May 1, 1997

Dear Contact Lens Care Product Manufacturer or Interested Person:

The enclosed GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS represents the special control which has been determined by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) as necessary to provide reasonable assurance of the safety and effectiveness of class II contact lens care products (listed below).

This document represents the agency's current thinking on the preparation of 510(k)s for contact lens care products. It does not create or confer any 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.

The draft guidance was initially provided to the public on April 1, 1996, at which time the agency requested comments from interested persons. As discussed at the July 26, 1996, meeting of the Ophthalmic Devices Panel (Panel), FDA has evaluated the comments received and has revised the guidance document to incorporate changes resulting from comments determined to have scientific merit.

PLEASE NOTE THAT THE MAY 1, 1997, DOCUMENT REPLACES THE APRIL 1, 1996, VERSION AS THE APPROPRIATE GUIDANCE DOCUMENT THAT CONTAINS THE "SPECIAL CONTROLS" WHICH SHOULD BE FOLLOWED FOR SUBMISSION OF A 510(k). PLEASE READ THIS DOCUMENT CAREFULLY BECAUSE IT CONTAINS IMPORTANT ADDITIONS, DELETIONS, AND REVISIONS FROM THE APRIL 1, 1996, VERSION.

The Safe Medical Devices Act (SMDA) requires that the Food and Drug Administration (FDA) issue an order placing class III transitional devices in class II if FDA has not determined that the devices must remain in class III. FDA also requires that appropriate regulatory safeguards (i.e., special controls) be in effect when reclassification occurs. The order will be published in the FEDERAL REGISTER announcing the reclassification of soft (hydrophilic) and rigid gas permeable contact lens care products and heat disinfection units. Reclassification will be effective 30 days from date of publication of the order. Devices covered by this reclassification include generic types of devices as follows:

1. Rigid Gas Permeable Contact Lens Care Products: A rigid gas permeable contact lens care product is a device intended for use in the cleaning, conditioning, rinsing, lubricating/rewetting, or storing of a rigid gas permeable contact lens. This includes all solutions and tablets used together with rigid gas permeable contact lenses.

2. Soft (Hydrophilic) Contact Lens Care Products: A soft (hydrophilic) contact lens care product is a device intended for use in the cleaning, rinsing, disinfecting, lubricating/rewetting, or storing of a soft (hydrophilic) contact lens. This includes all solutions and tablets used together with soft (hydrophilic) contact lenses and heat disinfecting units intended to disinfect a soft (hydrophilic) contact lens by means of heat.

Specific devices covered by this reclassification include:

- Saline Solutions (including dry products/tablets)
- Cleaners (Daily Cleaners and Periodic Cleaners)
- Chemical Disinfecting Products for Contact Lenses
- Multi-Purpose Solutions
- In-Eye Contact Lens Solutions (e.g., Lubricating and/or Rewetting Drops)
- Heat Disinfecting Units

The reclassification order does not apply to such contact lens care products as contact lens cases and cleaning accessories (e.g., mechanical cleaning aids and cleaning pads) because these devices have not been separately classified. In the near future FDA intends to revise 21 CFR 886.5918 and 886.5928 to include such care products as contact lens cases and cleaning accessories (e.g., mechanical cleaning aids and cleaning pads). For this reason, we have included guidance on submitting a 510(k) for these contact lens care products in the enclosed document.

This guidance should be used for all premarket notification submissions made after reclassification occurs. Manufacturers should be aware that although this document represents the special control required by SMDA, it is expected to be impacted by ongoing policy initiatives within CDRH and FDA's efforts to harmonize its data requirements with international standards. Any significant updates or changes in data requirements will be announced at forthcoming meetings of the Panel. Although comments received to date have been considered prior to this revision, interested persons may submit written comments at any time, which will be incorporated in future updates of this guidance if CDRH determines that they are appropriate. Comments should be submitted to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

and

Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

The guidance document is available on the CDRH Worldwide web home page at "http://www.fda.gov/cdrh." You are encouraged to obtain electronic copies; however, if you are unable to do so, you may obtain a hard copy by faxing your request to the Division of Small Manufacturers Assistance (DSMA) [fax: (301) 443-8818].

I would like to take this opportunity to thank the Panel members, contact lens industry and other interested persons for taking the time and effort to evaluate and comment on this special controls document. In addition, I would like to thank the members of the Vitreoretinal and Extraocular Devices Branch and others who have worked extremely hard in preparing this guidance document.

Questions concerning this guidance document may be addressed to James F. Saviola, O.D., or Muriel Gelles at (301) 594-1744.

Sincerely yours

A. Ralph Rosenthal, M.D.
Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Guidance for Industry

PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS

This document represents the agency's current thinking on the preparation of a 510(k) for contact lens care products. It does not create or confer any 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. The guidance is available on the Worldwide web on CDRH's home page at "http://www.fda.gov/cdrh."

While this guidance document represents a final document, comments and suggestions may be submitted at any time for agency consideration to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857 or by writing to James F. Saviola, O.D., Chief, Vitreoretinal and Extraocular Devices Branch (HFZ-460), Division of Ophthalmic Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850. This guidance document replaces the draft PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS, which issued on April 1, 1996.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health
May 1, 1997

PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR
CONTACT LENS CARE PRODUCTS

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I. INTRODUCTION

The Safe Medical Devices Act of 1990 (SMDA) requires that the Food and Drug Administration (FDA) issue an order placing class III transitional devices [e.g., contact lens care products such as soft (hydrophilic) and rigid gas permeable contact lens solutions (including dry products/tablets) and heat disinfection units] in class II if FDA has not determined that the transitional devices must remain in class III. The order, issued by FDA, is effective 30 days after publication in the FEDERAL REGISTER. It includes reclassification of rigid gas permeable and soft (hydrophilic) contact lens solutions (including dry products/tablets) and heat disinfection units (defined in 21 CFR 886.5918, 886.5928, and 886.5933, respectively) from class III (premarket approval) into class II (special controls). This guidance document sets forth the general information and special controls FDA believes are needed to assure the safety and effectiveness of contact lens care products such as rigid gas permeable and soft (hydrophilic) contact lens solutions (including dry products/tablets) and heat disinfection units and the evidence that demonstrates the substantial equivalence of these devices to legally marketed devices [21 CFR 807.92(a)(3)]. For purposes of this guidance document, the term "class II" is used to describe a generic type of contact lens care product. However, each manufacturer [i.e., 510(k) holder] should be aware that an unapproved individual contact lens care product is not a class II device until it has been determined to be a class II device by classification through the premarket notification (510(k)) process.

Definition of Contact Lens Care Products Covered by this Guidance Document:

A. Class II contact lens care products are defined in 21 CFR 886.5918 and 886.5928, and generally include:

- Saline Solutions
- Cleaners (Daily Cleaners and Periodic Cleaners)
- Chemical Disinfecting Products for Contact Lenses (including Conditioning Solutions for Hydrophobic Lenses)
- Multi-Purpose Solutions
- In-Eye Contact Lens Solutions (e.g., Lubricating and/or Rewetting Drops)
- Heat Disinfection Units

B. Contact Lens Cases and Contact Lens Accessories (e.g., Mechanical Cleaning Aids and Accessory Cleaning Pads):

Although contact lens cases and contact lens accessories have not been separately classified as of the date of this guidance, in the past FDA has reviewed applications for these devices through the 510(k) process. The Center for Devices and Radiological Health (CDRH) believes that it is appropriate to include guidance for submitting 510(k)s for these devices in this document. At this time the Ophthalmic Devices Panel (Panel) has recommended that contact lens cases be classified in class II; however, final classification has not occurred to date. The remaining unclassified lens care products will be brought before the Panel for classification in the near future. For this reason we have

included guidance on information that should be included in 510(k)s for these devices.

