This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

GRZAN

SHELF LIFE OF MEDICAL DEVICES

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NOTE: The excerpts of documents included throughout this paper have been edited.

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INTRODUCTION

The potential benefit from the use of a medical device ranges from relieving minor irritations to correcting life threatening conditions. If the device design and manufacturing processes are done adequately, there is a high probability that the device will perform as desired at the time it is manufactured. However, there are many naturally occurring factors that can affect how long after manufacturing the device will maintain the ability to fully perform the intended function.

Shelf life is the term or period during which a commodity remains suitable for the intended use. An expiration date is the termination of shelf life, after which a percentage of the commodity, e.g., medical devices, may no longer function as intended. To determine if a particular device requires a shelf life and assign an expiration date, there are a number of different parameters that must be considered. The device must be analyzed to determine if it is susceptible to degradation that would lead to functional failure and the level of risk that the failure would present. For some devices, e.g., tongue depressors, it is not reasonable to assign a shelf life because of the small likelihood of time-dependant product degradation and the lack of serious consequences if it did fail to perform as designed. For certain devices susceptible to degradation that are intended to treat life-threatening conditions, e.g., pacemakers, the failure rate should approach zero within the labeled shelf life.

The purpose of this document is to:

- inform readers of the Food and Drug Administration (FDA) regulations and policies relating to shelf life of medical devices.
- discuss the various parameters that determine the length of time a particular device will remain within acceptable specifications;
- outline the different activities that can be undertaken to establish the shelf life of a device; and

STABILITY CRITERIA AND VARIABLES

The United States Pharmacopoeia (USP) defines stability as "*the extent to which a product retains, within specified limits, and throughout its period of storage and use, i.e., its shelf life, the same properties and characteristics that it possessed at the time of manufacture.*" There is no one exhaustive set of criteria that would apply equally to all medical devices. The USP has a section <1191> entitled "Stability Considerations in Dispensing Practice" that supplies general information on this topic. It includes a list of five sets of criteria for acceptable levels of stability for drug products as follows on the next page:

1. chemical,
2. physical,
3. microbiological,
4. therapeutic, and
5. toxicological.

Although this set of criteria applies specifically to the evaluation of drug product stability, it is useful as a starting point in developing a set of criteria to evaluate the stability of medical devices.

The following outline may be useful in identifying parameters that could significantly affect the shelf life of a device, even though all of the criteria will not apply to every device. This outline is based on the criteria listed above with the addition of biocompatibility.

1. Chemical

1.1 Degradation: Do any active ingredients or components of the device degrade over time in a manner which adversely affects device safety or performance?

1.2 Interactions: Do ingredients or components interact to alter the device? Does the device have interactions among the various components that cause degradation of the ability to perform the intended function?

1.3 Device and Packaging Interaction: Is there interaction between the device and package that has undesirable affects?

1.4 Radioactive Decay: Does the device contain radioactive material with a relatively short half-life? Do the radioactive decay by-products alter the safety or effectiveness of the device either by themselves or through further interaction?

1.5 Manufacturing: Do any of the manufacturing processes alter the chemistry of the raw materials, components, or finished device in a manner which adversely affects device safety or performance?

2. Physical

2.1 Physical Characteristics: Does the device have physical characteristics that vary with time; e.g., appearance, viscosity, elasticity, tensile strength, burst strength, or electrical resistance? In some cases, a significant change in appearance may cause concern to the user even though the performance of the device is not affected.

2.2 Manufacturing Process: Do the different steps in the manufacture of the device affect the physical characteristics of the individual components or the finished device in a manner which adversely affects device safety or performance?

2.3 Storage Conditions: Do the storage conditions, e.g., temperature, humidity, light, etc., have an affect on the device in a manner which adversely affects device safety or performance?

3. Microbiological

3.1 Sterility: Do sterile devices remain sterile? Maintenance of sterility is primarily determined by the maintenance of package and seal integrity.

3.2 Environmental Control: Is an environmental control program needed during manufacturing or storage to monitor and adjust the microbial load in or on the device and packaging below an established tolerance level to prevent adverse degradation of the product?

3.3 Antimicrobial Effectiveness: Does the device lose the ability to perform the intended antimicrobial function?

3.4 Integrity: Do the device's barrier characteristics change?

3.5 Preservative Effectiveness: If the device uses a preservative system, how long does the preservative system retain effectiveness within tolerance levels?

4. Therapeutic: Does the ability of the device to perform the intended therapeutic or diagnostic function change under storage or use conditions?

5. Toxicological: Do device degradation by-products form during storage or use that produce an adverse toxic effect?

6. Biocompatibility: Does the biocompatibility of the product change adversely during storage or use?

There are numerous variables that affect the shelf life of a medical device. Some of these were discussed in the stability criteria outline above while additional product dependent variables are listed below. Although manufacturers may not be able to control all of the variables, their affect on device performance can be minimized if properly considered. Each of the categories listed below should be addressed during the preproduction estimation of product shelf life and the actual determination of the shelf life for normal production units. A written procedure for determining the necessity of a shelf life and setting the shelf life of a finished medical device should be used to avoid missing an important aspect and to provide needed

documentation. While developing these written procedures for determining a shelf life of a device, the stability criteria and the product specific variables that follow should be assessed.

