. Vendors are usually responsible for validating that the materials are compatible with the sterilization process, and that compliance qualification tests are conducted. Appropriate materials have been selected and validated for compatibility with the intended product by the manufacturer. But how will we assemble the product into the package using the most efficient and consistent process? The package-sealing equipment for the job is identified and purchased; however, it must be properly installed before producing finished packages. ISO 11607 states that "before starting final process development, it shall be demonstrated that the process equipment and ancillary systems are capable of consistently operating within the established design and operating limits and tolerances." Clause 5 of the ISO standard addresses all of the issues in validation, such as equipment qualification, process development, process performance qualification, process control, and process certification and revalidation.

An equipment installation qualification is important because all production facilities have specific requirements for utilities, cleanliness, temperature and humidity, and other variables. For this reason, the equipment should be installed in its intended production location before qualification. The equipment is run at its operating limits to determine its performance capabilities relative to the manufacturer's specifications. In addition, all equipment change parts and accessories are assembled and checked out for proper fit. This phase of the validation includes verifying that the equipment will perform its intended function, establishing calibration and maintenance procedures, and identifying

23.22 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

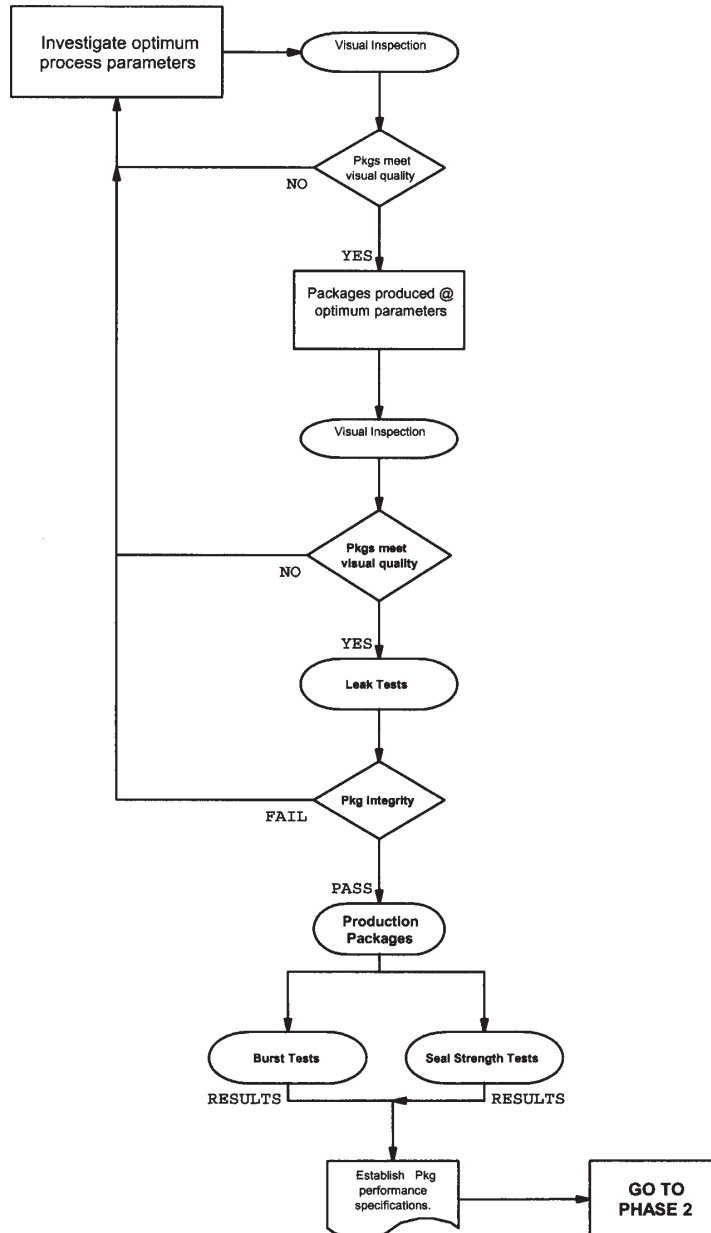


FIGURE 23.1 Flowchart of package manufacturing process qualification steps, phase 1.