As FDA re-evaluates its data requirements for contact lens care products and works to harmonize its requirements with international standards, significant changes in our guidance may be forthcoming. Such changes may include modifications in test methods, definitions, and especially in the design of clinical trials for care products, all of which are now being considered. Any changes in requirements will be announced at forthcoming meetings of the Panel and copies will be placed on the CDRH Worldwide web (www) home page at "http://www.fda.gov/cdrh." You are encouraged to obtain electronic copies; however, if you are unable to do so, you may obtain a hard copy by faxing your request to the Division of Small Manufacturers Assistance (DSMA) (see list of fax and telephone numbers at end of the Introduction section).

Purpose of Document:

This document is intended to provide comprehensive directions to enable a manufacturer of a contact lens care product to submit a 510(k) that FDA believes adequately demonstrates whether the device is substantially equivalent to a legally marketed device.

This document represents the agency's current thinking on the preparation of a 510(k) for contact lens care products. It does not create or confer any 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. It sets forth the preclinical and clinical testing that FDA believes would be acceptable to establish substantial equivalence as required by section 513(i) and 513(f) of the act.

While use of this document to prepare preclinical and clinical protocols will not ensure investigational device exemptions (IDE) approval or 510(k) clearance, following the recommendations of this document should ensure that the necessary tests are conducted. A substantial equivalence determination for a 510(k) can be expected to follow if tests are conducted properly, data are adequately analyzed and presented, applications are submitted in accordance with applicable regulations, and the test results show that the contact lens care product is substantially equivalent to a legally-marketed contact lens care product.

Persons may choose to follow the guidance herein or may follow different data collection and preparation procedures and protocols. If a person chooses to follow different collection and preparation procedures and protocols, a person may discuss the matter in advance with CDRH to prevent the expenditure of money and effort on an activity that may later be determined to be unacceptable. If alternate procedures are used, the applicant should be prepared to demonstrate to CDRH's satisfaction that such procedures demonstrate the substantial equivalence in terms of safety and effectiveness to the predicate device.

Guidance is provided on the preclinical and clinical tests which should be used to demonstrate substantial equivalence. If clinical performance data are

needed, this guidance provides directions for obtaining an IDE [see Investigational Device Exemptions (21 CFR 812) section].

The comprehensive guidance document includes matrices and descriptions of the types of preclinical testing (e.g., manufacturing/chemistry, toxicology, and microbiology) that should be completed prior to submitting a 510(k) or, if clinical performance data are necessary to demonstrate substantial equivalence, prior to seeking IDE approval from an institutional review board (IRB). The document also includes recommended test methods for meeting these requirements.

The clinical portion of this document includes the major elements of clinical performance data collection and suggested methodologies to be included in the protocol. The clinical protocol is part of the investigational plan that must be submitted to an IRB in order to obtain approval of an IDE under 21 CFR Part 812.

Other elements of the guidance document include: (1) general information on the applicable regulations and requirements for labeling of contact lens care products, (2) requirements for modifications of a legally marketed contact lens care product (see manufacturing/chemistry, toxicology, and clinical recommendations), and (3) general information needed in a 510(k) submission.

Preclinical or clinical data in other documents on file with CDRH may be incorporated by reference into a 510(k). To be referenced, documents such as IDEs, 510(k)s, premarket approval applications (PMAs) or device master files (DMFs) should have been submitted by the applicant, or the applicant should provide CDRH with appropriate authorization from the submitter. This authorization should be in the form of a letter addressed to the Document Mail Center, HFZ-401, CDRH, 9200 Corporate Blvd., Rockville, Maryland 20850, referencing the correct document number.

The Division of Ophthalmic Devices (DOD) should be consulted if questions remain after reading this document (see list of telephone numbers at end of Introduction section).

Pertinent Regulations:

The FDA regulations especially relevant to class II contact lens care products are:

- Device Classes (section 513(a)(1) of the act)
- Establishment Registration and Device Listing for Manufacturers of Devices (21 CFR 807)
- Premarket Notification Procedures (21 CFR 807, Subpart E)
- Investigational Device Exemptions (21 CFR 812)
- Protection of Human Subjects; Informed Consent (21 CFR 50)
- Institutional Review Boards (21 CFR 56)
- Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR 58)
- Determination of Safety and Effectiveness (Defines Valid Scientific Evidence) (21 CFR 860.7)
- Good Manufacturing Practice for Medical Devices: General (21 CFR 820)

- Medical Device Reporting (21 CFR 803)
- Labeling [21 CFR 801 (see Section V, Labeling)]

Each of these regulations is briefly discussed below.

Device Classes [Section 513(a)(1) of the Act]:

Class II devices are subject to both general and special controls. General controls include the prohibition on adulteration (section 501 of the act); prohibitions on misbranding (section 502 of the act); banned devices (section 516 of the act); notification of risks and repair, replacement, or refund (section 518 of the act); records and reports (section 519 of the act); restricted devices (section 520(e) of the act), good manufacturing practices (section 520(f) of the act); registration of establishments (section 510 of the act); listing of devices (section 510(j) of the act); and submission of a premarket notification (section 510(k) of the act). Special controls may include the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines [including guidelines for the submission of clinical data in 510(k) submissions in accordance with section 510(k)], recommendations, and other appropriate actions as deemed necessary to provide reasonable assurance of the safety and effectiveness of the device.

Establishment Registration and Listing for Manufacturers of Devices (21 CFR 807):

Medical device manufacturers, initial distributors (U.S. importers), and distributors are required to register their establishments by supplying CDRH with the information required on registration form FDA 2891 (Initial Registration of Device Establishments). Manufacturers are also required to list their devices in commercial distribution in the U.S. by completing form FDA 2892 (Medical Device Listing). Foreign manufacturers may, but are not required to register; however, they must list their devices. Questions about registration and listing may be addressed to DSMA (see fax and telephone numbers at the end of the Introduction section).

Premarket Notification Procedures (21 CFR 807, Subpart E):

Most devices are cleared for commercial distribution or marketing in the U.S. through the 510(k) process. In this process, the manufacturer makes a 510(k) submission to CDRH and must receive a letter (order) from CDRH permitting commercial distribution. This order is based on CDRH's finding the device substantially equivalent to a device legally marketed in the U.S. The manufacturer must provide in the submission, among other things, evidence of such substantial equivalence. What constitutes substantial equivalence is explained in section 513(i)(1)(A) of the act. Substantial equivalence means that a device has the same intended use and the same technological characteristics (i.e., design, material, function, and other similar features) as the predicate device; or has the same intended use and new technological characteristics, but it can be demonstrated that the device is as safe and effective as the predicate device and does not raise different types of questions regarding safety and effectiveness from the predicate device.