1. Storage conditions, e.g., temperature variations, relative humidity, ventilation, air pressure, air-borne contamination, visible light and other radiation, etc.

2. The nature of the device and intended use, e.g., medical gloves are made of latex because of the intended use even though latex deteriorates with age.

3. The components used to manufacture the device, e.g., some devices contain a battery or other components that would suffer degradation of function with the passage of time.

4. Method of manufacture, e.g., an in vitro diagnostic device that is aseptically packaged may have a shorter shelf life than one that is terminally sterilized.

5. Packaging, e.g., products that are packaged in different size containers may each have a different stability shelf life due to the different ratio of product to package surface area contact.

6. Transportation conditions; e.g., vibration, shock, temperature, humidity, etc.

RECOMMENDATIONS

The concept of shelf life or expiration dating should be incorporated into product reliability during the process of developing or improving a device for commercial distribution. The result is to make sure that, if the device is used in accordance with the labeling, the device will perform in the intended manner. Developing an appropriate set of specifications for the device's characteristics and assigning tolerance values for these characteristics is essential to the process of shelf life determination. The events that can cause a device to no longer perform in the intended manner may originate:

- internally, e.g., device component interactions or degradation can cause the device operating characteristics to fall outside of the prescribed tolerances; or

- externally, e.g., the shipping or storage conditions can cause a breakage in the device, a failure of the barrier properties of a sterile package or degeneration of the device itself.

A device's "shelf life" should not be confused with a device's "useful life." The useful life of a device is the duration of actual use or the number and duration of repeat uses before some change results in the device's inability to achieve its intended function.

Establishing a Shelf Life

The best time to begin considering device shelf life is during preproduction planning and review while the device is being formulated before any concrete decisions about the device have been made and changes can be readily adapted. When design, material and process factors that influence shelf life are identified early in the process, redesigning the device parameters involve the least cost. The materials, components and packaging that are to be used in the manufacture of the device may need to be examined for their individual shelf life characteristics in addition to their effect on the shelf life of the finished device. Some materials and components may need special handling to maintain their characteristics within the desired specifications. Also, the intended use of the device is an important consideration because this will greatly influence the tolerance level of shelf life or other failure of the device.

Begin by establishing a target shelf life for the finished device that allows adequate time for shipping, storage and use. Evaluate the proposed materials and components used to produce and package the device. Also, a review of the literature should be conducted and, where feasible, data for similar devices collected. The method of manufacturing may need to be tailored to the materials or different materials may need to be selected that don't interfere with, and are not affected by, the manufacturing process. For devices that are found to have good stability characteristics, larger production runs may be practical to permit savings in production costs. With all devices there must be sufficient inventory control to produce, ship and sell the device within the shelf life period to avoid the monetary losses associated with recovering an out-of-date product, reworking a product, or otherwise disposing material to prevent unnecessary health risks for the consumer. If the shelf life considerations are implemented properly, they will add to product quality and actually decrease total production cost.

For devices that are intended to be sterilized, the affect of the sterilization procedure on both the device and the package must be considered. It is much easier to rule out a package with water soluble sealants and select packaging that is compatible with steam sterilization, if steam sterilization is selected as the most desirable procedure before a contract with a package supplier is signed. There are numerous reference works available that cover packaging technology and various sterilization technologies.

Procedure for Testing Shelf Life

A written procedure for establishing and monitoring shelf life of medical devices should include the following:

1. Organizational units responsible for the various phases of the shelf life testing program should be included in the written procedure.

2. A Finished Device Sampling Plan, including the purpose for collecting the samples, the number of finished devices to be collected, frequency of sampling, sample selection criteria, and lots to be sampled.

3. Raw Materials, Components and Packaging Evaluation Plan, to determine if any of these have their own individual shelf life considerations and how they affect the shelf life of the finished device. This plan should include obtaining data from suppliers, obtain new data as appropriate, and recording data for current and future designs.

4. A Plan for Storage of Shelf Life Samples, including storage conditions and the environmental conditions to be controlled, monitored and recorded.

5. Accelerated Aging Parameters, including information that validates the accelerated system. The results need to be supported by real time testing of shelf life samples to confirm the tentative shelf life data collected from the accelerated tests.

6. Simulation of Shipping and Handling Stresses Plan, including vibration tests, temperature extremes challenge, actual shipping and intentionally mishandling the device to determine the affect of unusual circumstances.

7. Follow-up procedures should be included in the written plan that outline the steps to be taken based upon the results of the shelf life testing. These procedures must also cover conspicuously placing the expiration date on appropriate raw materials in storage and on the finished device to aid in stock rotation. The results of the shelf life testing may indicate a need to set limits on the time the device is held in storage, redesign the packaging of the device, or control the environmental conditions to minimize the degradation.

REGULATIONS

The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register by the Executive Departments and Agencies of the Federal Government. FDA regulations are grouped in Title 21 of the CFR, and the regulations that govern medical devices are contained in Parts 800 to 1299. The regulations that apply specifically to shelf life and expiration dating of medical devices are listed below:

In Vitro Diagnostic Regulation - 21 CFR Part 809

1. The paragraph below outlines the labeling requirements for the primary container or wrapper of the retail package.

   21 CFR 809.10(a)(5): *For a reagent, appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include*

such information as conditions of temperature, light, humidity, and other pertinent factors. For products requiring manipulation, such as reconstitution and/or mixing before use, appropriate storage instructions shall be provided for the reconstituted or mixed product which is to be stored in the original container. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods such as those described in § 211.166 of this chapter.