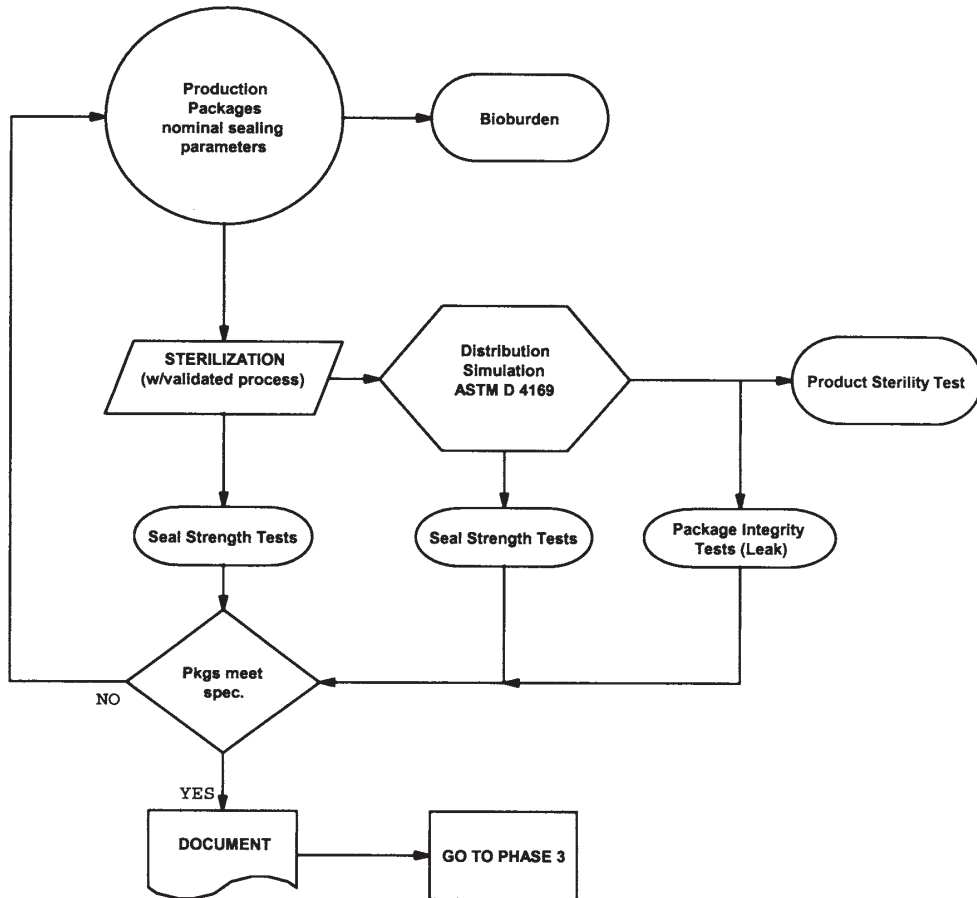


FIGURE 23.2 Flowchart of package process performance qualification steps, phase 2.

monitoring and control issues. Standard operating procedures (SOPs) must be written for calibration, maintenance, and repair.

Facilities management has confirmed that the equipment has been properly installed and that it performs in accordance with the manufacturer's specification. We can now begin to produce finished packages on the new equipment. The operational or process performance qualification is designed to provide a rigorous test to the effectiveness and reproducibility of the process. This is the most critical and time-consuming phase of the validation process. It requires a large degree of performance testing and evaluation. Tests must be chosen that measure relevant performance characteristics of the package for important attributes such as seal strength and integrity. ISO provides examples of tests that may be used for measuring these attributes, including ASTM F-88, ASTM D-903, ASTM F-1140 for seal strength, and several unpublished methods such as internal pressure, dye penetration, gas sensing, and