The 510(k) notification requirement applies (21 CFR 807.81): whenever a manufacturer markets a device for the first time; when there is a change in the intended use; or whenever a legally marketed device is modified in a way

that could significantly affect its safety and effectiveness. It is not intended that a 510(k) be submitted for every change, but only where such changes could significantly affect safety or effectiveness. CDRH believes that the manufacturer is best qualified to make the initial determination, which should be based on the exercise of good judgment, adequate supporting data, and sufficient documentation in conjunction with general written policies and guidance from CDRH. The manufacturer should be aware, however, that if he or she makes a decision not to submit a new 510(k), CDRH can overrule that decision and take appropriate regulatory action. If a manufacturer does make a change or modification to the device and does not submit a 510(k), he or she should document the reason for not submitting a 510(k) in the good manufacturing practice (GMP) device master record and make it available to FDA upon request.

Subpart E of 21 CFR 807.81 (Premarket Notification Procedures) provides guidance on the type of changes for which an applicant must submit a 510(k) if the change could significantly affect the safety and effectiveness of the device. Additionally, you should contact DSMA (see fax and telephone numbers at the end of the Introduction section) to obtain a copy of the most recent CDRH general guidance on changes to an existing device that may require submission of a new 510(k). Manufacturers should be aware, however, that a device specific guidance document such as the "GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS" supersedes or provides additional guidance to a CDRH general guidance involving device modifications that may require submission of a new 510(k). If, after attempting to evaluate the change, manufacturers are still uncertain about the need for a 510(k), they may write a letter explaining the changes in detail, referencing the 510(k) number, and mail it to the Document Mail Center, CDRH (address above).

Once a 510(k) has been submitted, additional information may be requested by CDRH, in which case the 510(k) application will be placed on hold. A letter is issued stating that the file will be retained for 30 days while waiting for the submitter's response. If a response is not received within 30 days, the 510(k) may be deleted. The submitter should respond within 30 days or, if the 30-day period cannot be met, request an extension by letter to the Document Mail Center, CDRH (address above), referencing the 510(k) number. When CDRH receives the additional information, the review period begins again. This happens each time additional information is requested.

Premarket notification review allows CDRH to find not substantially equivalent (NSE) devices that: (a) present new types of questions of safety and/or effectiveness relative to the predicate devices; (b) appear to perform less safely or effectively than legally marketed devices; and (c) have indications that are a new intended use.

If CDRH determines that a device is NSE, the manufacturer may appeal the NSE decision, file a reclassification petition, or submit a PMA. When a manufacturer and CDRH disagree about the NSE decision for a device, the following applies:

- A 510(k) that is determined to be NSE is automatically classified into class III, and unless reclassified into class I or II, is subject to premarket approval. The manufacturer may request

reconsideration of an NSE decision. The 510(k) Staff may be contacted for information on how to request reconsideration of an NSE decision (telephone number at end of the Introduction section).

- Under section 513(f) of the act, a manufacturer of a class III device may petition CDRH for reclassification of this device into class I or class II. CDRH will refer a petition to the appropriate FDA advisory panel for review and recommendation. The content and format requirements of a reclassification petition are in 21 CFR 860.123.

- If determined to be NSE because of lack of performance data, the manufacturer may resubmit another 510(k) with additional data.

A 510(k) should be dated, and list the applicant's (submitter's) name, address, contact person (if different from applicant), telephone number, and must be signed by the applicant. The 510(k) should contain a table of contents, be submitted in duplicate on standard sized paper with pages numbered, securely bound (if necessary), and three-hole punched. The manufacturer should designate in the cover letter that the submission is a "510(k) notification." All attachments to the 510(k) submission should be appropriately identified. The general information section should include:

- the trade name (proprietary name) for the device;

- the identification of the predicate or legally marketed device to which substantial equivalence is being claimed;

- the common name or the classification name (21 CFR 807.87) of the device;

- a description of the device that is the subject of the 510(k);

- a statement of the intended use of the device;

- a statement of how the technological characteristics of the device compare to those of the predicate device;

- the establishment registration number [although not required in a 510(k), the applicant will need to register his or her establishment within 30 days of product release];

- the address of the manufacturing facility/facilities, including the sterilization site(s);

- the class in which the device has been placed (class I, II, or III) under section 513 of the act, and, its appropriate panel, if known (if the submitter determines that the device has not been classified, a statement of that determination and the basis for that determination);

- the reason for the premarket notification [e.g., a new device or a modification to an existing device (if the 510(k) is for a modification, describe in detail the reason for the modification and provide the equivalent device's 510(k) number)];

- compliance with the requirements of the act under section 513 special controls (class II devices);

- copies of draft labeling and available advertising for the device;

- engineering drawings (for care products such as heat disinfection units, lens cases, etc.);

- under 21 CFR 807.92 and 807.93 the 510(k) submitter must include either a summary of the safety and effectiveness information upon which the substantial equivalence determination is based, or a statement in the 510(k) that the submitter will make available the safety and effectiveness information to interested persons upon request. If a statement is provided, it should be (1) dated (2) signed by the certifier, (3) made on a separate page of the premarket notification submission, and (4) clearly identified as "510(k) statement" which contains the following:

  > "I certify that, in my capacity as [The Position Held In Company by Person Required To Submit The Premarket Notification, Preferably The Official Correspondent In the Firm], of [Company Name], I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61."

- a dated and signed statement certifying that the submitter believes, to the best of his or her knowledge, that all data and information submitted in the premarket notification are truthful and accurate, and that no material fact has been omitted in accordance with 21 CFR 807.87(j).

Subpart E of Section 807 of 21 CFR and the booklet "Premarket Notification 510(k): Regulatory Requirements for Medical Devices" (HHS Publication FDA 92-4158) provide detailed explanations and examples of ways that companies can comply with the 510(k) requirements. DSMA can provide you with the regulation and this booklet, answer questions, and provide guidance regarding the regulatory process. DSMA's fax and telephone numbers are listed at the end of the Introduction section.

Investigational Device Exemptions (21 CFR 812):

Data from clinical testing may be necessary to demonstrate the substantial equivalence of a contact lens care product to a legally marketed device. To collect these clinical data, an approved IDE is required before the sponsor (usually the manufacturer) can distribute investigational medical devices for clinical testing. The IDE regulation describes procedures for obtaining an

approved IDE and outlines the responsibilities of a sponsor and an investigator during a clinical investigation with a medical device.

FDA considers clinical studies of certain solutions intended to be used directly in the eye to be significant risk investigations which require both IRB and FDA review and approval prior to initiating clinical studies. Examples of significant risk investigations include studies of: (1) solutions containing new types of active ingredients that have no history of ophthalmic use and cannot be adequately characterized from a safety standpoint by the preclinical testing contained in this guidance, or (2) solutions containing biologic or pharmaceutical ingredients that could present a risk to the health and safety of the subjects, and would involve overlapping jurisdiction with other Centers within FDA.

