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QUALITY CONTROL OF PACKAGES FOR STERILE PRESENTATION

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ABSTRACT

Published commentary relating to various defects in package systems which are intended to maintain sterility of a product for presentation onto a sterile field is discussed. Specific areas of concern which may affect the sterility of the package are highlighted. Testing methods involving instrumentation to characterize material and intact package are presented.

INTRODUCTION

A number of packages designed to maintain sterility of a product, whether it is the primary package for a medical device or a secondary package for a pharmaceutical such as a parenteral product in a vial, have received considerable comment by some regulatory authorities. Much of the commentary has been related to package integrity. A breach of package integrity may result in contamination of a sterile product which counters the original intent of a sterile product.

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BACKGROUND

At a meeting of the Technical Association of the Pulp and Paper Industry, September 9-11, 1984[1], Virginia Ross, sterilization project officer of the FDA's Center for Device and Radiological Health stated that for the fiscal years 1980 to 1984, "47% of the sterility related recalls were the result of defects in packaging". As further indicated by Ross, of these recalls 31.4% were related to holes in the package and 26.3% to problems with seams or seals. In all 57.7% may be directly attributable to package integrity problems. In reviewing "The Gray Sheet" for 1985, these problems are continuing as evidenced by at least eight more recalls due to "defective seals which could compromise sterility".

These defects may possibly be traced to inadequacies in test procedures associated with these packaging systems. The Code of Federal Regulations, Title 21, Part 820.130, Current Good Manufacturing Practice for Medical Devices, Subpart G. Packaging and Label Control, 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". More appropriately, alteration and damage should be specified to include any defect which may result in non-sterile contents. There should also be a statement referencing the need for testing, similar to that as issued in the CFR, Title 21, Part 211.167, Current Good Manufacturing Practices for Finished Pharmaceuticals, Sub-part I - Laboratory Controls, Special Testing Requirements, "For each batch of drug product purporting to be sterile and/or pyrogen free, there shall be appropriate laboratory testing to determine conformance to such requirements".

The FDA does state in the Draft Guidelines for Packaging for Human Drugs and Biologicals that, "Appropriate laboratory examination should be conducted to assure that contamination with microorganisms will not occur through the container or closure". This can be interpreted to pertain only to product sterility integrity as related to primary packaging. It does not necessarily relate to sterility being maintained by secondary packaging. It also does not relate to the possibility of using physical tests correlated with microbiological tests to support package integrity. Therefore, it is necessary to define and standardize test procedures.

In this direction the Health Industry Manufacturers Association (HIMA) working with the FDA is expected to publish in 1986 a monograph which will offer guidance on requirements for validation, testing and process control of sterile product packaging. Also in conjunction with the FDA, the American Society for Testing and Materials and the Association of Official Analytical Chemists are developing specific physical and microbial packaging tests. It is anticipated that the availability of these test procedures will allow the industry to incorporate them as a basis for development.

Tests and associated protocols required to assure the integrity and quality of a sterile product package should be defined early in the development stages of the package design. Specific tests monitoring designated parameters need to be incorporated into all critical steps in the life of the package including manufacture, processing, shipping and storage. Therefore, quality control of a package system begins with the initial manufacturing of the materials (plastic films, paper, porous plastics, etc.) destined for the final package structure. At this stage of development, not only are physical parameters and formulation consistencies important, but

even more important, are factors (defects) which can adversely affect the integrity of the final package. Considerable time and money can be saved, if the appropriate testing is used in this initial stage of manufacture.

CAUSES OF DEFECTS

Defects, which can jeopardize integrity, in materials of this nature can be inherent to the methods of manufacture. These can be both repetitive and random. Because of the potential of random defects, materials designated for a sterile package should be statistically sampled and inspected for defects such as holes, tears or punctures which would adversely affect integrity. Currently at this stage of manufacture most standard procedures call for only random sampling for defect detection which is based on visual inspection procedures. The deficiencies of this are evident because of the level of acuteness of the human eye. The human eye can detect a hole of about 50 microns in diameter, whereas microbes can penetrate holes of less than 1 micron. Clearly in regard to the manufacture of materials designated for sterile packaging, instrumentation to supplement visual inspection as required.