23.24 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

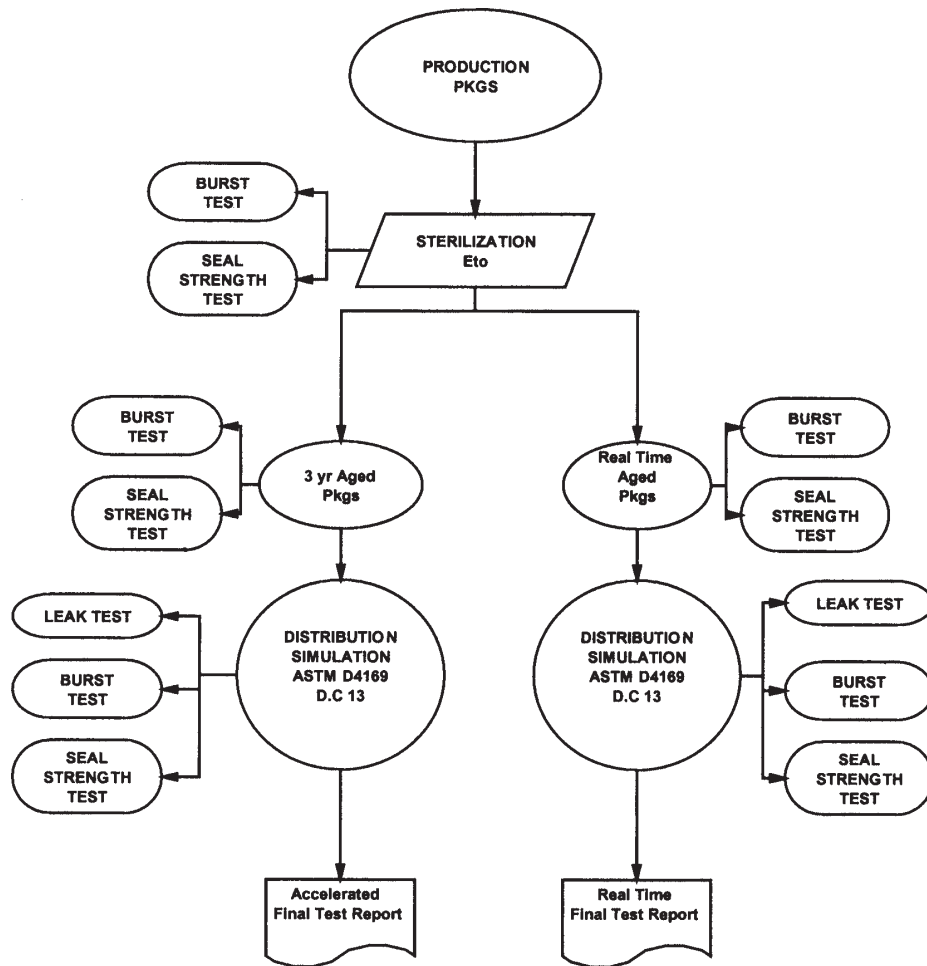


FIGURE 23.3 Flowchart of final package performance qualification, phase 3.

vacuum leak tests for package integrity. These are physical test methods that ISO acknowledges can be used for demonstrating the integrity of the sterile package.

The first step in this phase of the validation is to establish the process parameters that produce acceptable package performance. This may be accomplished by testing packages produced from a matrix of process parameter variable combinations, or by a design of experiments (DOE) which will test only packages produced at the extreme range of the process parameters. Where limited quantities of packages are available, one combination of process parameters may be used to produce packages on the basis of historical experience and then test them for strength and integrity. If these process

parameters do not produce packages meeting the prescribed performance specifications, then the process parameters are adjusted until acceptable packages are produced. The flowchart in Fig. 23.1 depicts one process for establishing the machine process parameters.

The packages are produced under normal operating conditions and on process equipment that has completed an installation qualification. When the optimum machine process parameters have been established, it is essential to determine the effects of sterilization, storage, and shipping and handling on the performance of the critical package attributes. This can be accomplished by measuring the seal strength and integrity after each of the individual processes and after the cumulative effects of all the processes. The flowchart in Fig. 23.2 depicts how this can be accomplished in a comprehensive protocol.

Through the rigorous step of process performance qualification, the manufacturing department has now documented the machine process parameters and established the package performance specifications for the package system being developed. The department is satisfied that the process is in control after measuring the consistency with which packages meet the performance specifications.

One final phase of the process validation should be to demonstrate that the combined effects of manufacturing, sterilization, storage, and handling do not have an adverse effect on the performance of the package produced under standard operating procedures. Clause 6 of the ISO standard address the issues associated with final package qualification. The flowchart in Fig. 23.3 depicts one protocol for assessing the integrity of the package after exposure to simulated, but realistic, events that the package will encounter during its useful life. These events may include, but are not be limited to, the manufacturing process itself, the sterilization process, storage or aging, and handling and shipping hazards.

23.6.6 Conclusion

Medical devices are developed using engineering principles and process qualification techniques to ensure that they perform as intended. So too must the package design and development process be qualified and validated. The complete validation requires a series of qualifications of the entire system, which ensures that the package will perform in harmony with the product in a consistent and safe manner. This is accomplished by developing a comprehensive plan that cannot be simplified or short-circuited. Product engineering has realized that, to accomplish the task of package process validation, the package system must be developed in tandem with the product development. Otherwise, delays of 6 to 12 months could result while the package system is being validated. The ISO 11607 standard provides guidance to assist medical device companies in developing a sterile medical device package system that performs efficiently, safely, and effectively in the hands of the caregiver. Since the standard provides designers and manufacturers of medical devices with a *framework* of laboratory tests and evaluations that can be used to qualify the overall performance of the package, there are many means within this framework to achieve the end result.

23.7 SHELF LIFE STUDIES

This section provides guidance for conducting accelerated aging studies for medical device packages. Developers of medical device packaging have struggled for years to justify shelf life claims and establish expiration dating for packaged medical devices. Much has been published over the past decade describing techniques for conducting accelerated aging programs. However, the theory of accelerated aging is complex enough for homogeneous materials, let alone device systems involving several different materials, such as complete medical device packages. The rapidly changing marketplace, technological developments, and regulations that govern them, demand that the manufacturer be responsive, which places a priority on the ability of the manufacturer to develop products meeting

23.26 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

all of the regulatory burdens in a timely and expeditious manner. Establishing shelf life claims can be a significant bottleneck in the product development timeline. Real-time aging protocols would significantly hamper the product development cycle, as well as its marketability, and are impracticable in today's fast-paced environment.