FDA considers most clinical studies of contact lens care products to be non-significant risk investigations since the active ingredients can be adequately characterized from a safety standpoint by the preclinical testing contained in this guidance. The abbreviated requirements of the IDE regulation [21 CFR 812.2(b)] apply for non-significant risk investigations, which basically require the following:

1. The sponsor must submit and obtain approval for a non-significant risk device study from a properly constituted IRB (21 CFR 56), or FDA if no IRB exists (21 CFR 812.62(b)), prior to distributing devices for a clinical investigation (21 CFR 812.30).

2. All test subjects must give their informed consent (21 CFR 50) before being treated with the investigational device. Informed consent is obtained on a written form advising the subjects of their rights as voluntary research subjects, apprising subjects of risks, benefits, and alternate procedures, if any, and test procedures involved.

3. All investigations must be properly monitored.

4. Certain recordkeeping and reporting requirements must be met [see 21 CFR 812.2(b)(1)(v)-(vi)].

FDA review and approval is not required for an investigation of a non-significant risk device. A sponsor needs to obtain IRB approval and follow the requirements of 21 CFR 812.2(b)(1)(i) through (vii).

Under the abbreviated requirements for non-significant risk device clinical studies (21 CFR 812.2(b)), an IRB must determine that a particular contact lens care product poses a non-significant risk. For a device investigation to be determined to be non-significant risk, a sponsor must provide an IRB with a statement of why the investigation does not pose a significant risk, and the IRB must agree with this assessment. The IRB must also approve the investigation as a non-significant risk study.

IRBs should be provided with all information necessary to reach a sound decision. This information, in the case of a contact lens care product, should include informed consent forms and the clinical protocol. It is important to note that, in the case of non-significant risk investigations, although preclinical data are not required to be submitted to CDRH until a 510(k) is submitted, the sponsor should conduct preclinical tests prior to

initiating a clinical study to predict product performance and to protect the health of the subjects. The purpose of preclinical tests is to evaluate whether subjects will be at undue risk, and thus preclinical test results should be submitted to the IRB for its review prior to testing in humans.

IDE Study Design:

Sponsors of investigations should consider carefully how to adequately demonstrate the substantial equivalence of their specific devices to legally marketed devices and design their study to assure that the data provide valid scientific evidence, as defined in 21 CFR 860.7; to answer all clinical objectives properly; and to form a sound basis to support the intended use and claim(s) being made in the labeling.

Manufacturers should carefully review the clinical recommendations in this guidance document, which have been designed to assist in developing adequate clinical protocols. In addition, they should consult with the DOD scientific staff, if necessary, when preparing their clinical protocol. The preparation of an adequate protocol is one of the most important aspects of the clinical investigation and essential for a successful 510(k) when clinical performance data are required to demonstrate substantial equivalence. The protocol should be designed to fully support the proposed labeling claim(s) and intended use of the device. The sponsor is responsible for ensuring that the study design is appropriate and that all necessary tests are completed. If alternative tests are more appropriate than those listed or additional tests must be conducted, the overall design of the study and its justification are the responsibility of the study sponsor.

Information available to sponsors includes the IDE regulation (21 CFR 812) and related information. Please contact the IDE Staff or DOD for further guidance (see telephone numbers at the end of the Introduction section).

Protection of Human Subjects; Informed Consent (21 CFR 50):

The fundamental purposes of IRB review and of informed consent are to assure that the rights, safety, and welfare of subjects are protected. A signed informed consent form is evidence that the information required by section 50.25 has been provided to a prospective investigational subject. IRB review of the form to ensure that the subject is given adequate information concerning the study serves a dual function: protection of the subject and documentation that the institution complied with applicable regulations. Informed consent must be obtained in accordance with the informed consent regulation, and any informed consent form used must embody the elements of informed consent required by 21 CFR 50.25. The consent form itself is an aid to ensure that adequate information is provided to the subject. The signed consent form provides documentation of a subject's consent to participate in a study. The entire informed consent process involves giving a subject information concerning the study, providing adequate opportunity for the subject to consider all options, responding to the subject's questions, ensuring that the subject has comprehended this information, and, finally, obtaining the subject's voluntary consent to participate. Informed consent must be documented pursuant to 21 CFR 50.27 and is required by 21 CFR 50.20 for all subjects in clinical investigations of medical devices. Specific questions may be addressed to the IDE Staff (see telephone number at the end of the Introduction section).

Institutional Review Boards (21 CFR 56):

An IRB is a board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct continuing review of biomedical research involving human subjects in accordance with FDA regulation. The purpose of IRB review is to assure that:

- risks to subjects are minimized, and are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- informed consent will be sought from each prospective subject or the subject's legally authorized representative and will be documented;
- where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects; and
- there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The IRB regulation outlines membership and review requirements. All IRBs must conform to and comply with all requirements in this regulation.

Specific questions may be addressed to the IDE Staff (see telephone number at the end of the Introduction section).

Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies (21 CFR 58):

The purpose of this regulation is to assure the high quality of nonclinical laboratory testing required to evaluate the safety of medical devices. Sponsors should state in all submissions whether or not nonclinical laboratory tests were conducted in accordance with this regulation. When procedures are not conducted in accordance with the GLP regulation, justifications should be provided.

Specific questions may be addressed to the IDE Staff (see telephone number at the end of the Introduction section).

Determination of Safety and Effectiveness (Defines Valid Scientific Evidence) (21 CFR 860.7):

This regulation defines what does and does not constitute valid scientific evidence for the purpose of determination by FDA that there is reasonable assurance that a device is safe and effective for its intended use. Although a 510(k) only requires a demonstration of substantial equivalence to a legally marketed device, this demonstration is in terms of the device being as safe and as effective as a legally marketed device and that the device does not raise different types of questions of safety and effectiveness than the predicate device.

Specific questions about the interpretation of this regulation should be addressed to DOD (see telephone number at the end of the Introduction section).

Good Manufacturing Practice for Medical Devices: General (21 CFR 820):

The Good Manufacturing Practice (GMP) for Medical Devices General Regulation, required by section 520(f) of the act, covers the methods used in, and the facilities and controls used for, the design, manufacture, packaging, storage, and installation of devices. It covers the following general areas: organization and personnel; buildings; equipment; controls for components, processes, packaging, and labeling; device holding, distribution, and installation; device evaluation; device and manufacturing records; complaint processing; and quality assurance (QA) system audits.

SMDA amends section 520(f) of the act to authorize the inclusion of preproduction design validation in the GMP regulation. A revised GMP regulation was published in the FEDERAL REGISTER on October 7, 1996 [61 FR 52601] that incorporates preproduction design controls.

Specific questions on GMP requirements may be addressed to DSMA (see fax and telephone numbers at the end of the Introduction section).

Medical Device Reporting (21 CFR 803):

The Medical Device Reporting (MDR) regulation requires all manufacturers of medical devices to report to FDA within 30 days whenever the firms receive or otherwise become aware of information that reasonably suggests that one of their marketed devices: (1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and that the device or any other similar device would be likely to cause or contribute to a death or serious injury if the malfunction were to reoccur.

Manufacturers and importers of devices are required to establish and maintain an MDR file and to permit any authorized FDA employee at reasonable times to have access to, and to copy and verify the records contained in this file. FDA considers any expression of dissatisfaction, be it oral or written, regarding identity, quality, durability, reliability, safety, effectiveness, or performance of a device, to be a complaint. However, not all complaints meet the MDR reporting criteria.