During the fabrication stage of packages, additional tests should be performed. Regardless of the fabrication methods whether it consists of thermoforming or pouching with associated sealing and die cutting, the integrity of the package should be verified. Holes, for example, can easily be generated by such artifacts as burrs, sharp edges, or foreign materials during handling or processing. In the case of thermoforming, inappropriate heating parameters can cause an uneven flow of materials creating weak areas or holes in the formed component. Also critical are sealing operations during the initial fabrication and during final sealing of the product in the

package. Therefore, sealing parameters have to be established and proven for designated seal strengths. The importance of seal parameters is evidenced by the fact that the major cause of sterile package failure is seal integrity, visualized as partially or completely opened seals. Once again as demonstrated by these seal and material integrity concerns, defined tests and associated protocols are very important.

Regardless of the sterilization procedures used, the sterilization process in itself can adversely affect the integrity of the package. The presence of heat and/or moisture can in certain cases weaken the seal, creating a defective package. This is particularly important in processes involving the use of vacuum drying cycles, such as found in steam sterilization procedures. Unless care is taken, undesirable internal pressures can be generated in the package. If this occurs, the build-up of the pressure would happen when the package would be most vulnerable. This would be at a time when the high temperature environment resulting from autoclaving is still present, thus the adhesive could be in a temporary state of weakness at the moment the vacuum is pulled. If paper is a component of the package, it would also be in a weakened state because of the water present. Both could lead to a breach in the integrity of the package.

With ethylene oxide (EtO) sterilization there are several process factors which can adversely affect package integrity. As with autoclaving, but to a lesser degree with EtO, there are concerns with temperature, humidity and vacuum. More important are concerns of chemical compatibility associated with the sterilization process and the adhesive. An incompatibility can cause seals to weaken. Dr. Carl D. Marotta has published on this subject.[2,3]

Sterilization by ionizing radiation can also be detrimental to a package. Both gamma and electron beam irradiation can initiate chemical reactions leading to modifications in plastics and adhesives. It is important to note that the results of the chemical reactions may not be evident until later in the life of the package. The potential of this happening highlights the necessity to follow package integrity over time during developmental and shelf-life stages.

Shipping could be considered the next stage in the life of the package. Without a proper package, the product when subjected to the physical rigors of shipping will never reach its destination in its intended sterile state. It is necessary during the package developmental stage to design an appropriate package and document its effectiveness in remaining intact during shipping by performing statistically valid shipping tests incorporating appropriate integrity testing.

Because the physical and chemical properties of a package can change over time, it is important to document the ability of the package to maintain its integrity over the period of intended shelf-life. As pointed out for irradiation sterilization, this is particularly necessary when using processes that are known to be or have the potential of being detrimental to the materials used in the package. This is also desirable when storage conditions such as high temperatures and/or humidity or freezing are anticipated.

METHODS

As has been discussed, all stages in the life of the package and its associated processing and handling, can create situations in which package integrity can be affected with resulting loss of sterility. It is therefore

essential that a structurally sound package be used for these sterile presentations. To insure this, industrial standards should employ tests verifying integrity at all critical stages of manufacture. Similarly, parameters should be closely reviewed for the manufacture of films, papers or any materials that are to be used for fabrication of packages destined for sterile presentations. Identity tests such as infrared scans should be specified and documented. For porous materials, porosity ranges necessary for the intended sterile processing should be determined. Basis weight specifications for paper components should be defined. Visual inspection protocols need to be established for detection of holes, tears, and punctures, presence of coatings and for contamination such as dirt, grease, ink transfer, or excessive coating buildup. Physical dimension specifications and appropriate measurement protocols also need to be stated. All of these parameters and integrity testing are important to the fabrication of a package. This testing should be incorporated in the initial stages of manufacture. However, as previously indicated, the technology should be developed to achieve the desired objectives. Future applications involving laser technology as scanning devices have a strong potential to fulfill this need. Using these scanners in line in the manufacture of materials such as plastic films and medical grade paper, 100% inspection could be accomplished documenting the material quality.

