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The Effect of accelerated aging on peelable medical products seals

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THE EFFECT OF ACCELERATED AGING ON PEELABLE MEDICAL PRODUCTS SEALS

BY

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M.S. Degree

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INTRODUCTION

By the end of 1993 the nations of Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, the Netherlands, Portugal, and the United Kingdom will have completed the formation of a united trading block known as the European Community (EC). The formation of the EC allows the member nations to remain competitive in a global market place where many of their individual economies could not.

Foundations for the EC had been laid down over 30 years ago with the treaty of Rome. The Treaty of Rome established a customs union and required the elimination of quantitative restrictions and all measures designed to protect domestic markets from foreign competition. However, internal and external forces like unemployment and increased import competition perpetuated a protectionist climate that effectively stifled the momentum towards further integration. By the early 1980's it was apparent that protectionist measures were ineffective. New momentum toward further integration and cooperation among member nations was growing.[1]

A 1985 paper entitled "Completing the Internal Market" outlined a detailed plan for further European integration. The paper included about 300 specific measures aimed at the removal of all obstacles to the free movement of goods,

people, services and capital by December of 1992.[2] With the ratification of these measures by the member nations, a $4.6 trillion market will emerge operating on one set of rules.

Within the total EC market, the medical device industry accounted for approximately $7.4 billion in 1987, and this segment continues to grow. Eighty percent of United States medical device exports to the EC were received by five member nations throughout 1987 and 1988 (Germany 25%, France 16%, the UK 16%, the Netherlands 15%, and Italy 10%). Including both exports and production by US subsidiaries based in the EC, the United States holds over 50% of the EC market share for medical devices.[3]

EC markets are most commonly regulated by EC directives. These directives outline all aspects of the manufacture, labeling, distribution and sale of goods in the EC. The complexity of these guidelines varies with each industry. It is section 14.1 of the EC Council Directive of June 20 1990, Number L189/23 for the medical device industry on which this study focuses. Section 14.1 outlines the labeling procedure for sterile medical device packages. What is important about section 14.1 is its inclusion of an <u>expiration dating clause</u>. This is a new consideration for device manufacturers and most are generating shelf life data for the first time. The

question is, are peelable device package seals effected by age, and if so to what extent?

The paramount concern for the medical device industry is the maintenance of sterility. The integrity of medical device packaging can be compromised in a number of ways, among them are "pinholes" (tiny voids in the packaging materials or seal area large enough to allow the penetration of micro organisms into the package), damage to the package, and ineffective seals. "According to the FDA reports approximately 30% of all sterility related medical device recalls in the fiscal year 1985 were for packaging defects, usually involving seal integrity."[4] Typically package seals are either manufactured improperly or damaged through stresses incurred after the manufacturing process. One of these manufacturing stresses may even be the sterilization process itself, where gas sterilization is employed. Sterilizing gas, most commonly ethylene oxide, is forced with positive pressure into the package through a micro-porous vent in the package. The gas is then drawn out of the package by vacuum. In his article "Seal Fatigue in ETO Sterilization", Carl Moarotta discusses the process factors and material variables present in ETO sterilization that can lead to partial or complete separation of package seals. The process factors alone or in combination that contribute to seal degradation are: temperature,

prehumidification, the rate of pressurization and degassing, length of the cycle, and sterilization gas mixture. The most important of these process factors is the rate of pressurization and vacuum degassing. If the rate of pressurization or vacuum degassing is too rapid, stress will be exerted on the package seal area as the sterilization gas is forced into or drawn out of the package. The stress created can damage or completely rupture package seals. This can be avoided through proper design of the sterilization cycle to include gradual pressurization and vacuum degassing. The material variables include: chemical compatibility, sensitivity to moisture, reactivity to sterilizer gasses, hot strength, and plastic flow. In order to minimize seal fatigue these variables are considered and materials are selected for their compatibility with each other and the sterilization cycle . For example, high porosity can be used to compensate for poor hot strength by increasing gas flow and reducing pressure induced stresses Likewise a high hot strength adhesive can be used to compensate where a less porous material is required. Through evaluation of the sterilization procedure and material selection, the phenomena of seal fatigue is minimized.[5]

The polymer EVA (ethyl vinyl acetate) is commonly used to create a peelable seal. EVA is ideal because it has

enough cohesive force to maintain package integrity while remaining peelable, creating an easy opening feature for the product user. The incorporation of easy open features is more than a convenience. Features like peelable seals help to minimize the potential for cross contamination that could be introduced by difficult opening operations, the use of tools or improper handling. EVA also has the added advantages of peeling cleanly so that particulate contamination is greatly reduced and is compatible with both gas and radiation sterilization.