Copies of the MDR regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by contacting DSMA (see fax and telephone numbers at the end of the Introduction section).

Management Initiatives:

On June 30, 1993, new policies to improve the device approval process were announced by CDRH. These new policies are as follows:

- **Expedited review**: To assure that those devices which represent major advancements in medical care reach the market without delay, CDRH has put into effect a "fast track" review system for them. These device applications will be placed in a separate queue and not treated under the usual "first-in, first-reviewed" policy. Included in the expedited review category will be devices used to treat serious conditions for which no alternative treatments exist and devices that offer decidedly greater clinical benefits or lower risks than existing technologies.

- **Refuse-to-accept policy**: In the past, inadequate and incomplete applications wasted a great deal of CDRH's time. Reviewers were obliged to "re-cycle" these applications, going back to the company repeatedly to request needed information or to clarify poorly presented data. To address this problem, the agency has established a "refuse-to-accept" policy that will specify the minimum criteria for accepting an application. If these are not met, the application will be rejected.

  Some specific reasons to refuse to accept a 510(k) submission for contact lens care products would be failure to include information establishing substantial equivalence, a 510(k) summary of safety and effectiveness or 510(k) statement, or a truth and accuracy statement.

- **Setting review priorities using risk assessment (previously called "Triage")**: Early in the review process, CDRH will determine the potential health hazard posed by each device and will focus most of its attention on those devices that pose a significant risk to patients. Devices with minimal risk potential will receive a less extensive review.

  To achieve this, three review tiers have been identified: Tier I - Essentially a focused labeling review for intended use/indications for use; Tier II - Routine scientific and labeling review (the majority of 510(k)s will be in this tier); and Tier III - Intensive scientific and labeling review, using a team review approach, for all first and second of a kind devices utilizing new technology or having new intended use(s), as well as other devices determined by their inherent risk to require an intensive review.

  Contact lens care products, including solutions that incorporate traditional preservative systems and intended uses, are currently assigned to a Tier II review.

- **Status reports to manufacturers**: In the past, device manufacturers have often not been able to determine the status of their 510(k) submissions as they proceed through the review system. This has proven a major source of frustration, particularly since lack of information can interfere with sound business planning. To address this problem, CDRH has established a computerized system through which manufacturers will receive a status report on their 510(k) submissions within 3 days of requesting it, if the application has been under review over 90 days.

More information is available on each of these policies in ODE Blue Book memos available by contacting DSMA (see fax and telephone numbers at the end of the Introduction section).

Special Controls:

This guidance document sets forth the special controls which have been determined at this time by CDRH to be necessary to provide reasonable assurance of the safety and effectiveness of class II contact lens care

products in the absence of an applicable standard. These special controls consist of the recommended protocols for the preclinical and clinical data that FDA believes establish substantial equivalence under section 513 of the act and identify modifications to contact lens products that FDA believes would require submission of a new 510(k) and labeling guidance.

CDRH has carefully considered these recommendations, but also recognizes that it is important to be open-minded about new tests which can be, and are, suggested. If different procedures are chosen by the applicant, a full justification should be submitted. The justification should clearly explain how the alternative procedure can provide the valid scientific evidence needed to demonstrate substantial equivalence. The absence of any justification and supporting evidence may mean that the application will be found unacceptable during scientific review.

DOD may be consulted prior to the initiation of any tests if, after reading the guidance document, questions remain concerning a specific test recommendation for a contact lens care product (telephone number listed below).

Fax and Telephone References:

DSMA: Fax: (301) 443-8818 (For copy of guidance document, refer to shelf number 674)
Telephone: (800) 638-2041 or (301) 443-6597

DOD: Fax: (301) 480-4201
Telephone: (301) 594-1744

IDE Staff: Telephone: (301) 594-1190

510(k) Staff: Telephone: (301) 594-1190

II. GENERAL MANUFACTURING INFORMATION

This section of the guidance contains the general manufacturing information that should be submitted in a 510(k) for contact lens solutions and tablets. For purposes of this guidance, we have focused primarily on active ingredients. However, manufacturers should also assess the effects of inactive ingredients (e.g., buffering agents and tablet coatings) on such factors as pH, tonicity, solution compatibility, enzymatic activity, preservative effectiveness, disinfection efficacy, preservative uptake/release, and critical micelle concentration of surfactant.

In 510(k) submissions, applicants should provide the general information listed below as well as the information in Section III (Product Specific Guidance), Section V (Labeling), and other applicable sections of the guidance. Applicants are reminded that when test data are submitted, complete reports of the tests as well as summary information should be included in the 510(k).

A. General Manufacturing Information for Contact Lens Solutions and Tablets:

The applicant should document and summarize the following manufacturing/chemistry information:

1. Chemical Composition of the Contact Lens Solution or Tablet:

The chemical composition of the contact lens solution or tablet should include all active and inactive ingredients and their functions.

Note: For purposes of this guidance:

- **An "active ingredient" is generally defined as any chemical component that is included in the formulation of a contact lens solution or tablet in sufficient concentration to achieve the intended purpose of the specific product (e.g., a surfactant for a daily cleaner, an anti-microbial agent for a disinfecting product, an enzyme for an enzymatic tablet or a preservative for preserved lens care products).**

- **An "inactive ingredient" is generally defined as any chemical component other than an active ingredient (e.g., buffering agents and water) that is included in the formulation.**

If the components meet United States Pharmacopoeia (USP), National Formulary (NF), or American Chemical Society (ACS) specifications, this should be noted. If sorbic acid is used as a component, aldehyde should be quantified and its specification justified. For any non-compendial component, the applicant should establish approved raw material specifications in accordance with GMPs and submit them in the 510(k) (e.g., characterization data on this component and/or analytical results from manufacturing batches used for preclinical and clinical tests).

When applicable, a side-by-side comparison of the composition of the new device compared to the predicate device should be provided. If the new solution or tablet is identical to the predicate device in terms of concentrations of active and inactive ingredients, the general manufacturing information can be limited to a description of the manufacturing process with a flow chart, demonstration of product sterility and sterilization validation, shelf-life data, and a description of the packaging, including tamper resistant features. If the new solution or tablet is not identical to the predicate device in terms of concentrations of active and inactive ingredients, all general manufacturing information outlined below should be addressed in the 510(k). Whenever new claims are made for a marketed device, supporting information should be provided.

2. A brief description, including a flow chart, of the manufacturing process should be provided.

3. Sterility: In accordance with 21 CFR 800.10, all contact lens solutions should be sterile. Sterility should be demonstrated using USP <71>, Sterility Tests, or by an equivalently validated sterility test method. Product sterility or validated package integrity testing should be performed to support the shelf-life requested in the 510(k). [Section VI.E (Shelf-Life Protocol)].

   For general information and references dealing with the development and validation of sterilization cycles, manufacturers should refer to USP <1211>, Sterilization and Sterility Assurance/General Information. Manufacturers should validate their product sterilization system(s) and cycle(s) using a suitable validation method and demonstrate the efficacy and compatibility with the product and/or container. Manufacturers should use the most recent edition and include reference(s) for the validation method in the 510(k). Some additional references on sterilization validation methods are provided below:

   - ANSI/AAMI/ISO 11134: Sterilization of health care products - Requirements for validation and routine control - Industrial moist heat sterilization.