In the manufacture of the package or the package fabrication, the designated materials are formed and/or joined by sealing, to structure the required configuration. As in the manufacture of the films and medical grade paper, visual inspection and checks on physical dimensions are critical. At this stage and in subsequent processing sequences, and in

shipping and shelf-life considerations, integrity testing is equally important. There are a number of test procedures that can be used to establish and document these aspects. Some involve simple in-house made devices while others involve sophisticated scientific instruments. All can be used to generate useful information. The more elaborate instruments are, as a rule, more sensitive and therefore more appropriate for documenting package integrity.

One means available for monitoring factors which may influence the integrity of the package is a non-porous package tester[4] designed to test closed package systems consisting of non-porous materials. This system consists of a transparent vacuum jar in which a controlled vacuum can be maintained. In operation the package is submerged in a suitable medium such as water and a vacuum is applied. Holes in the package are visibly detected by a stream of air bubbles. An excellent feature of this system is that leaks can be readily located which is important in diagnosing their cause. This system can also be used for testing packages having a porous lid or window. In this method petroleum jelly or an equivalent is used to coat the porous area sealing the package. It is important to realize that defects in the porous area may not be detected if this method is used because the coating material could seal small holes. To increase the efficiency of this method a larger test chamber can be built for testing several packages at once. The chamber should be designed so that packages can be individually inspected during the test.

Another system[4] for leak detection is an adaptation of equipment used for seal strength monitoring. This system which pneumatically verifies open and closed package seal strength consists of a pressure control unit in line

with an air pressure source and either an open or a closed package test device. The control unit regulates and monitors the pneumatic pressure being applied to the package under test. The open package tester is used to test pouches sealed on three sides. In operation, the open end of the pouch is placed between rubber retaining bars which effectively seals the opening thereby allowing a positive pressure to be applied to the package. The closed package tester is used to test rigid containers or packages sealed on all sides. This instrument incorporates a needle system for penetration of the package to maintain internal pressure. For integrity testing an electrical vaporization chamber is connected in line with the air flow of the tester. Pellets of Vapel^{TM} (ARO Corporation, Buffalo, NY) are vaporized in the chamber to produce a colored vapor. The package being tested is pressurized with the colored vapor, which accumulates and causes a discoloration at the exact location of a leak. This system is potentially more sensitive than the submersion method. However the detection of small pinholes can be very difficult on a routine basis due to human vision limitations. This method is a destructive method whereas non-porous packages tested by submersion can be reclaimed.

Dye tests which are commonly used have a low measure of sensitivity. These methods are routinely used by a number of companies for quality control during fabrication of packages, particularly pouches. It involves introducing a dye solution into the pouch which has been randomly sampled, hanging it for a period of time and inspecting for penetration of the dye through the seals or walls. A variation of this method can be used for final 100% inspection of non-porous packages, both flexible and rigid. In this method, large pressure chambers can be filled with the packages to be

tested and covered with the dye solution. An ampule dye test chamber can be utilized with only minor modifications for this procedure. It is desirable to use additives such as alcohol or surfactants to increase sensitivity by reducing surface tension. The sensitivity can also be increased by alternately pulsing the chamber with a slight pressure, then with a slight vacuum. This will not only increase the sensitivity but will reduce test time. With this method holes or seal channeling are readily visible by the presence of dye residue inside the package, even after rinsing and drying the outside surface. However, it can be difficult to determine the exact location of the leak.