2. The paragraph below outlines the information that is to be included in the package insert or other labeling that accompanies the product.

21 CFR 809.10(b)(5)(iv): *Appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, and other pertinent factors. For products requiring manipulation, such as reconstitution and/or mixing before use, appropriate storage instructions shall be provided for the reconstituted or mixed product. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods such as those described in § 211.166 of this chapter.*

3. The paragraph below describes a requirement for the labeling of "general purpose laboratory reagents".

21 CFR 809.10(d)(1)(v): *Appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, and other pertinent factors. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods such as those described in § 211.166 of this chapter.*

4. The paragraph below from the drug regulation is referred to in the three regulations above and specifically requires a written stability testing program that may include accelerated shelf life testing, but also indicates that real time testing must be performed to verify the validity of the accelerated testing results.

21 CFR 211.166: *(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall include: (1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability; (2) Storage conditions for samples retained for testing; (3) Reliable, meaningful, and specific test methods; (4) Testing of the drug product in the same*

container-closure system as that in which the drug product is marketed; (5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted. (b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

5. The paragraph below requires an expiration date based upon the recommended storage conditions for the reagent unless there is a visible alteration of the product or a simple test method by which the user can determine if the reagent meets appropriate specifications.

   21 CFR 809.10(a)(6)(i): *An expiration date based upon the stated storage conditions.*

Premarket Approval (PMA) - 21 CFR Part 814

The PMA requirements concerning shelf life do not stipulate which devices require a shelf life nor do they stipulate the parameters that must be considered in establishing a shelf life. It is the responsibility of the sponsor of the PMA to make the initial determination of whether their device requires a shelf life and the device characteristics that will be considered.

1. The paragraph below outlines the information that is to be contained in a PMA and requires a section of the PMA to include the results of nonclinical laboratory studies including studies of shelf life.

   21 CFR 814.20(b)(6)(i): *A section containing results of the nonclinical laboratory studies with the device including microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate.*

2. Paragraph (a) below covers the type of changes to a device that require a supplemental PMA application, and expiration dating is specifically covered in section (8). It is advantageous to have a protocol for extending shelf life approved by FDA in the original PMA, since the change in product expiration date can be made as soon as the evaluation is completed instead of having to submit an additional PMA supplement and awaiting FDA approval.

21 CFR 814.39(a)(8): *Extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA. If the protocol has been approved, the change shall be reported to FDA under paragraph (b) of this section.*

3. The Center for Devices and Radiological Health (CDRH) has determined that if a protocol for testing the shelf life of a device has been approved by FDA in the original PMA or a PMA supplement, revising the shelf life of the device based on data collected according to the protocol is a change that does not affect the device's safety or effectiveness. Therefore, the change can be made and FDA notified in the next periodic report.

   21 CFR 814.39(b): *An applicant may make a change in a device after FDA's approval of a PMA for a device without submitting a PMA supplement if the change does not affect the device's safety or effectiveness and the change is reported to FDA in postapproval periodic reports required as a condition to the approval of the device, e.g., an editorial change in the labeling which does not affect the safety or effectiveness of the device.*

Good Manufacturing Practices (GMP) - 21 CFR Part 820

The GMP requirements outline elements of a quality assurance system that point to the desired goals, not as an intricate set of instructions. This approach is beneficial to manufacturers that may have already implemented quality control procedures which include shelf life; or who are contemplating a new device that has unique aspects which would not fit into a "cookbook" approach. Some GMP elements that impact on shelf life are reprinted below.

1. The paragraph below requires the establishment of a quality assurance program that would include an expiration date if appropriate.

   21 CFR 820.5: *Every finished device manufacturer shall prepare and implement a quality assurance program that is appropriate to the specific device manufactured and meets the requirements of this part.*

2. This section requires an environmental control program when it is necessary to prevent contamination of the device and to provide proper conditions for the operations performed to manufacture, store and distribute the device.

   21 CFR 820.46: *Where environmental conditions at the manufacturing site could have an adverse effect on a device's fitness for use, these environmental conditions shall be controlled to prevent contamination of the device and to provide proper conditions for each of the operations*

performed pursuant to § 820.40. Conditions to be considered for control are lighting, ventilation, temperature, humidity, air pressure, filtration, airborne contamination, and other contamination. Any environmental control system shall be periodically inspected to verify that the system is properly functioning. Such inspections shall be documented.

3. Both the manufacturing specifications and the manufacturing processes must be written and include a formal method to control changes to these procedures. This GMP requirement includes an evaluation of any change to the shelf life characteristics of the device resulting from a specification or process change.

   21 CFR 820.100: *Written manufacturing specifications and processing procedures shall be established, implemented, and controlled to assure that the device conforms to its original design or any approved changes in that design.* (also, see subparts F and J)

4. The paragraph below requires written procedures for warehouse control and distribution. This could include controlled storage; e.g., refrigeration, humidity control, etc., and first-in, first-out shipping, as needed to protect the device.