   - ANSI/AAMI/ISO 11135: Medical devices - Validation and routine control of ethylene oxide sterilization.

   - ANSI/AAMI/ISO 11137: Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization.

   - ISO/TR 13409: Sterilization of health care products - Radiation sterilization - Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches.

   - Validation of Aseptic Filling for Solution Drug Products. Technical Monograph No. 2. Parenteral Drug Association.

- Guideline on Sterile Drug Products Produced by Aseptic Processing June 1991. Prepared by: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Office of Regulatory Affairs, FDA.

- USP <1211> Sterilization and Sterility Assurance of Compendial Articles: Aseptic Processing.

In accordance with the Office of Device Evaluation (ODE) 510(k) Blue Book Memorandum #90-1 dated February 12, 1990, the applicant should provide the following information in the 510(k) submission to support validation of a traditional sterilizing system [e.g., steam under pressure, ethylene oxide (ETO), gamma radiation or aseptic fill process]:

a. the sterilization method that will be used;

b. a description of the method that will be used to validate the sterilization cycle, but not the validation data itself;

c. the sterility assurance level (SAL) which the manufacturer will meet;

d. a description of the packaging to maintain the device's sterility (this should not include the package integrity testing data);

e. if sterilization involves ETO, the maximum levels of residues of ETO, ethylene chlorhydrin, and ethylene glycol which remain on the device or components of the device (e.g., bottles or container closure system); and

f. the radiation dose, if radiation sterilization will be used.

Applicants should provide, in the 510(k), a description of the quality assurance procedures and sterility test methods used to provide routine sterility assurance.

4. Microbial Limits Test: Manufacturers of nonsterile contact lens products marketed in dry or tableted formulation should submit data from USP microbial limits testing to demonstrate acceptable microbiological quality, when applicable. These data may be omitted if the manufacturer provides data demonstrating that the level of the active ingredient concentration is inhibitory.

5. In accordance with 21 CFR 800.10(b), contact lens solutions packaged in multi-dose containers should be formulated and packaged as to volume and type of container and appropriately labeled to afford adequate protection and minimize the hazard of injury resulting from contamination during use (e.g., preserved multi-dose solutions, unit-dose containers, discard time periods).

6. Preservative Effectiveness: Manufacturers of preserved solutions should demonstrate preservative effectiveness initially and at the shelf-life requested in the 510(k). See Section VI (Recommended Test Methods) Micro--Appendix A, for guidance on the recommended

preservative effectiveness test with microbial rechallenge on day 14.

7. Shelf-Life (Stability) Data Including Product Specifications, Container and Container Sizes:

   Please refer to Section VI E. (Shelf-Life Protocol) for guidance on establishing, or extension of, shelf-life.

8. Tamper Resistant Packaging: All solutions and tablets must meet the requirements of 21 CFR 800.12, Contact Lens Solutions and Tablets; Tamper-Resistant Packaging.

9. Solution Compatibility Under Recommended Care Regimen: Compatibility of the solution with the lens type (hydrophilic or hydrophobic) indicated for the product specific use should be assessed. For guidance, see applicable testing matrix and Section VI (Recommended Test Methods) Chem--Appendix C.

10. Preservative Uptake/Release: Preservative uptake/release data should generally be submitted in a 510(k) for a solution containing new preservatives for contact lens use. When applicable, manufacturers should assess the effects of inactive ingredients (e.g., buffering agents, etc.) on preservative uptake/release. However, a manufacturer may justify omission of these data in a 510(k) provided:

    a. the manufacturer demonstrates that the proposed preservative system is essentially identical in terms of chemical composition and intended use (hydrophilic lenses or rigid gas permeable lenses) to the preservative system of the predicate device; and

    b. the manufacturer demonstrates that the new preservative does not raise toxicological concerns and the new preservative carries no charge or the same charge as the lens material (e.g., generally negatively charged).

    CDRH considers hydrophilic contact lenses to represent a worst case. Therefore, manufacturers who already have SE clearance for a contact lens care product intended for use with hydrophilic contact lenses do not need, unless otherwise notified, to submit additional preservative uptake/release data for adding use with hydrophobic lenses to labeling.

For guidance, see applicable testing matrix and Section VI (Recommended Test Methods) Chem--Appendix A, if the above criteria cannot be met.

B. Other Contact Lens Care Products:

Other contact lens care products included in this guidance include heat disinfecting units, lens cases, and contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads). See Section III (Product Specific Guidance) and Section V (Labeling) for guidance on these devices.

III. PRODUCT SPECIFIC GUIDANCE

This section is a composite of mini-guidances (hereafter referred to as product specific guidance) for each of the devices included in the GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS. Each product specific guidance contains its own testing matrix (when applicable) to provide applicants with a summary chart and narrative explanation of preclinical and clinical testing recommendations for collecting performance data. CDRH expects that these data either be submitted or that the testing areas be addressed in the 510(k), unless the applicant provides a justification for why the data are not applicable.

The product specific matrices also apply when a marketed product is changed in a way that could significantly affect its safety or effectiveness [e.g., change or modification in the active ingredient(s)]. Applicants are reminded that when performance data are submitted in a 510(k), data should include full reports, where applicable, of the test data as well as summary information.

Please note that the information and data elements included in the General Manufacturing Information section are not repeated in each product specific guidance section, but are included by reference. In addition, Section V (Labeling) includes both general and product specific labeling guidance.

Product specific guidances included in this section are:

1. Saline Solutions

2. Cleaners (Daily Cleaners and Periodic Cleaners)

3. Chemical Disinfecting Products for Contact Lenses (e.g., chemical disinfecting solutions, chemical disinfection systems, and conditioning solutions).

4. Multi-Purpose Solutions

5. In-Eye Contact Lens Solutions (e.g., Lubricating and/or Rewetting Drops)

6. Heat Disinfecting Units

7. Contact Lens Cases

8. Contact Lens Solution Accessories (e.g., Mechanical Cleaning Aids and Accessory Cleaning Pads)

The following matrices (including preclinical and clinical guidance) and Section V (Labeling) set forth the special controls determined by CDRH to be necessary to assure the continued safety and effectiveness of the devices and the information that should be provided in a 510(k).

The applicant should compare product active ingredient(s) with those of the predicate device and refer to the appropriate section of the applicable matrix for guidance.

A. SALINE SOLUTIONS

A saline solution is generally defined as a contact lens care product (e.g., solution, capsule or tablet) containing sodium chloride as the principal active ingredient in an aqueous based solution formulation to produce a physiologically balanced saline solution (approximately 0.9% by weight). These products are either pre-formulated sterile solutions or packaged as salt tablets or capsules which require distilled water as a diluent to produce a non-sterile "homemade" saline solution. They are intended to be used with soft or rigid gas permeable contact lenses for one or more of the following:

- rinsing after cleaning to remove loosened debris and cleaning solution
- rinsing prior to lens insertion
- keeping lenses wet during heat disinfection
- storage after disinfection
- a diluent for dissolving lens care tablets (e.g., enzyme or disinfecting tablets)
- a diluent for use in hydrogen peroxide disinfection systems (limited use)

Pre-formulated sterile saline solutions can be marketed in formulations that are preserved or unpreserved; buffered or unbuffered. These solutions can be packaged in various containers (e.g., aerosols, non-aerosol, unit-dose or multi-dose).