The adoption of the European Medical Device Directive (MDD) in June of 1998 and the mandatory implementation of the CE label on all sterile medical devices marketed in the European Community have resulted in the compulsory use of expiration dates on all medical device packages. In order to obtain the CE label, *all* the "Essential Requirements" of the directive must be met. The MDD states that "the label must bear...where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month."

The MDD's "Essential Requirements" are complied with by using harmonized standards. These standards may be European Norm (EN) or International Standards Organization (ISO) standards that meet the essential requirements of the Directive. For the development of medical device package systems, ISO 11607 has been developed and is used to meet essential *packaging* requirements of the Directive. Specifically, for meeting the Directive requirement as stated above, the ISO 11607 provision states "for medical devices with a defined shelf life, the manufacturer shall have documented evidence that the performance of the packaging is not adversely affected by storage under specified conditions for a period not less than the shelf life of the medical device." The net result is that manufacturers must supply documented evidence to support product-expiration claims. This is accomplished by monitoring measurable characteristics before, during, and after the test to determine the effects of time on package performance.

Expiration claims could be documented by real-time shelf life testing, however, the timelines for product development would be adversely affected. The developers of the ISO 11607 standard recognized this hindrance and therefore have allowed that "accelerated aging tests may be undertaken in addition to real-time aging tests by storage under conditions of increased severity." This provision is beneficial; however, no guidance is provided as to what conditions of adverse severity are permissible or technically reliable. It therefore has become crucial that guidance and standards be provided to help manufacturers establish product shelf life and expiration claims.

23.7.1 10 Degree Rule

There are no published standards for performing an accelerated aging study. Some guidance on accelerated aging of packages has been provided in the past. A landmark technical paper by Robert Reich (1988) introduced the Von't Hoff theory as an appropriate rationale for the accelerated aging of packaging. This theory, based on the Arrhenius rate kinetics theory of materials, states simply that a rise in temperature of 10°C will double the rate of a chemical reaction. The rule is commonly expressed as a Q_{10} value. So, for example, a doubling of the chemical reaction rate makes the Q_{10} value 2.0. The aging factor (AF) is derived from the following equation:

$$AF = Q_{10}^{(T_H - T_L)/10}$$

where Q_{10} = rate of chemical reaction (usually 2.0)

T_H = high temperature (test temperature)

T_L = low temperature (ambient)

Figure 23.4 indicates the relationship between the aging temperatures versus equivalency to a 1-year room temperature aging using various Q_{10} values. Other authors such as Geoffrey Clark (1991) of the Food and Drug Administration (FDA) have used the Q_{10} rule as rationale for accelerated aging protocols. Clark's guidance document, *Shelf Life of Medical Devices* uses a test temperature of 40°C and a Q_{10} value of 1.8 for intraocular and contact lenses. This guidance has been applied by industry to other medical devices and package systems and represents a very conservative estimate for real-time aging equivalents.

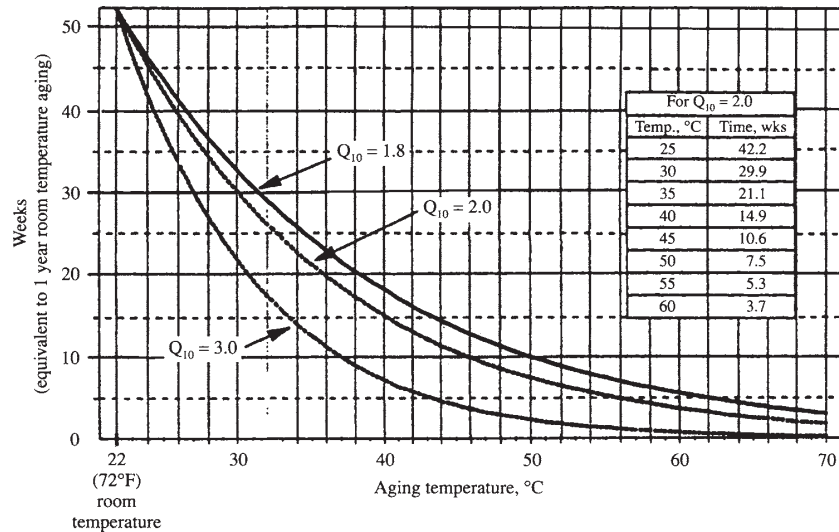


FIGURE 23.4 Accelerated aging of polymers: time versus temperature. Time (weeks) equivalent to one year room temperature aging when a polymer is heat aged at a selected temperature (°C). (From Hemmerich, K., "General Aging Theory and Simplified Protocol for Accelerated Aging of Medical Devices," *Medical Plastics and Biomaterials*, July/August 1998, pp. 16–23.) $Q_{10} = \Delta 10^{\circ}\text{C}$ reaction rate constant; $Q_{10} = 1.8$, conservative rate as suggested by G. Clark (FDA, 1991); $Q_{10} = 2.0$, conventionally accepted rate for first order chemical reaction; $Q_{10} = 3.0$, more aggressive rate; 60°C is the suggested upper temperature for most medical polymers.