The Code of Federal Regulations or CFR under Title 21, subpart G contains regulations pertaining to packaging and labeling of medical devices. The CFR specifies in general terms how device labeling is to be handled. Section (e) of subpart G in the CFR, entitled "Labeling Materials" states, "Labeling materials issued for devices shall be examined for identity and where applicable, the correct expiration date, control number, storage instructions, handling instructions, and additional processing instructions. A record of such examination, including the date and person performing the examination, shall be maintained in the device history record."[6] The key phrase is "where applicable", the inclusion of an expiration date is left to the discretion of the manufacturer where there is no regulatory precedent.

In order to meet the regulations of the CFR, American medical device manufacturers operate according to good manufacturing practices or GMP's which are monitored by the Food and Drug Administration (FDA). The system focuses on total quality assurance in the manufacture, handling and packaging of products to insure the manufacture of a reliable sterile device. Under the GMP system the quality and reliability of a device is understood or implied. This differs from the EC system where the directives for the device industry call on the manufacturers to make specific statements about the devices application limitations and sterility. This European method is illustrated in section 14.1 of Council Directive of June 20 1990, No L 189/23, the sterile device must be marked with:

- the method of sterilization,
- an indication permitting this package to be recognized as such,
- the name and address of the manufacturer,
- a description of the device,
- if the device is intended for clinical investigations, the words: "exclusively for clinical investigations",
- if the device is custom-made, the words: "custom-made device",

- a declaration that the implantable device is in sterile condition,
- the month and year of manufacture,
- an indication of the time limit for implanting the device safely.[7]

Essentially what this means is that the EC is placing the burden of liability for the device on the manufacturer. In fact, most of this is not new, device manufacturers have previously been providing the bulk of this information. What is new about this EC Directive is the inclusion of a shelf life by expiration dating for all device packaging and its impact on the medical device industry. It is uncommon for device manufacturers to include expiration dates because they are not required by the CFR. Those manufacturers interested in the European market are now in the process of generating shelf life data for the first time, as a consequence of the new EC regulations.

Real time aging studies would certainly offer the best documentation for any expiration date claims made by device manufacturers. However, considering the time required to generate real time data, manufacturers are turning to accelerated age studies to support expiration date claims.

The concept of accelerated aging was first used in the chemical industry to explore the degradation of chemical compounds and was later applied to the pharmaceutical

industry as a tool to predict the shelf life of drug compounds. Accelerated aging works on the principle of kinetics. As the temperature increases the rate of chemical reactions increase. The rate of increase is linear therefore a direct relationship between temperature and the rate the chemical reactions can be established. This concept is more thoroughly addressed under the "SAMPLE PREPARATION" section.

Overall, the formation of the EC is a positive development for American device manufacturers marketing their products in Europe. While short term, device manufacturers are forced to meet the new EC directives, in the long run they can look forward to more efficient manufacturing and packaging brought about by the European standardization.

OBJECTIVE

This study addresses the question of the effects of accelerated aging on peelable medical device package seals. The effects of aging on device seals is a previously unexplored area. With the formation of the EC and more specifically its requirement for expiration dating the sterility of a device package, seal integrity over time becomes an important consideration.

HYPOTHESIS: Post sterilization seal strength does not degrade over time.

To test this hypothesis the seal area of device packages that had been subjected to an accelerated aging cycle were compared to a control group of new device packages of the same size and style. The seal area of both groups tested, i.e. new packages and aged packages, were isolated by sealing the porous side of the package. A burst tester was used to determine the seal strength of both groups and the results of the testing were compared for variation.

METHODOLOGY

The seal strength of a package can be evaluated in a number of ways. Methods commonly employed are vacuum testing, tensile testing and burst testing. However each test method has its advantages and short comings.

VACUUM TESTING:

Vacuum testing uses a submersion chamber in which the package is placed. Subsequently a vacuum is drawn on the chamber causing the trapped air in the package to expand. If the vacuum is increased, the seal area of the package will eventually rupture. Vacuum testing has the advantage of making the detection of pinholes easy. Pinholes are voids in the package material or the seal area large enough to allow the entry of micro organisms, compromising sterility. Vacuum testing also has the advantage of locating voids in the seal area of a package that would be difficult or impossible to detect with manual inspection. Vacuum testing is an excellent means to identify sealing problems by showing where the weak or defective portion is located so that equipment adjustments can be made. However submersion of a package in order to vacuum test is not practical when a material like paper or TYVEK^{R} is used. Air can escape through the porous material instead of exerting force on the seal area confounding the results. A second

problem is the saturation of the package material, i.e. medical grade paper, when submerged. This reduces the strength of the paper enough to create material failures rather than the desired seal failure.