   21 CFR 820.150: *There shall be written procedures for warehouse control and distribution of finished devices to assure that only those devices approved for release are distributed. Where a device's fitness for use or quality deteriorates over time, there shall be a system to assure that the oldest approved devices are distributed first.*

FDA POLICIES

CDRH has issued various policy and internal guidance documents to assist CDRH employees and the regulated industry in understanding what information will be required to satisfy the regulatory requirements for commercial distribution of a medical device. The policies that are in effect for the applications submitted to satisfy these premarketing clearance and distribution requirements are discussed below.

Premarket Notification (510(k))

There currently is no written policy concerning the determination of shelf life for a device that is the subject of a 510(k) submission. However, CDRH has issued an internal guidance document, 510(k) Sterility Review Guidance #K90-1, to set forth the procedure to be used by the Office of Device Evaluation (ODE) and the Office of Compliance and Surveillance (OCS) in reviewing 510(k)s for sterile devices. The 510(k) Sterility Review Guidance document lists the information that is to be included in a 510(k) for a sterile device regardless of how the device is labeled for shelf life. The guidance also acknowledges that certain sterilization processes have a deleterious effect upon a

nonsterility aspect of the device, e.g., the shelf life of the sterilized device could vary due to the use of different sterilization procedures. The 510(k) Sterility Review Guidance document can be used by medical device manufacturers when preparing a 510(k) application for a sterile medical device to make sure the application contains all the information required by CDRH. An excerpt of #K90-1 follows:

The following information concerning the specifications related to sterility should be collected and reviewed by ODE during the review of the 510(k) for a sterile device:

- *the sterilization method that will be used;*
- *a description of the method that will be used to validate the sterilization cycle, but not the validation data itself;*
- *the sterility assurance level (SAL) for the device which the firm intends to meet;*
- *a description of the packaging to maintain the device's sterility (this is not to include packaging integrity testing data);*
- *if sterilization involved ETO, the maximum levels of residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol which remain on the device;*
- *whether the product is "pyrogen free" and a description of the method used to make the determination;*
- *the radiation dose, if radiation sterilization will be used.*

Only this information will be collected regardless of how the device is labeled, i.e., whether it is labeled sterile, sterile until opened or damaged, or sterile until a stated expiration date.

We recognize that certain sterilization processes have deleterious effect upon a nonsterility aspect of the device. These effects have to be factored into the equivalency decision.

The pilot program that is outlined in #K90-1 with the Division of Cardiovascular Devices (DCD), 510(k) Staff and OCS participating is still in effect. As of March 1991, there have been no decisions made regarding expanding the program to the other divisions, modifying or removing this portion of the guidance or evaluating the effectiveness of the program.

Investigational Device Exemption (IDE)

There currently is no written policy concerning the determination of shelf life for a device that is the subject of an IDE. The current CDRH policy for shelf life determination for devices undergoing clinical investigation allows each of the operating divisions within ODE to determine:

- which devices require an established shelf life prior to the clinical study; and

- the methods to be used for validating a shelf life of a particular device.

Premarket Approval (PMA)

The current policy concerning the determination of shelf life for a device that is the subject of a PMA is entitled "Office of Device Evaluation Shelf-Life Policy for PMAs" issued March 7, 1984. This policy for shelf life determination for devices marketed through the PMA process allows each of the operating divisions within ODE to determine:

- which devices require an established shelf life; and
- the adequacy of the proposed methods for validating a shelf life for a particular device.

The policy also requires that the labeling for the device include the shelf life and discusses the process for extending the shelf life by submitting a PMA supplement or following an approved protocol as previously discussed. The text of the policy follows:

A. *The ODE Divisions have the responsibility to determine whether the sponsor must submit data in support of shelf life dating of a PMA device. The Divisions have the responsibility for maintaining a list of generic classes of devices which require shelf life dating and supplying the list to the PMA staff.*

B. *The Divisions have the responsibility for evaluating the data to determine whether they are appropriate and adequate and to reach a conclusion regarding the shelf life of the device.*

C. *The approval order (approval letter) shall include the shelf life of the device. This is an important element of the record of approval of the device and the shelf life must be officially noted.*

D. *The sponsor may extend the shelf life of an approved device through the use of methods and tests described in the PMA which were reviewed and approved by FDA to establish the shelf life. Under these conditions, the sponsor need only advise FDA of the extension in routine reports submitted under the PMA.*

E. *The sponsor must submit a supplement if the sponsor proposes to extend the shelf life based on methods or tests other than those used in the approved PMA and the sponsor may not extend the shelf life without FDA approval of the supplement.*

F. *The device labeling must include an expiration date based upon an approved shelf life period.*

CDRH GUIDANCE

The following documents are issued by CDRH and contain guidance on the methods to be used in determining a shelf life for various medical devices. It is important to note that only the first document is a true guidance document that has undergone the process of announcement in the Federal Register and response to comments received, while each of the others is a draft guidance document.