TESTING MATRIX FOR SALINE SOLUTIONS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge or Bacteriostasis for Unpreserved Products	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study				60 subj/1 mo

FOOTNOTE A: **If the saline solution has a pH of 7.2 $\pm$ 0.2 and tonicity of 290-320 mOsm/kg, manufacturers do not need, unless otherwise notified, to submit solution compatibility data.**

Pre-formulated Saline Solutions:

Manufacturing/Chemistry:

Pre-formulated Sterile Saline Solutions: Pre-formulated sterile saline solutions are generally maintained in the comfort range (e.g., pH = 6.6-7.8 and tonicity of 290-320 mOsm/kg) to avoid eye irritation when used in accordance with the recommended lens care regimen. In addition to the information listed in the General Manufacturing Information section and in the matrix, the following information should be provided:

1. Heat Disinfection: If the saline solution is indicated for use during heat disinfection, the effect of heat disinfection on pH, tonicity, and preservative concentration should be assessed and data submitted.

2. Diluent for Lens Care Tablets: If the saline solution is indicated for use as a diluent for enzyme tablets, tablet disintegration time and enzymatic activity time profile as indicated in labeling should be assessed, compared to a control (e.g., approved diluent), and data submitted.

Microbiology:

This section, Section II (General Manufacturing Information) and the matrix include microbiological guidance for all pre-formulated saline solutions.

1. Preservative Effectiveness: Applicants should refer to the preservative effectiveness portion of Section II (General Manufacturing Information) and Section VI (Recommended Test Methods) Micro--Appendix A for guidance. In addition, applicants should be aware that passing preservative effectiveness test with rechallenge on day 14 allows manufacturers to label preserved saline solutions for lens storage up to 30 days following disinfection. Labeling instructions for 30-day storage in preserved saline should include instructions for lens case care and the need to re-disinfect lenses after the recommended storage time.

   Manufacturers submitting 510(k)s for salines preserved with sorbic acid or sorbate-based preservatives may omit the microbial rechallenge in preservative effectiveness testing. However, testing should continue as directed by the protocol in Section VI (Recommended Test Methods) Micro--Appendix A for 28 days, including enumeration of surviving microorganisms at 21 and 28 days. In order to support labeling claims for long-term storage of lenses following heat disinfection (up to 30 days), the 510(k) should include data demonstrating that passing preservative effectiveness test results were obtained using a rechallenge on day 14.

2. Multi-dose saline products may contain bacteriostatic agents (e.g., boric acid or borate) instead of traditional preservatives. In lieu of a preservative effectiveness test, a bacteriostasis

test may be conducted and the product labeled with the appropriate discard date [see Section VI (Recommended Test Methods) Micro--Appendix C].

Toxicology:

See Testing Matrix for Saline Solution and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

Clinical data are not generally required to be submitted in a 510(k) for saline solutions provided the saline solution is formulated, packaged and labeled in an equivalent manner to the predicate device.

Homemade Saline Solutions (Salt Tablets/Capsules System):

A homemade saline solution is made from a salt tablets/capsules system that generally consists of salt tablets or capsules containing Sodium Chloride USP and a plastic mixing bottle of a specified size. The system is packaged with labeling instructions to use over-the-counter (OTC) distilled water as a diluent for dissolving the salt tablet or crystals. The prepared saline solution is used with soft (hydrophilic) contact lenses for rinsing PRIOR to heat disinfection and in the lens case for keeping lenses hydrated during heat disinfection. See Section V (Labeling) for guidance on recommended indications for use statements and warnings.

Chemistry:

Sodium Chloride USP or equivalent is recommended for use in manufacturing salt tablets or capsules.

Microbiology:

Microbiology testing data are generally not required to be submitted when a salt tablet or capsule system is formulated using Sodium Chloride USP, packaged and labeled in an equivalent manner to the predicate device. Microbial issues are addressed in Section V (Labeling).

Toxicology:

See Section VI (Recommended Testing Methods, Toxicology Testing for Containers) Tox--Appendix A, for guidance on recommended tests for including in the 510(k) for the container/closure system for salt tablets/capsules systems. Toxicology information is generally not required to be submitted for salt tablets or capsules formulated using Sodium Chloride USP.

Clinical:

In the early 1980s, the Ophthalmic Devices Panel recommended and CDRH concurred, that the unit-dose aspect of the salt tablets/capsules system is such that clinical testing to establish the safety and effectiveness of the product would not be needed if the salt tablets/capsules system is formulated using Sodium Chloride USP, packaged and labeled in an equivalent manner to the predicate device.

B. CLEANERS

Daily Cleaners:

A daily cleaner is generally defined as a contact lens care product containing one or more active ingredients in sufficient concentrations to loosen and remove loosely held lens deposits and other contaminants on the surface of contact lenses. A daily cleaner may also be indicated for use as a component of a lens care disinfection regimen, or as a labeled intended use for a multi-purpose lens care solution.

Daily cleaners are generally marketed as pre-formulated solutions and labeled for use in conjunction with digital manipulation (e.g., fingers) or an accessory device (e.g., mechanical cleaning aids) for a specific period of time to accomplish the intended purpose. Sufficient data should be submitted in the 510(k) to support the effectiveness of the daily cleaner when used for the minimum time period recommended in the labeling.

TESTING MATRIX FOR DAILY CLEANERS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	X	X	X	X
Cleaning Effectiveness - Critical Micelle Concentration	X	X	X	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Microbial Limits Test (Dry Products/Tablets Only)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		FOOTNOTE A	FOOTNOTE B	60 subj/3 mo

FOOTNOTE A: **Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected (i.e., a higher concentration of the active cleaning ingredient in a multi-purpose solution with a daily cleaning claim may require submission of clinical data while an increase in concentration of the active ingredient in a daily cleaner may not). If necessary, a 30 subject/1 month clinical study should be conducted.**

FOOTNOTE B: **If active ingredient is a surfactant, sponsor may use either appropriate in vitro tests or conduct a clinical test with 60 subject/3 months to establish the efficacy of the lower concentration of active ingredient.**

Chemistry:

The following chemistry tests are applicable to a daily cleaner containing a surfactant(s) as the active ingredient. Manufacturers of daily cleaners containing active ingredients other than surfactants may wish to consult DOD before initiating test protocols. The information included in Section II (General Manufacturing Information), the testing matrix, and listed below should be provided in the 510(k):

1. Surface Tension of the Solution: [See Section VI (Recommended Test Methods) Chem--Appendix B, for recommended methodology)].

2. Micelle Concentration of the Surfactant in the Solution: [See Section VI (Recommended Test Methods) Chem--Appendix B for recommended methodology].

3. Other scientifically valid method: Supporting literature and/or method validations testing information should be provided.

Microbiology:

See Testing Matrix for Daily Cleaners, Section II (General Manufacturing Information), and Section VI (Recommended Test Methods) Micro--Appendix A, for guidance on recommended tests for including in a 510(k).