TENSILE TESTING:

Tensile testing consists of cutting standard width one inch samples of the seal area from various locations of the package. These samples are then tested for pull strength on a tensile tester. The values may be averaged to determine the seal strength of the package. Tensile testing can be employed with a paper or TYVEK^{R} sided pouch but is not an effective means of testing the entire seal area intact. This may lead to inadvertent omission of a poorly sealed area in the package. In addition tensile testing is labor intensive and handling of samples introduces a large potential for human error. The test samples can be damaged during cutting procedures or when placed in the jaws of the tensile tester. If the sample is not properly aligned in the jaws of the tensile tester inaccurate results are also likely to occur.

BURST TESTING:

Burst testing injects air into a sealed package at a controlled rate. The backpressure developed inside the package is measured by a sensitive gauge or sensor within the burst test unit. Typically the burst test units hold

the highest internal pressure reading measured by the sensor prior to seal failure giving the seal strength of the package. Although burst testing can not detect pinholes, it does have the advantage of testing the entire seal area intact while maintaining dry test conditions making it suitable for moisture sensitive package materials like medical grade paper.

EQUIPMENT

Burst testing was the test method selected because the seal area could be tested in its entirety, under dry conditions (both requirements of the packages provided for testing). Modern Controls Inc. agreed to provide the burst test apparatus for the evaluation, a MOCON Skye unit, model number 1520S.

SAMPLE PREPARATION

In the interest of isolating the seal area of the packages and eliminating any potential variability in the porosity of the package, the paper backing of the pouches was sealed with 0.08 mm pressure sensitive case packing tape. Special care was taken during this procedure to insure that the seal area was not stressed. This effectively eliminated the escape of air through the paper side of the pouch. Sealing the porous side of the package also allowed for a slower pressure increase rate. The slower pressure increase rate decreased the likelihood of "shocking" the package seals (a reduction of seal strength brought about by rapid inflation of the package).

The test packages and the accelerated aging cycle used for the study came from ETHOX CORPORATION. The concept of accelerated aging schemes applied to medical device packaging is borrowed from the test methods used in the pharmaceutical and chemical industries. The theory behind it is based on using a thermodynamic temperature coefficient. "A rule that was first formulated by Von't Hoff states that a rise in temperature of $10^{o}C$ will double the rate of a chemical reaction. This rule is usually expressed as a Q_{10} value i.e., the ratio of the rate of reaction at two temperatures $10^{o}C$ apart. If the

rate of the reaction is doubled, then $Q_{10} = 2$. This is also the most common approach used in the medical device industry for conducting packaging studies. It is generally extrapolated as indicated in the following example:

> If $Q_{10} = 2$ and the accelerated aging temperature = 71°C (160°F), or 55°C over ambient temperatures, then the aging factor is $2^{5.5}$, or 45 times. Therefore, 52 weeks/45 = 1.1 week, or approximately 1 week at 71°C (160°F) is equivalent to 1 year at ambient temperature conditions."[8]

It is important to realize that the $Q_{10} = 2$ principle is not linear and the Q_{10} value at higher temperatures gradually drops off to a $Q_{10} = 1$ or lower. This is recognized by the federal standards which set 71°C as the maximum temperature for accelerated testing of packaging materials. Few device packages are composed of a single material, therefore in order to simplify the equation and make it more manageable, the $Q_{10} = 2$ principle also assumes a single reaction rate for a package. In fact a package composed of more than one material is likely to have different reaction rates acting on the different materials. This may lead to different modes of failure that might not occur with real time aging studies. Therefore it is important to realize individual reaction rates occurring in a given package, and approximately select a test temperature that will not create unrealistic circumstances for that given package.[9]

Environmental conditions should also be taken into consideration in designing an appropriate accelerated aging scheme. Both relative humidity (high and low) and low temperatures have been shown to contribute to package failure. Changes in humidity will cause fluctuations in the moisture content of paper products effecting their strength. Likewise plastic packaging's material properties are altered under cold conditions. Low temperatures can reduce flexibility of films and under extreme conditions make them brittle. Therefore a well thought out sequence should include periods of high and low humidities as well as a period of cold storage. Some or all of these conditions will be encountered during distribution both domestically and overseas.

The aged packages used in this study were exposed to 130^{o}F @ 70% RH for eight weeks, frozen to 0^{o}F for 24 hours, thawed to ambient temperature for an additional 24 hours, and then exposed to 130^{o}F @ less than 15% RH for another eight weeks to achieve an equivalent to four years real time as shown in the following calculation:

ACCELERATED TEMP. $130^{o}F = 54.4^{o}C$
AMBIENT TEMP. $62^{o}F = 16.7^{o}C$

$54.4^{o}C - 16.7^{o}C = 37.7^{o}C$

$37.7^{o}C / 10 = 3.7$

THE AGING FACTOR IS $2^{3.7}$ OR 13 TIMES THE AMBIENT RATE.
52 WEEKS / 13 = 4 WEEKS.
THEREFORE: 4 WEEKS @ $130^{o}F$ IS EQUIVALENT TO 1 YEAR @ AMBIENT TEMPERATURE CONDITIONS ($62^{o}F$).