1. **"Guidance Document for Class III Contact Lenses"**; April 1989; issued by the Division of Ophthalmic Devices (DOD) within ODE. Contact Lenses may be stored up to 20°C above room temperature to simulate accelerated passage of time. The guidance includes a mathematical formula for calculating the simulated age of the subject devices. Stability of physical, chemical and optical specifications must be determined along with a test for sterility. An excerpt from the Shelf life section follows:

   "*A. Shelf life:*

   The manufacturer must demonstrate the stability of the parameters of the finished lens over time as packaged and stored under the proposed storage conditions.

   The aging of the lens in its storage container can be extrapolated to the proposed storage temperature. As a rule of thumb, every 10°C increase for the tested temperature above normal storage temperature will enhance the expiration date by a factor or two. A total of 10-20 lenses randomly selected from 2-3 lots are required for shelf life tests. The stability tests should include physical and optical parameters and the physical appearance of the lens in addition to sterility data. In addition, additional parameters should be monitored for lenses containing color additives, ultraviolet absorbers, or other chemicals during the testing period.

   3. Sterility Stability (shelf life)

   The manufacturer must demonstrate that lenses will remain sterile for the recommended shelf life as packaged. This applies to all hydrophilic lenses as well as hydrophobic lenses that will be labeled as sterile. This requirement does not apply to hydrophobic lenses where the sterilization requirement has been waived.

   To fulfill this requirement, the manufacturer should test 10-20 lenses that have been packaged and stored for the proposed shelf life. Samples from two or three lots of approximately the same age should be tested for sterility using methods such as USP XXI sterility testing.

Method for calculation of shelf life (expiration date) is included in Micro Appendix D.

MICRO APPENDIX D

MICROBIOLOGY REQUIREMENTS FOR ESTABLISHMENT OR EXTENSION OF SHELF LIFE (EXPIRATION DATE) FOR CONTACT LENSES

Shelf life sterility stability must be demonstrated by one of the following two tests:

I. Sterility tests, lenses stored at ambient temperature, or
II. Accelerated shelf life sterility study, lenses stored at elevated temperature to 45° C.

Protocols:

I. Conduct sterility re-check tests according to USP XXI (Sterility Tests pp. 1156-1160) on 10-20 shelf life samples which have been stored at ambient temperature, preferably from several different lots of the approximate age for which shelf life is requested.

Examples: Six month old lenses stored at ambient temperature (generally 23-25°C), with an additional 6 months customarily added to actual shelf life age, are granted a 12-month (1 year) expiration date if they have passed the sterility stability testing and the other (physical/chemical) stability requirements. One year old lenses, stored at ambient temperature, similarly are given an 18 month expiration date if they have passed the sterility stability testing and the other stability requirements.

II. Accelerated shelf life studies may be run by storing samples at higher temperatures for a shorter period of time and mathematically correlating increased temperature with time.

a. Raise temperature a maximum of 20-25°C above ambient temperature (45°C maximum).
b. The acceleration factor for 10°C rise is 1.8.
c. Sterility tests according to USP XXI are run on these samples.

Example of calculation:

3 month old lenses, stored entire 3 months at 40°C.

1. Age of lens = 3 months

2. Ambient temperature = 25°C
3. Q_{10} = 1.8

4. *Acceleration factor (based on 15° temperature difference): $(1.8)^{1.5} = 2.41$*
5. *Length of time at elevated temperature = 3 months*
6. *Estimation of shelf life*
   a. *age x acceleration factor = accelerated age*
      3 months x 2.41 = 7.2 months
   b. *accelerated age + actual age = shelf life*
      7.2 + 3 = 10.2 months

   NOTE: The customary "additional 6 months "is not given for accelerated shelf life."

2. **"Testing Guidelines for Class III Soft (Hydrophilic) Contact Lens Solutions"**; Draft - July 15, 1985; issued by DOD within ODE. Contact Lens Solutions may be stored up to 20°C above room temperature to simulate accelerated passage of time. The guidelines include a mathematical formula for calculating the simulated age of the subject devices. Stability of Ph, viscosity, ingredient concentrations, appearance, preservative concentration, and preservative effectiveness must be determined along with a test for sterility. An excerpt from the Guidelines concerning shelf life follows:

   "*b. <u>Solution Stability Testing</u>*

   The manufacturer must demonstrate the stability of the solution over time as packaged and stored under the proposed storage conditions.

   The size of the container tested should be the same as that intended to be marketed. Generally, if the solution is susceptible to chemical oxidation or reduction, the greater the internal contact of the solution with the container surface the greater the chance of chemical degradation. The degradation therefore, is more likely to occur in smaller containers because the ratio of solution to internal surface area increases as the container size decreases. For this reason, it is our policy to approve a solution for marketing in a container larger than that used for stability testing, but not a container smaller than tested. FDA believes that this policy should extend to containers not more than 8 times the size tested provided that containers are constructed of the same material.