Karl Hemmerich (1998) described the 10-degree rule (Q_{10}) in his article "General Aging Theory and Simplified Protocol for Accelerated Aging of Medical Devices." In it, he concludes, "the 10-degree rule will likely be conservative in the prediction of shelf life. However, the technique depends on numerous assumptions that must be verified by real-time validation testing conducted at room temperature." Reich suggested that using this approach for accelerated aging of medical grade packaging *should be used with some reservations, since the rate kinetics of the (packaging) systems are not fully understood*. Further, the Q_{10} values are based on the rate kinetics of a single chemical reaction, but the concept of accelerated aging of packages involves *assumptions regarding the uniform aging rates of one or more packaging materials, plus any adhesive reactions*. In addition, caution should be exercised that the aging temperatures do not produce unrealistic failure conditions that would never occur under real-time, ambient conditions. A temperature of 60°C is the suggested upper temperature limit for most medical polymers.

Reich concludes, however, that the *concept can be useful (as a rationale) for the accelerated aging of packages*. Hemmerich concurs that "this type of conservative relationship is appropriate for a wide range of medical polymers that have been previously characterized." Nevertheless, "the simplified protocol for accelerated shelf-life testing is not a replacement for more complex and advanced accelerated aging (techniques)."

23.7.2 Advanced Aging Techniques

John Donohue and Spiro Apostolou (1998) offer more complex and advanced techniques for predicting shelf life of medical devices. Their contention is that the Arrhenius and Q_{10} techniques are not

reliable predictors of future performance for most medical devices. However, the D&A and Variable Q_{10} techniques “are relatively easy to use and have been shown to be more accurate in predicting actual shelf life.” The D&A technique assumes nothing, and uses only the data to predict the future. The level of damage (LOD) of a physical performance property—such as brittleness, number of package seal failures, or color of a plastic at various elevated temperatures and time intervals—is used to predict the LOD of the same physical property of real-time aged materials. Short-term (i.e., 1 year) real-time data is required to establish the benchmark performance for comparison to the same property measured at various elevated temperatures, and for subsequently predicting longer-term real-time performance or time to equivalent damage (TED).

The Q_{10} method assumes that the ratio of the times to equivalent damage at low temperatures (usually 10°C apart) has a constant value. In fact, the Q_{10} will decrease with increasing temperature. Donohue and Apostolou suggest the use of a modified method, the variable Q_{10} method, in which the ratio of the times to equivalent damage for two temperatures is used as a variable. In this method the TED ratio is equal to the Arrhenius equation, and the Q_{10} is determined with the TED ratio as a variable as follows:

$$Q_{10}^{(T_H - T_L)/10} = \frac{\text{TED at } T_L}{\text{TED at } T_H}$$

So

$$Q_{10} = \left(\frac{\text{TED at } T_L}{\text{TED at } T_H} \right)^{1/[(T_H - T_L)/10]}$$

Again, it is necessary to acquire performance data for ambient storage conditions as well as for elevated conditions in order to determine the TED ratio, and before this method can be employed for predicting a variable Q_{10} .

Lambert and Tang (1997) describe a method of aging using an iterative process that provides an opportunity to refine and validate the initial, conservative aging factor (Q_{10}). The basic concept is to collect a number of parallel real-time aged and accelerated aged data points at early time points such that a correlation between the two can be developed, thereby defining the actual aging factor of the system under investigation. One limitation of this method is that real-time aged package performance data is required in which to compare accelerated aged data and make iteration on the conservative Q_{10} .

The American Society for Testing and Materials (ASTM) Committee F-2 on Flexible Barrier Materials published ASTM F-1980, “Standard Guide for Accelerated Aging of Sterile Medical Device Packages.” The scope of the Guide is to *provide information for developing accelerated aging protocols to rapidly determine the effects due to the passage of time and environmental effects on the sterile integrity of packages and the physical properties of their component packaging materials*. The information obtained from utilizing this Guide may be used to support expiration date claims for medical device packages. It is hoped that it will provide the necessary rationale for accelerated aging protocols that satisfies both the FDA’s Quality System Regulations (QSR) and the essential requirements for packaging in the MDD.