The packages were tested on the closed package tester (provided with the burst test unit from Modern Controls Inc.) which allowed for unsupported testing of the package. Thus preventing the possibility of any undue force being applied to the seal area of the specimen.

Both groups of packages tested were manufactured to identical specifications. The packages were vented pouches intended for ETO sterilization, with a clear film side for identification of the product and EVA coated medical grade paper on the opposite side (SEE fig. 1 for dimensions).

ETHOX
SK 150 FOUR POCKET
INSTRUMENT HOLDER POUCH

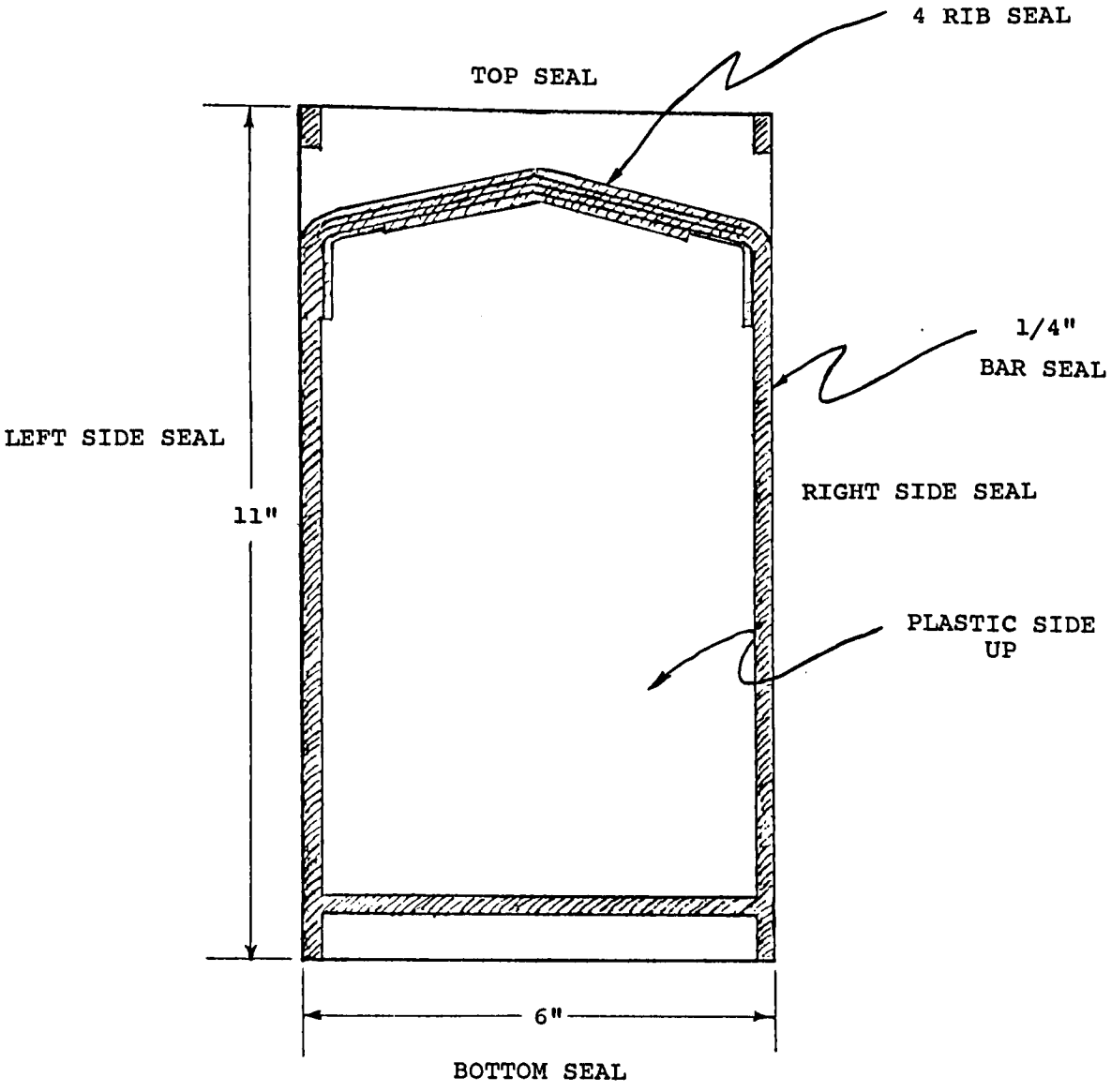


FIG. 1

PROCEDURE

1. The inflation rate of 5 psi/min was selected and set on the equipment. A slow inflation rate is used so that the seal area was not "shocked" or weakened during the preinflation of the test package.
2. Clear case sealing tape was applied to the paper side of the pouch. Care was taken so that the seal area was not damaged and only the porous areas were covered.
3. A hole approximately 2mm in diameter was made in the center of the film side of the pouch.
4. An adhesive backed rubber septum (provided by MOCON for use with the Skye burst test unit) was applied over the hole in the film side of the pouch. NOTE: Care was taken to be certain that the hole in the septum is centered over the hole in the package to insure unrestricted air flow.
5. The needle of the closed package tester was inserted into the hole in the septum.
6. The test cycle was initiated by depressing the start button on the burst test unit.
7. The psi burst test value displayed on the burst test console was recorded following the rupture of the package seal.