   The aging of the solution in the storage container should be initiated as soon as possible. The stability tests should include pH, viscosity, preservative concentration, physical appearance, and concentrations of major ingredients (e.g., surfactant, enzyme, etc.). Stability results obtained at the corresponding storage temperature of the solution are the basis for the establishment of an expiration date. Accelerated aging up to 50° C may be used as supporting evidence of stability. As a rule of thumb, every 10° C increase for the tested temperature will enhance the

expiration date by a factor of two compared to the normal storage temperature e.g., testing solution at 45°C for 3 months corresponds to the normal storage temperature e.g., testing solution at 25° C for 12 months (2x2x3). A total of 3 containers of solution randomly selected from 3 lots are required for shelf life tests of each container size. The analytical methodology for all tests should be described in detail. FDA does not restrict the method used; however, all analytical methods should be scientifically sound. The following is a suggested protocol:

1. *Number of Samples: 3 containers of solution randomly selected from 3 lots for each storage temperature and storage container size.*
2. *Parameters monitored: pH; viscosity*; preservative concentration; physical appearance: (color, clarity, and integrity.**); and concentration of other major ingredients: (e.g., enzyme activity, *** surfactants****)*
3. *Test method:*
   - *a) Measure and record pH, viscosity, preservative concentration, physical appearance, and major ingredients before study.*
   - *b) Record lot number, beginning date, and storage temperature for the study.*
   - *c) Measure and record pH, viscosity, preservative concentration, physical appearance, and major ingredients after study.*
   - *d) Record terminating date, lot number and storage temperature*
   - *e) Determine how many parameters have fallen beyond their specifications and discuss their impact on safety and effectiveness of the solution.*
   - *f) Calculate the expiration date.*
   - *g) Summary of results and proposed shelf life.*
4. *Appendix*
   - *a) Analytical methodology of parameters monitored.*
   - *b) Ethylene oxide residues (ethylene oxide, ethylene chlorohydrin, ethylene glycol) of plastic bottle/closure if sterilized by ethylene oxide gas. Aeration time and temperature should be specified and residues should be below the proposed FDA guidelines (Federal Register, vol. 43, no. 122, June 23, 1978: ethylene oxide, 10 ppm; ethylene chlorohydrin, 20 ppm; ethylene glycol, 60 ppm).*

* *Not applicable for solution without thickening agents and polymers.*

** *The physical and chemical integrity of the plastic bottle (e.g., discoloration, solution leakage, and surface cracks with or without repeatedly applying a light pressure on bottle) should be a part of*

the stability program if the bottle is sterilized by gamma radiation.

*** *For enzyme tablet or solution.*

**** *Not applicable for solution without surfactants.*

Shelf life Testing Requirements (Second Microbiology Requirement):

1. *Shelf Life Sterility*

The manufacturer must demonstrate that the contact lens solution(s) will remain sterile for the recommended shelf life as packaged. This applies to all solutions that will be labeled as sterile.

To fulfill this requirement, the manufacturer should test 10-20 samples (of one type) that have been packaged and stored for the proposed shelf life. Samples from two or three lots should be tested for sterility using methods such as USP XX sterility testing. A separate shelf life sterility test must be performed for each type of lens solution manufactured.

2. *Shelf Life Preservative Effectiveness*

For any preserved solution, the preservative effectiveness must be demonstrated for the proposed shelf life. Samples from two or three lots to total a minimum of ten samples are tested according to the FDA modification of the USP Preservative Effectiveness Test.

3. *Extension of Shelf Life protocol- see Appendix K*

APPENDIX K
Protocol for Shelf Life Extensions

Microbiological Requirements

Shelf life sterility stability must be demonstrated. Also for a preserved solution, the shelf life stability of the preservative must be demonstrated.

A. *Shelf life sterility stability must be demonstrated by one of the following two tests:*

   I. *Sterility tests, solutions stored at ambient temperature.*

   or

   II. *Accelerated shelf life sterility study, solutions stored at elevated temperature to 50° C.*

B. *For preserved solutions, the Preservative Effectiveness Test is requires in addition to the sterility test.*
   I. *Preservative Effectiveness Test, solutions stored at ambient temperature.*

or

II. Accelerated Preservative Effectiveness study, solutions stored at elevated temperature to 50° C.

Protocols:

A. Sterility Stability Tests

I. Conduct sterility re-check tests according to USP XXI (Sterility Tests pages 1156-1160) on at least 20 shelf life samples which have been stored at ambient temperature. Samples may be of different sizes and should be from several different lots of the approximate age for which shelf life is requested. Each sample should be properly identified in the raw data as to lot number and package size.

Example: Six month old solutions, stored at ambient temperature, with an additional 6 months customarily added to the actual shelf life age, are granted a 12 month (1 year) expiration date if they have passed the sterility stability testing and the other stability requirements.

II. Accelerated shelf life studies may be run by storing samples at higher temperatures for a shorter period of time and mathematically correlating increased temperature with time.

a) Raise temperature a maximum of 20-25° C above ambient temperature (50° C maximum).
*b) For microbiology, the acceleration factor for each 10° C rise is 1.8.**
c) sterility tests according to USP XXI are run on these samples.

Example of calculation:

6 month old solution stored at 45° C

1. Age of solution = 6 months
2. Ambient temperature = 25° C
3. Q_{10} = 1.8
4. Acceleration factor (based on a 20° C temperature difference): $(1.8)^2 = 3.24$
5. Length of time at elevated temperature = 6 months
6. Estimation of shelf life
a) time at elevated temperature x acceleration factor = accelerated age 6 months x 3.24 = 19.44 months
b) accelerated age + actual age = shelf life
19.44 + 6 = 25.44 months
approximately 2 years

Note: The customary additional 6 months is not given for accelerated shelf life.