The Guide provides referenced documents (many of which are cited in this article) that give credibility to the current suggested methodology for aging medical device packages. The Guide condones the simplified Q_{10} method as a rationale for using accelerated aging for medical device packages. The basic eight-step concept was flowcharted by Lambert and Tang as shown in Fig. 23.5. The Guide states, “Conservative accelerated aging factors must be used if little information is known about the package under investigation.” Although the method provides conservative estimates of product/package shelf life, resulting in longer test durations than would be necessary using more complex aging methods, it does not require benchmark real-time data up-front in the development process that could further delay introduction of new products. In addition, it requires fewer samples and conditioning resources. Still, it may be advantageous to refine the aging process in subsequent studies using the more complex techniques summarized in this article. With more information about the system under investigation and with information demonstrating the correlation between real-time

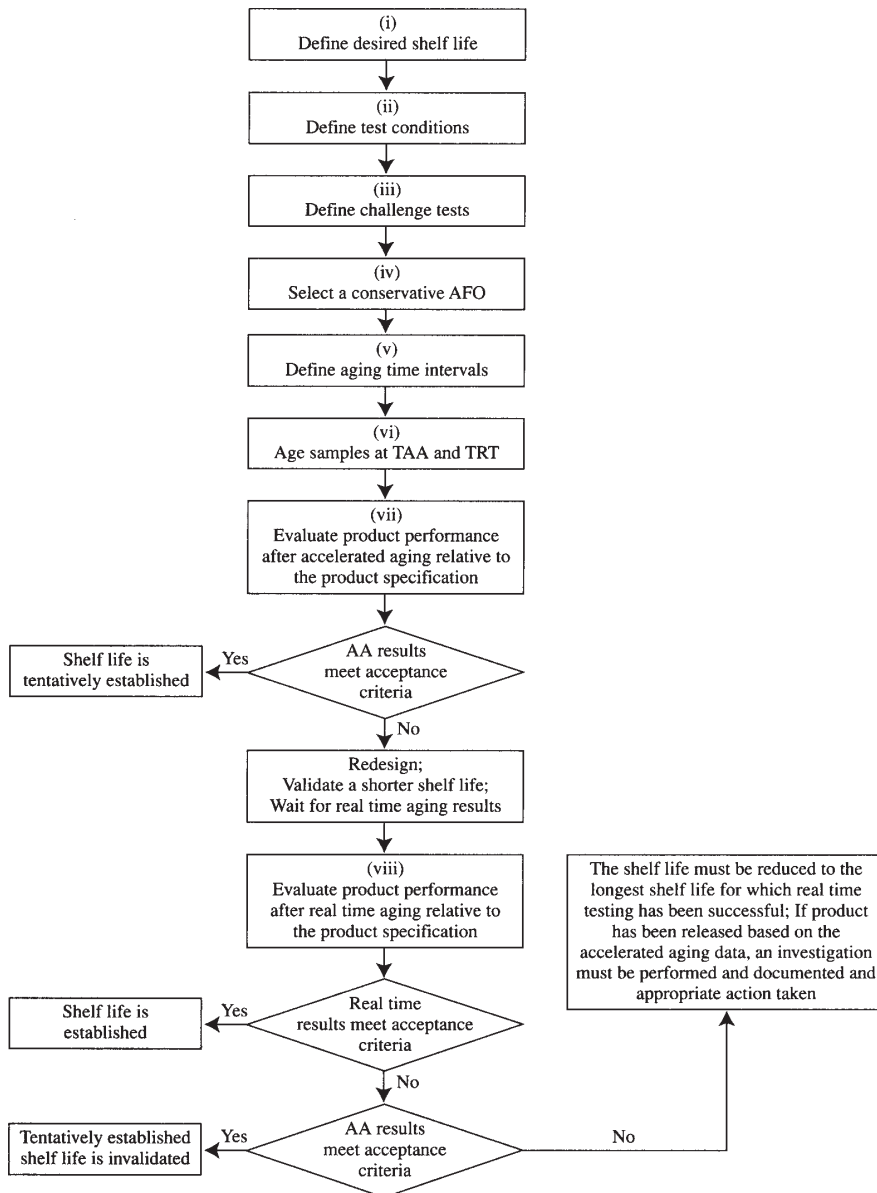


FIGURE 23.5 Eight-step process for accelerated aging.

23.30 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

performance and accelerated aging performance, more aggressive and accurate aging factors may be defined.

23.7.3 Conclusion

There is no shortage of rationale to support accelerated aging protocols as demonstrated by the published literature. Any manufacturer using techniques described in the literature will be successful in meeting the provisions of national and international regulations. Some techniques require very little information about the system under investigation and make assumptions about material rate kinetics resulting in conservative estimates, while others require real-time performance data in order to define material rate kinetics and predict long-term performance. Which technique to choose for an accelerated aging program will depend upon the manufacturer's resources, expertise, and product development time lines.