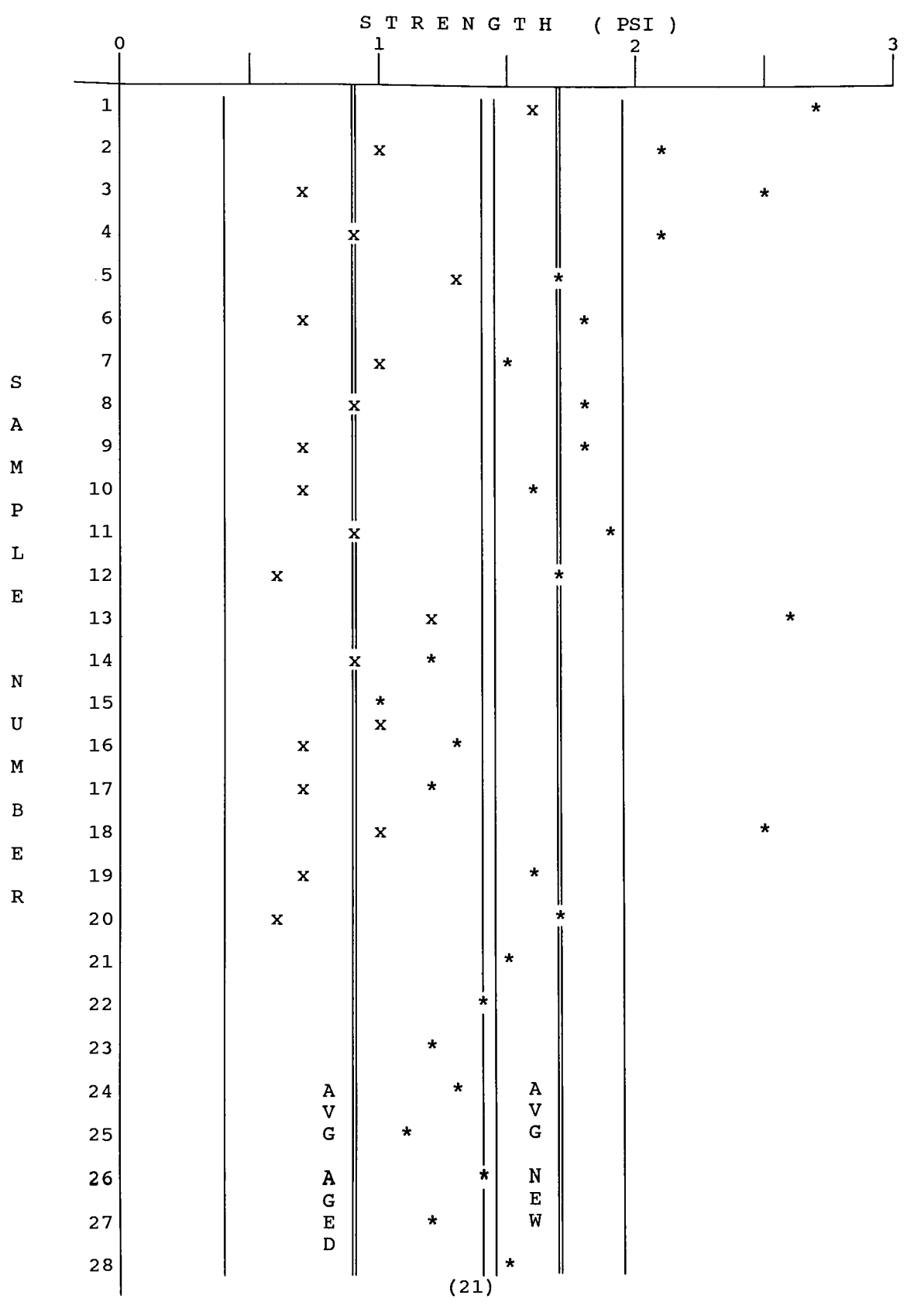
DATA SUMMARY

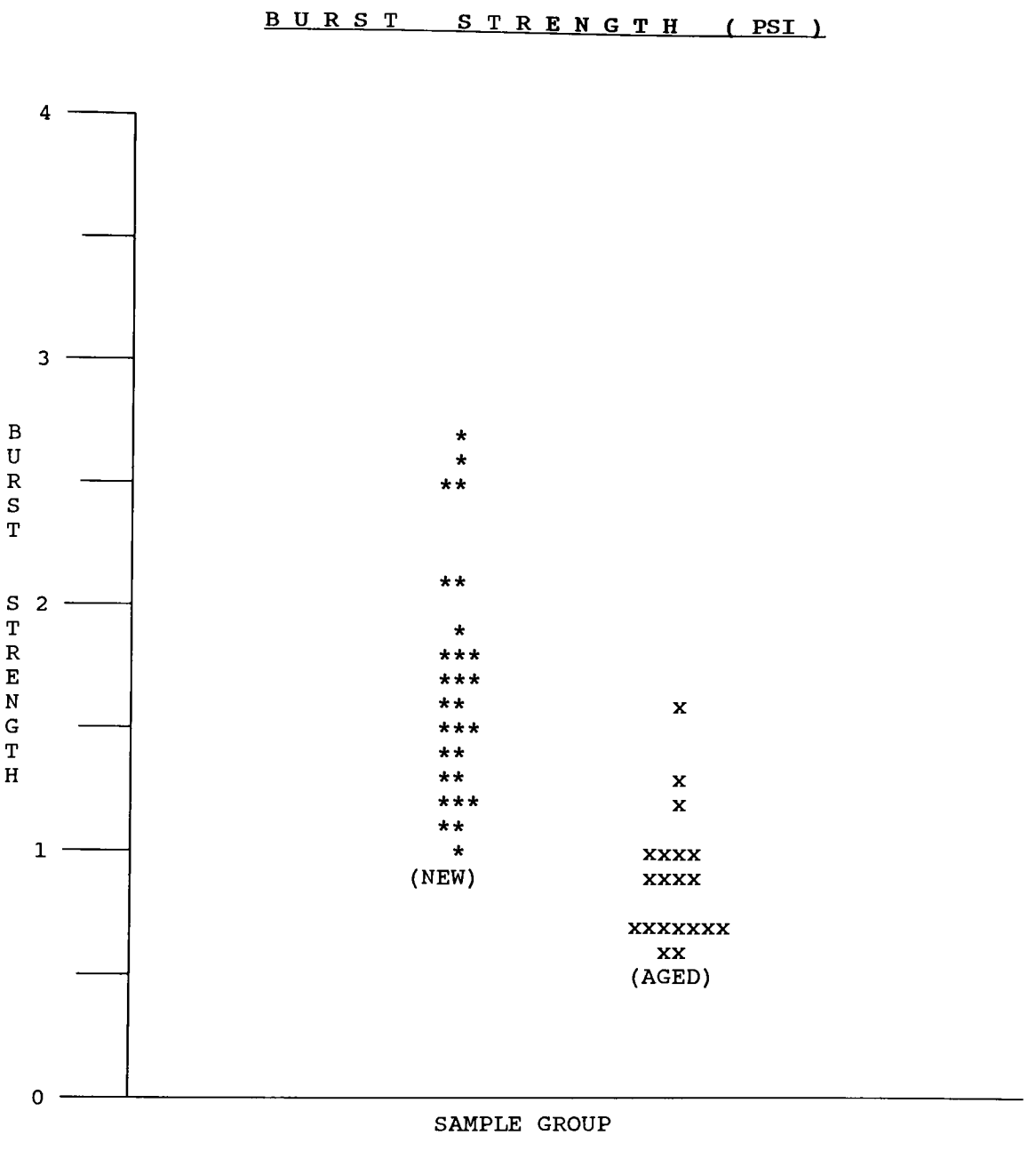
The first column "sample #" indicates the number of the sample tested. The second column "burst value (PSI)" indicates the internal package pressure at seal failure. The third column "location" indicates where on the package the seal failure occurred.

LOTUS 123 spreadsheet software was used to create the data tables listing all samples tested in each population (new and accelerated aged packages) and generate the population mean, min, max, range and standard deviation.

The new package population had a mean burst value of 1.7 psi, with a 2.7 psi maximum value and a 1.0 psi minimum value creating a range of 1.7 psi with a standard deviation of 0.5. Seal failures on each package tested occurred along one of the side package seals with 36% on the left side seal and 64% on the right side seal.