B. Preservative Efficacy Test

For shelf life stability any preserved solution must pass the FDA modification of the USP Preservative Effectiveness Test against all five of the challenge organisms. Refer to page 53 of the FDA Guidelines for Testing Contact Lens Solutions; also to USP XXI, page 1151."

3. **"Guidelines for Intraocular Lenses"**; Draft - June 9, 1980; issued by DOD within ODE. The Intraocular Lenses guidelines allow accelerated aging but do not give parameters to be used in designing an accelerated aging program and also state that room temperature storage is usually the most valuable. Stability of the mechanical and optical properties are to be measured against the original measurements along with a test for sterility.

"*d. Storage Stability*

The storage stability of the intraocular lens is an important factor in the overall investigation of a new lens material. A study of the aging of the lenses and their containers must be initiated as soon as possible. These stability tests made at regular intervals should include all parameters cited previously. [The parameters are as follow: 1. permeability (small molecules, proteins, oxygen); 2. chemical and physical stability (ultra-violet, boiling water, steam, ethylene oxide, radiation, caustic solution); 3. light transmittance (white light); 4. extractables (if none, state methodology); 5. physical property profile (elongation, deformation, tensile strength); 6. average molecular weight, molecular weight distribution; 7. infrared spectroscopy, ultraviolet spectroscopy; 8. nuclear magnetic resonance spectroscopy; 9. melting point, glass transition temperature; 10. solubility in water, saline, selected solvents; 11. refractive index; 12. elemental analysis of metals and nonmetals; 13. surface microscopy (scanning electron microscopy); 14. biocompatibility (i.e. tissue culture); and 15. heat deformation temperature]. *Special importance should be given to monitoring change in mechanical and optical properties. Accelerated aging may be used as supporting evidence of stability. Stability results obtained at the storage temperature of the device are the basis for the establishment of an expiration date. In the case of packaged lenses, room temperature is usually the most valuable. Other temperatures, low and elevated (below freezing and approximately 50 degrees C.) are helpful for the determination of product stability. Some plastics may be susceptible to temperature variations. Freezing of the aqueous phase may seriously alter the structure of the lens.*

In view of the temperature fluctuations that can occur during shipment of the lens, the manufacturer should make an effort to provide a method to monitor the environmental extremes incurred during transit. A disposable, maximum-minimum temperature indicator, serving as a package insert, to warn the surgeon of potential temperature related alterations of the lens, should be considered."

4. **"General Guidance for Modifying Condom Labeling to Include Shelf Life"**; Draft - October 1989; issued by the Division of Obstetrics/Gynecology, Ear, Nose, Throat, and Dental Devices (DOED) within ODE. The Condoms guidance references test methods specified in American Society for Testing and Materials (ASTM) Standard Specifications for Rubber Contraception (Condoms), D 3492-89. This includes accelerated aging at 70°C and testing the tensile strength and ultimate elongation of the material after the aging process. Excerpts from these two documents follow:

4.1 Excerpt from **"General Guidance for Modifying Condom Labeling to Include Shelf Life"**: *"If a manufacturer, repacker or importer of condoms intends to modify the product labeling to include a shelf life or expiration date, a premarket notification (510(k)) must be submitted to the FDA. FDA requires data from real time aging of condoms to support the labeling modification. FDA, in the absence of real time aging data, will allow a tentative expiration date based on accelerated aging data, provided the manufacturer also initiates studies to determine the real shelf life. Appropriate records are to be maintained for FDA inspection and also, when real time shelf life is confirmed, the manufacturer should notify FDA in a supplement to the 510(k). In the event that the real time aging data does not support the tentative expiration date, the manufacturer should immediately inform FDA and take all necessary steps to correct the labeling. In addition, a supplement to the 510(k) must be submitted amending the expiration date. FDA will accept test methods specified in American Society for Testing and Materials (ASTM) Standard Specifications for RUBBER CONTRACEPTIVES (CONDOMS), D 3492, or any other demonstrably valid method for accelerated testing. For non-latex condoms, and for condoms that contain a spermicidal lubricant, details of the shelf life test methodology need to be provided."*

4.2 Excerpt from ASTM # D 3492-89: *"6.3 Accelerated Aging -- Heat condoms to be aged in original packages at 70° ± 2°C for 166 ± 2h in accordance with test Methods D 573 or D 865. Determine tensile properties not less that 16h or more than 96h after heating."*

5. **"Guideline for the Manufacture of In Vitro Diagnostic Devices"**; Second Draft - February 1990; issued by the Division of Compliance Programs (DCP) within OCS. The

in vitro diagnostic products guidance allows the use of accelerated shelf life studies if followed by real time studies. The procedure to be used in establishing the shelf life of an in vitro diagnostic device should be discussed with the Division of Clinical Laboratory Devices (DCLD) within ODE before initiating the studies, since DCLD did not issue the in vitro diagnostic products guidance document.

"3.9 STABILITY STUDIES AND EXPIRATION DATING

Section 820.100(a)(1) requires that procedures for specification control measures be established to assure that the design basis for the device, components, and packaging is correctly translated into approved specifications. When IVD stability is a design concern, appropriate procedures such as stability studies are conducted and an expiration date, supported by the studies, is established to define the period in which stability is assured. The expiration date is included as part of the product specifications for the IVD and its components, as required by 820.181(a).