23.8 FINAL PACKAGE VALIDATION

The efficacy of sterile medical device packages at the point of end use is of great concern to not only the producer of the product, but also the general public, and foremost the regulatory community. The Food and Drug Administration (FDA) has the regulatory responsibility to ensure that medical devices perform their intended function and pose no undo risk to the patient. Not only must the product itself meet stringent regulatory requirements, but the package must also perform consistently under variable manufacturing conditions, sterilization procedures, distribution hazards; and perhaps over an extended shelf life. It is apparent that over the years, the FDA has become increasingly concerned over the number of packaging-related field failures, and has issued a growing number of FDA-483 observations (Spitzley, 1991). Nonetheless, there have been few guidelines for determining the effectiveness of sterile medical packages. Industry and medical device organizations have been working for a number of years to develop standard test methods and guidelines for validating the integrity of packages, and to answer the questions of what constitutes the best package and how to ensure that it performs as intended.

It is generally accepted industry practice to evaluate the integrity of sterile medical device packages by subjecting a fully processed package to extremes in sterilization processes, performing a simulated shelf life or accelerated aging study, conducting a simulated distribution and handling stress test, and then evaluating the efficacy of the package for sterility through microbial challenge or physical test methods.

23.8.1 Shelf Life/Accelerated Aging/Expiration Dating

FDA requires documented evidence to support published expiration dates on medical device packages. The European Union has required expiration dates on all medical device packages as specified in the EC Directive 93/42/EEC, which states, "The label must bear...where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month." Manufacturers are being forced to comply with European directives based on ISO Standards. As the FDA is moving toward harmonization with the European standards through revision of its GMP, and through adoption of ISO and CEN Standards, the need for guidance on the performance of accelerated aging protocols is crucial.

The net result of publishing expiration dates is that there must be some documented evidence that supports the product expiration claims, thus the need to perform shelf life studies. However, real-time shelf life studies are not an alternative in a fast-changing industry that can see two to three generations of products developed over the time it would take to document a 2-year shelf life claim.

So, the need for accelerated aging protocols as an alternative in developing a product and introducing it into the marketplace in a timely fashion is essential, although concurrent real-time studies should be performed to substantiate results of accelerated studies.

Ideally, accelerated aging involves a single measurable characteristic under extreme conditions to simulate, in a short time, the conditions the package would likely be subjected to during its designated shelf life (Henke and Reich, 1992). The protocol shown in the flowchart rotates the packages through three environments designed to simulate the aging process—high temperature and high humidity, high temperature and low humidity, and freezing conditions. Low temperature is included since it has been implicated in package failure through cold creep and material embrittlement, and packages may, in fact, be exposed to these temperatures in wintertime distribution systems or in the cargo areas of aircraft.

There are no published standards for performing an accelerated aging study. Recently, Geoffrey Clark of CDRH's Division of Small Manufacturers Assistance stated FDA's position that companies develop their own packaging test protocols based on the regulations appropriate for a given device (Henke and Reich, 1992). These regulations are found mainly in the 21 CFR and guidance documents published by CDHR. The information in these documents can be reduced to four basic principles for determining shelf life and consequent expiration dating:

- Determine an acceptable target expiration date based on R&D data, on the likely distribution and storage conditions that the product will encounter prior to its use, and on the company's marketing strategies.
- Select the parameters that will be tested.
- Conduct the testing under consistent procedures.
- Once all the testing has been completed, validate the test data (Henke and Reich, 1992).

Notice that these principles do not explicitly define the test parameters. However, the guidance documents developed by CDHR do provide accelerated aging protocols for specific devices within their jurisdiction based on the Q_{10} theory for chemical reactions. So, the theory postulated by Von't Hof using the Q_{10} value (which states that a rise in temperature of 10°C will double the rate of chemical reaction) is the most convenient method of estimating the approximate ambient storage time equivalent at a selected accelerated aging temperature, despite the known limitations and concerns for use on complex and dissimilar material structures.

For the example shown in the flowchart, using an accelerated aging temperature of 55°C, the equivalent ambient storage time for 1 year is 26 days. Caution must be taken not to accelerate the aging too much, since elevating the temperature of packaging materials could result in a mode of failure that might never be observed in real life (material/product interaction, creep, deformation, etc.) (Reich et al., 1988).

It appears that the protocol offered in this example, using the Q_{10} theory as a basis, is becoming a default model for establishing data for expiration date claims. Until industry devotes the time and effort involved in correlating real-time aging performance to simulated aging performance, it appears this is the best methodology available.