The aged package population had a mean burst value of 0.9 psi, with a 1.6 psi maximum value and a 0.6 psi minimum value creating a range of 1.0 psi with a standard deviation of 0.2. As with the new package population, the aged package population seal failures occurred along one of the side seals, 50% along the right and 50% along the left.


STRENGTH (PSI)
0
1
2
3
SAMPLE NUMBER
AVG AGED
AVG NEW
(21)


BURST STRENGTH (PSI)
4
3
2
1
0
BURST STRENGTH
*
*
**
**
*
***
***
**
***
**
**
***
**
*
(NEW)
x
x
x
xxxx
xxxx
xxxxxxx
xx
(AGED)
SAMPLE GROUP

DATA

ETHOX SURGI-KIT P/N 150 Four Pocket Instrument Holder
New Packages:

SAMPLE #	BURST VALUE (PSI)	LOCATION
1	2.7	LEFT SIDE
2	2.1	RIGHT SIDE
3	2.5	RIGHT SIDE
4	2.1	RIGHT SIDE
5	1.7	LEFT SIDE
6	1.8	LEFT SIDE
7	1.5	RIGHT SIDE
8	1.8	RIGHT SIDE
9	1.8	RIGHT SIDE
10	1.6	RIGHT SIDE
11	1.9	RIGHT SIDE
12	1.7	LEFT SIDE
13	2.6	LEFT SIDE
14	1.2	RIGHT SIDE
15	1.0	RIGHT SIDE
16	1.3	LEFT SIDE
17	1.2	LEFT SIDE
18	2.5	RIGHT SIDE
19	1.6	RIGHT SIDE
20	1.7	RIGHT SIDE
21	1.5	LEFT SIDE
22	1.4	RIGHT SIDE
23	1.2	RIGHT SIDE
24	1.3	RIGHT SIDE
25	1.1	LEFT SIDE
26	1.4	RIGHT SIDE
27	1.2	RIGHT SIDE
28	1.5	LEFT SIDE
AVERAGE	1.7	
MAXIMUM	2.7	
MINIMUM	1.0	
RANGE	1.7	
STD DEV	0.5	

LEFT SEAL FAILURES 10 (36%)
RIGHT SEAL FAILURES 18 (64%)

DATA

ETHOX SURGI-KIT P/N 150 Four Pocket Instrument Holder
Accelerated Aged Packages:

SAMPLE #	BURST VALUE (PSI)	LOCATION
1	1.6	LEFT SIDE
2	1.0	LEFT SIDE
3	0.7	LEFT SIDE
4	0.9	RIGHT SIDE
5	1.3	RIGHT SIDE
6	0.7	LEFT SIDE
7	1.0	RIGHT SIDE
8	0.9	RIGHT SIDE
9	0.7	LEFT SIDE
10	0.7	LEFT SIDE
11	0.9	RIGHT SIDE
12	0.6	LEFT SIDE
13	1.2	LEFT SIDE
14	0.9	LEFT SIDE
15	1.0	RIGHT SIDE
16	0.7	LEFT SIDE
17	0.7	RIGHT SIDE
18	1.0	RIGHT SIDE
19	0.7	RIGHT SIDE
20	0.6	RIGHT SIDE
AVERAGE	0.9	
MAXIMUM	1.6	
MINIMUM	0.6	
RANGE	1.0	
STD DEV	0.2	

LEFT SEAL FAILURES	10 (50%)
RIGHT SEAL FAILURES	10 (50%)

STATISTICAL ANALYSIS SUMMARY

The statistical analysis was performed on MINITAB statistical software. Data was entered and manipulated with the appropriate MINITAB commands to determine sample size, mean, median, standard deviation, minimum, maximum and quartiles one and three. A two sample T test with a 95% confidence interval was performed to test the validity of the hypothesis "Post sterilization seal strength does not degrade with time" with the null hypothesis "MU new = MU aged". The T test generated a T value of 7.44 and a P value of 0.0000 with 43 degrees of freedom. The 0.0000 P value indicates 0 probability that the null hypothesis is correct. Therefore, the samples represent separate populations.