Stability studies for all IVDs are required by Sections 809.10(a)(5) and 809.10(b)(5)(iv). These regulations require that storage instructions be stated on the immediate container label, kit or outer container label, and in the product insert for the product in its initial state and for products which are mixed or reconstituted prior to use. Where applicable, storage instructions should include temperature, light and humidity or other conditions. The immediate container label, and the kit or outer container label, are required by 809.10(a)(6) to state a means by which the user is assured the IVD meets appropriate standards of identity, strength, quality, and purity at time of use. This assurance can be an expiration date, an observable indication of product alteration, such as turbidity, or instructions for a simple function test. The following are means of complying with these regulations for establishing stability studies and expiration dating:

An expiration date is the usual method used to indicate stability for IVDs. The last date for the product to be used by the customer is defined as the expiration date.

The storage instructions and the expiration date are determined as part of product development for the proposed container/closure system. The device package and shipping container are evaluated as part of this development phase. For example, during product development an IVD labeled for storage at 2° to 8°C was found to be stable for 24 months. Studies were performed by the manufacturer which subjected the IVD to adverse shipping temperatures of -5°C and 37°C for one week each; however, the IVD was stable for only 6 months at 2° to 8°C after being subjected to these adverse shipping Conditions. A shipping container was then designed to maintain the IVD product at 2° to 8°C during adverse

environmental conditions that might be encountered during shipping to support the 24 month expiry period. This type of design effort supports the type of adequate package design requirements of Section 820.130.

Storage instructions for IVDs are required by 809.10(a)(5) to have reliable, meaningful, and specific test methods such as those in 21 CFR 211.166. Section 211.166 requires sample sizes and test intervals to be based on statistical criteria for each attribute examined to assure valid estimates of stability and also requires reliable, meaningful and specific test methods. Performance and identity testing on all IVD reagents and systems is included in the stability testing program. In addition, sterility testing on sterile labeled IVDs, and microbial limits testing on all microbiologically controlled IVDs, is included in the stability testing program. The finished IVD product is held under appropriate conditions to support the expiry period and storage instructions determined during the development phase. These are normally taken from the first three production batches.

Accelerated studies (i.e., at high temperature and humidity) are acceptable for some products to support tentative dates and storage conditions, as long as they are followed and supported by real time studies. Accelerated studies may not be appropriate for some products because of their complexity, because there is no adequate methodology to conduct accelerated studies, or because they are new products and there is insufficient historical data available.

Each IVD is evaluated for additional stability studies if there is any significant change which may affect stability in the manufacturing process or equipment, the components including the container/closure system, or shipping container."

6. Medical Gloves: Two separate CDRH documents concerning medical gloves contain references to shelf life. Excerpt from these are included in the following subsections.

6.1 **"United States FDA Pre-Marketing and Labeling Requirements for Medical Gloves"**; March 1990; issued by DSMA within the Office of Training and Assistance. This document describes the activities that must be completed to import and market medical gloves in the US. In the section that discusses the labeling requirements of medical gloves is stated "*Finally, Part 820, The Good Manufacturing Practices (GMP) regulation does not require lot numbers for surgical gloves. However, it is customary for surgical gloves to have a lot number, an expiration date, and data to support the expiration date. The GMP regulation does require manufacturers to establish a quality assurance program appropriate for the device being manufactured.*"

6.2 **"Guidance for the Content and Organization of a Premarket Notification [510(k)] for Surgeon's Gloves"**; August 1989; issued by the General and Plastic Surgical Devices Branch, Division of Surgical and Rehabilitation Devices within ODE. This document details the information that should be included in a 510(k) for surgeon's gloves and states that "*If a shelf life is to be included on the label of the finished gloves, the applicant must provide data supporting the proposed shelf life.*"

Additionally, DCD within ODE, has begun drafting a guidance document for determining the shelf life of products that are the subject of applications reviewed in DCD. This guidance document has not yet been issued in final or draft form. Their current policy is to determine if a shelf life is appropriate on a case-by-case basis for PMA products (class III devices). DCD is also participating in the pilot program that is outlined in the 510(k) Sterility Review Guidance mentioned previously.

The Division of Small Manufacturers Assistance (DSMA) was established to meet the requirements of the Medical Device Amendments that FDA establish an office to provide technical and other nonfinancial assistance to medical device manufacturers. The guidelines and other documents referenced throughout this paper are available from DSMA by calling 800-638-2041 (or 301-443-6597 in Maryland). DSMA is also ready to answer requests for other information or guidance concerning the obligations of medical device establishments.

GLOSSARY

510(k)	Premarket Notification
ASTM	American Society for Testing and Materials
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
DCD	Division of Cardiovascular Devices
DCLD	Division of Clinical Laboratory Devices
DCP	Division of Compliance Programs
DOD	Division of Ophthalmic Devices
DOED	Division of Obstetrics/Gynecology, Ear, Nose, Throat, and Dental Devices
DSMA	Division of Small Manufacturers Assistance
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
IDE	Investigational Device Exemption
OCS	Office of Compliance and Surveillance
ODE	Office of Device Evaluation
PMA	Premarket Approval
USP	United States Pharmacopoeia

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