23.8.2 Distribution Simulation Stress Testing

The second phase of the package validation protocol is based on the accepted fact that sterile medical device packages do not typically lose their sterility simply by being stored on a shelf. Package failures are a result of a dynamic event that may have occurred during the manufacturing process, during shipping and handling to the sterilization facility, or during distribution to the point of end use. All of these processes may subject the finished package to dynamic events involving handling shocks, vibration, and, high and low temperature extremes. The GMP for Medical Devices Part 820.130 states, "the device package and any shipping container for a device shall be designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution."

23.32 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

There are optional methods available to satisfy this segment of the package validation process. First, the package could be tested by simply shipping it to a destination using the anticipated shipping mode (overnight parcel, common carrier, etc.). This method, although economical, does not lend itself to a high degree of control and repeatability. Alternatively, laboratory simulations provide a means of subjecting packages to the anticipated distribution hazards of shock, vibration, and dynamic compression in a controlled and repeatable manner. Observations of the package performance, as it is subjected to various hazards, can be accomplished in the laboratory and corrective action can be taken to alleviate any anticipated problems in a timely fashion.

ISO/DIS 11607, "Packaging for Terminally Sterilized Medical Devices," references the International Safe Transit Association (ISTA) Project 1A preshipment test procedure and ASTM D-4169, "Performance Testing of Shipping Containers and Systems." This author believes that the ASTM procedure provides a better simulation of the distribution environment since it sequences a number of distribution "elements" or tests that use realistic test intensity levels. The ASTM method also allows users who have significant knowledge of their distribution system to design a test sequence that more closely matches their own environment.

The most typical distribution simulation used for medical device package validation is Distribution Cycle 13, which is designed for packages weighing less than 100 pounds that are being transported by air and motor freight (by UPS, Fed Ex, etc.). This test "provides a uniform basis of evaluating in the laboratory, the ability of shipping units to withstand the distribution environment. This is accomplished by subjecting the packages to a test plan consisting of a sequence of anticipated hazard elements encountered in the chosen distribution environment" (ASTM D-4169). The preferred method for performing the vibration test in Element G, "Vehicle Vibration," is the random option, since it provides the most realistic simulation of actual transport vibration environments.

23.8.3 Package Integrity Evaluation

Of course, to simply subject a medical device package to extremes in temperature and humidity conditions for an extended period of time, and then to "shake, rattle and roll" them during transportation simulation does not indicate the package's ability to maintain its sterile barrier. Herein lies one of the most controversial and difficult tasks facing the packaging engineer. What tests to use to determine the sterility of the package—microbial challenge or physical test methods?

FDA inspectors, reviewers, and compliance staff are increasingly asking for (microbial barrier) data during routine facility inspections, and as part of product submissions. Also, draft international standards contain provisions for specific microbial-challenge test protocols (Henke and Reich, 1992). However, microbial challenge testing is time-consuming, labor intensive, and costly. Also the method most commonly used is difficult to adapt to the myriad of package sizes currently available in the medical device industry (Freiherr, 1994). An alternative validation method would involve the use of microbial challenge to assess the barrier properties of various packaging materials, but would use various forms of physical testing to evaluate the integrity of the package as a whole (Freiherr, 1994). The premise for this method is that if the materials provide an adequate barrier and the seals and the material components of the package are undamaged and intact, then the package as a whole will provide a barrier to infectious agents. Regulators have some difficulty accepting this premise, however, since physical testing can indicate sterility of the package only indirectly, as opposed to the certainty of a direct microbial indicator inside the package.

The packaging task force assembled by the Health Industry Manufacturers Association (HIMA) is working to evaluate whether physical test methods are, in fact, more sensitive and better indicators of package sterility. Critics (of microbial challenge testing) note that physical testing methods (e.g., visual seal examination, burst and creep testing, seal strength tests, dye penetration tests, and black light fluorescence examinations) are more repeatable, reliable, and controllable (Spitzley; 1993). ASTM has developed test methods for determining tensile strength of materials, peel test methods for evaluating the peelability of lid stock from trays or pouches, burst resistance tests, and leak tests. Attempts to correlate these test methods with microbial challenge results are ongoing; however, no

scientific evidence has been generated to date to substantiate the efficacy of one method over another. Some combination of physical and microbial test methods for both materials and whole packages appears to be the most advantageous program for meeting the expectations of regulators and fulfilling the corporate responsibility of ensuring the safety and effectiveness of its products.

23.8.4 Summary

It is now generally recognized that manufacturers must conduct all three types of tests—physical, transportation simulation, and microbial challenge—to validate packaging materials and processes (Henke and Reich, 1992). The protocol presented here offers the most comprehensive and justifiable methodologies, based on the published literature, for determining the effectiveness of a medical device package design to maintain its sterile condition from the point of sterilization to point of end use.

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23.34 DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

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