MINITAB ANALYSIS

```
COLUMN          NAME          COUNT
C1              NEW              28
C2              AGED             20

CONSTANTS USED: NONE

MTB > DESCRIBE C1 C2

                    N       MEAN    MEDIAN    TRMEAN       STDEV
SEMEAN
NEW                28     1.6750    1.6000    1.6615      0.4695
0.0887
AGED               20     0.8900    0.9000    0.8667      0.2553
0.0571

                  MIN        MAX         Q1        Q3
NEW            1.0000     2.7000     1.3000    1.8750
AGED           0.6000     1.6000     0.7000    1.0000

MTB > TWOSAMPLE T C1 C2;
SUBC> ALTE +1.

TWOSAMPLE T FOR NEW VS AGED
        N       MEAN      STDEV     SE MEAN
NEW    28      1.675      0.470       0.089
AGED   20      0.890      0.255       0.057

95 PCT CI FOR MU NEW - MU AGED: (0.572, 0.998)

TTEST MU NEW = MU AGED (VS GT): T= 7.44  P=0.0000  DF=  43
```

POTENTIAL SOURCES OF ERROR

It important to consider the reliability of the data and where potential sources of error lie. This conclusion is based on a small sample population and although it appears to support a conclusion, a much stronger statement could be made with a larger test population.

The aging cycle used in this study may have had some impact on the results through over drying the paper beyond ambient conditions. Over drying should be considered as a potential contributor to the reduced seal strength.

Other potential sources of error exist in how the testing is performed. In order to generate comparable data sample preparation and test procedures must be identical.

Equipment is another area that must be considered. For instance, has the equipment been calibrated. Another equipment consideration, has the equipment been set up and operated properly.

RECOMMENDATIONS FOR FURTHER STUDY

It is possible to draw inaccurate conclusions about a population with too small a sample. As a next step to confirm this studies conclusions, this study could be repeated with an increased sample size. The larger samples would provide stronger data, lending greater statistical validity to the conclusion that seal strength decreases over time.

It should also be recognized that even though an accelerated aging regime is designed to mimic the effects of real time aging, stresses exerted on the package during the accelerated aging cycle may produce a result that differs from that observed with real time aging. Next steps should include a study of real time aged packages vs new packages to confirm the findings of this study.

One question that has come out of this study is the progression of the degradation. to address this a next step could be additional burst testing to determine the rate of seal degradation. New vs aged packages, aged to: one year, two years, three years, four years.

Variability of materials and the impact of aging on those materials could be addressed with additional burst testing of aged TYVEK^{R} vs aged medical grade paper to determine if seal integrity can be optimized.

CONCLUSION

Based on the statistical analysis we see two distinct populations indicating that accelerated aging has created a reduction of seal strength. Looking at the average burst strengths of new vs aged packages a 47% reduction in seal strength was observed. This information is significant because these packages have been thought of as static, remaining unchanged over time. Here we see this is not the case. These packages are dynamic and this could impact the sterile barrier of a package. However this information alone is of no value. The change must be put into context. Is the seal strength of the aged packages sufficient to maintain package integrity?

It is unreasonable to think that the loss of seal strength has occurred all at once. More likely the loss of seal strength is gradual. This is significant when we look at the demands placed on the sterile barrier of the package. Where do the greatest stresses to the package occur? The sterilization process and the distribution environment are where the greatest demands are placed on the package.

The packaging of sterile devices is performed under conditions that keep the initial bioburden to a minimum.

This in turn reduces the demands on the sterilization cycle. For this reason sterilization is performed shortly after the packing operation when the bioburden is at its lowest. It is at this time that the seals are at their optimum strength. Degradation due to aging will have no impact at the time of sterilization. Distribution is also likely to occur relatively early in the life of the package

The distribution cycle is the place where any product is most susceptible to damage. The risk to the package in distribution varies with the type of handling and how the product is shipped. Manual handling and mixed shipments will produce higher levels of stress to a package and are common in the wholesale distribution of medical products. Distribution from the manufacturer to the wholesaler and the wholesaler to the end user will occur within a year for most products. Assuming that the degradation of the seal strength is linear, the impact of distribution at this stage of the packages life is minimal given the distribution packaging has been properly designed.

Package material selection probably has an impact on the degradation of seal strength. The packages tested were heat sealed pouches manufactured from an EVA zone coated medical grade paper and "plastic" film. The film side of the pouch does not experience fluctuations in its material properties due to humidity. The paper side of the pouch

was selected to provide the porosity required for ETO sterilization. However paper is very susceptible to changes in its material properties due to the humidity of the surrounding environment and naturally dries with age. This moisture loss of the paper probably contributed to the reduction in seal strength.

A vented pouch manufactured with TYVEK^{R} rather than medical grade paper would provide the required porosity without material fluctuations induced by environmental factors. Seal strength does appear to degrade over time. Therefore shelf life regulations for medical product packaging is not an unreasonable regulation. This study demonstrates that it is possible to quantify the loss in strength and identify a point where the stresses placed on the package may compromise the sterility of the product. Through proper material selection and testing packagers can optimize the shelf life of a sterile product. With an understanding of the package's life cycle, the shelf life of the package can be identified to meet the EC directive.

FOOTNOTES:

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