An alternative test method employed is the carbon dust chamber. In this procedure the package is placed in a closed chamber which contains carbon dust. The package is subjected to the dust circulated by a fan. At the end of a predetermined stress period the inside of the package is visually examined for carbon particles. The sensitivity of this method is limited to the ability of the dust to penetrate pinholes and the ability to visually detect the carbon particles.

A system has been introduced recently for non-destructive leak detection of packages. This system[5] has the potential of providing the most sensitive of all leak detection procedures available to date. The manufacturer claims that under the right circumstances holes of one micron in size can be detected.

The system operates by detecting small amounts of a gas such as carbon dioxide as it escapes through pinholes or cracks in the package. The package headspace must contain a detectable gas at concentration levels that can be sensed against ambient background levels. Gaseous carbon

dioxide, if not a natural by-product of the manufacturing process, may be introduced as a flushing gas prior to applying the final package seal or by introducing it into a leaking package by pressurization in a 100% carbon dioxide environment. The package is then placed into a test fixture and a partial vacuum is applied thus drawing the carbon dioxide inside the package out through any holes. If the concentration of carbon dioxide in the test chamber outside the package exceeds that of normal atmospheric conditions, an infrared detector generates an audible signal indicating a failure.

The instrument is most sensitive when the carbon dioxide has been introduced into the package during manufacture. Forcing the carbon dioxide into the package after sealing, especially thru pinholes or small channels in the seals, is very difficult. To accomplish this, pressurizing over long periods of time, even when pulsing the pressure, is required. The physical characteristics of the package and/or the hole itself can prevent insufficient flow of the detection gas into the package under pressurization. For example, in a pouch, the hole in one side, under pressurization, could be forced against the opposite side thus sealing the hole, retarding or actually preventing gas flow. The potential of this happening is much greater in areas near the seals in pouches. Another disadvantage of this system is its failure to indicate the location of the leak which is critical to diagnosing the leak cause.

Other than sensitivity, the system offers a significant advantage in its ability to be automated for 100% inspection. The equipment can be modified to incorporate a turntable feature which has several test chambers. The test equipment can be positioned in line in the packaging

operation for 100% integrity evaluation before final packing into cartons or shippers.

All packages designed for sterile presentations involve seals. They can be permanent or peelable or a combination of both. Seals of appropriate strength are necessary to maintain package integrity through processing, shipping and storage. In the case of peelable seals, they must also remain functional throughout the life of the package. Care should therefore be taken in the initial design of the package to establish parameters required to produce a seal to withstand any conditions the package may encounter.

An extremely useful instrument[6] in setting these parameters is a highly sensitive, electronic weighing system with load cells that use strain gauges for detecting and recording tensile or compression loads. To determine the sealing parameters necessary to obtain a specific seal strength, one inch strips of the proposed materials are sealed over a range of testing conditions. These strips are then tested with the instrument fitted with a tension load cell to determine which sealing parameters give the desired seal strength. This equipment can then be used to follow the seal quality throughout the life of the package. This can be accomplished using either the one inch strip or the complete package. Testing the package to obtain a profile for the entire peelable seal is preferred. Using a one inch piece of the seal obviously does not prevent overlooking an isolated weak area.

Once the seal strength has been determined an adaptation of the open and closed package test system previously described can be used to monitor its integrity. This can be accomplished in either of two ways: firstly, determining the seal burst strength by applying constantly increasing

internal pressure until there is a seal rupture; secondly, by determining the ability of the seal to withstand a constant internal pressure over a period of time.

SUMMARY

This presentation has been made to stress the importance of an effective testing program for package manufacture and for successful processing and distribution of a package intended for deposition onto a sterile field. As discussed, considerable comment has been published questioning the package sterility because of package failure. A program using the suggested equipment would play a vital role in producing an acceptable product. To guide companies marketing products of this nature in fulfilling the responsibilities of producing a sterile package, industrial standards need to be clearly defined. By applying modern technology we can gain a better understanding of the nature and extent of package defects. The increasing popularity of sterile packaging will be developed with clearer characterization of packaging materials and test methods resulting in an acceptable package system.

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