Toxicology:

See Testing Matrix for Daily Cleaners, and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

See Testing Matrix for Daily Cleaners for guidance on size and scope of a clinical trial. Further clinical guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

In the absence of validated in-vitro data, applicants are advised that for cleaning studies (e.g., studies of non-surfactant agents) a cross-over design with additional in-vitro analysis of worn lenses is an example of one method to demonstrate substantial equivalence to the predicate device. Sponsors may choose to consult with DOD prior to developing their protocols.

Periodic Cleaners:

A periodic cleaner is generally defined as a contact lens care product (e.g., solution or tablet) containing one or more active ingredients (e.g., enzymes) in sufficient concentrations to loosen and remove deposits (e.g., proteins) from the lens surface and from within the polymer matrix. Periodic cleaners are recommended for removing lens deposits such as proteins or lipids that cannot generally be removed from lenses with the use of a daily cleaner. Periodic cleaners have traditionally been recommended for use on a weekly basis.

Periodic cleaners are generally marketed as pre-formulated solutions or as tablets containing the active ingredients. Labeling directions for the original enzyme preparations derived from pancreatin and papain stated that lenses should be soaked for a specified time period after the enzyme tablets are dissolved in diluents such as saline solutions, chemical disinfection solutions or multi-purpose solutions to release the active ingredients.

Later technological innovations of bacterial enzymes (e.g., subtilisin) have in some cases combined the enzyme soak with the soaking period of the disinfection process. Newer pre-formulated solutions are also added during the disinfection process, but on a daily rather than weekly basis.

Sufficient data should be submitted in the 510(k) to support the effectiveness of the periodic cleaner when used for the minimum time period recommended in the labeling. Consideration should be given to the active ingredients utilized as well as the predicate device labeling for general guidance in determining the recommended period of use.

TESTING MATRIX FOR PERIODIC CLEANERS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	X	X	X	X
Enzymatic Activity	X FOOTNOTE A	X FOOTNOTE A	X FOOTNOTE A	X FOOTNOTE A
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Microbial Limits Test (Dry Products/Tablets)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		FOOTNOTE B	30 subj/1 mo	60 subj/3 mo

FOOTNOTE A: **An In-vitro cleaning effectiveness test should be conducted statistically, using 30-day human-worn daily wear lenses (e.g., group 1 and group IV) to assess the effect of reducing enzymatic activity in this device compared to the predicate device with the same active ingredients.**

FOOTNOTE B: **Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected (i.e., a higher concentration of the active cleaning ingredient in a multi-purpose solution with a periodic cleaning claim may require submission of clinical data while an increase in concentration of the active ingredient in a periodic cleaner may not). If necessary, a 30 subject/1 month clinical study should be conducted.**

Chemistry:

In addition to the information listed in Section II (General Manufacturing Information) and as outlined in the testing matrix in this section, the following should be provided. (Consideration should be given to tablet preparations compared to liquid preparations.)

1. enzyme disintegration time (for tablet) and enzymatic activity time profile in the proposed diluents as indicated in the labeling;

2. the pH and tonicity of the spent solution when the enzymatic tablet is dissolved in, or added to, the proposed diluents;

3. if the enzymatic tablet is intended to be dissolved in, or added to, a chemical disinfection solution for simultaneously cleaning and disinfecting contact lenses, the effect of the enzyme on the effectiveness of disinfection should be assessed;

4. in-vitro cleaning effectiveness should be conducted for 30 days using human-worn daily wear lenses (group I and group IV for hydrophilic lenses) to assess statistically the effect of reducing enzyme activity in the device compared to the predicate device containing the same enzyme; and

5. if the enzyme in the device in the submission is identical to the enzyme in the predicate device, a side-by-side comparison of the information requested in items 1-3 should be submitted along with a discussion of why the safety of the new device and cleaning effectiveness are equivalent to the predicate device.

Microbiology:

See Testing Matrix for Periodic Cleaners, Section II (General Manufacturing Information) and Section VI (Recommended Test Methods) Micro--Appendix A, for guidance on recommended tests for including in a 510(k).

If a periodic cleaner is indicated for use simultaneously with a chemical disinfecting product, disinfection efficacy testing should be performed with the periodic cleaner present and data submitted in the 510(k).

Toxicology:

See Testing Matrix for Periodic Cleaners and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

See Testing Matrix for Periodic Cleaners for guidance on size and scope of a clinical trial. Further clinical guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

C. CHEMICAL DISINFECTING PRODUCTS FOR CONTACT LENSES

Contact lens disinfection is a critical step in the safe and effective reprocessing of lenses recommended for reuse. For purposes of this guidance document, contact lens disinfection is generally defined as a process that uses one or more contact lens care products designed to eliminate and destroy potentially harmful microorganisms on a contact lens. The contact lens disinfecting products that utilize anti-microbial ingredients for chemical disinfection of lenses are described below. (Heat Disinfection Units are discussed in Section III.F of this guidance.)

1. Chemical Disinfecting Solution: A chemical disinfecting solution is generally defined as a contact lens care product containing one or more active ingredients (e.g., preservatives or anti-microbial agents) in sufficient concentrations to destroy harmful microorganisms on the surface of a contact lens within the recommended minimum soaking time.

   In order for a contact lens care solution to be labeled as a contact lens "disinfecting solution," it should meet the primary performance criteria of the stand-alone procedure for contact lens disinfecting products [see Section VI (Recommended Test Methods) Micro--Appendix B Part 1 for methodology]. This criteria may also be satisfied by a hydrogen peroxide (H_2O_2) disinfecting solution.

2a. Chemical Disinfection System: A chemical disinfection system is generally defined as a combination of two or more products, when used in accordance with the labeled directions, results in the cleaning and disinfection of a contact lens.

   In order for the contact lens regimen to be labeled as a chemical disinfection system, it should at minimum meet the performance criteria of the regimen procedure [see Section VI (Recommended Test Methods) Micro--Appendix B Part 2].

   A chemical disinfection system (also referred to as a chemical disinfection regimen) generally consists of a daily cleaning solution, rinsing solution and soaking solution. Because all steps within the regimen (cleaning, rinsing and soaking) should be completed to obtain adequate contact lens disinfection, special labeling controls are required for these systems [see Section V (Labeling)].

2b. Disinfecting Systems Requiring Neutralization: Some disinfecting systems may require specially designed lens vials or neutralizing solutions. An example of current technology in this area is a H_2O_2 system. A H_2O_2 system is generally defined as a combination of two or more contact lens care products that, when used in accordance with labeled directions for use, will result in the adequate disinfection of a contact lens. H_2O_2 systems generally consist of the following:

a. H_2O_2 Solution: This product is generally defined as a contact lens solution containing the active ingredient, H_2O_2, in sufficient concentrations to destroy harmful microorganisms on the surface of a contact lens during the minimum recommended soaking time. In some cases, H_2O_2 solution may meet the primary performance criteria of the stand-alone procedure for contact lens disinfecting products in Section VI (Recommended Test Methods) Micro--Appendix B Part 1.

b. Neutralizer: This product is generally defined as a contact lens care product (e.g., disk, tablet, or solution) containing one or more active ingredients in sufficient concentration to neutralize the irritating and toxic effects associated with the residual H_2O_2 remaining on the lenses after soaking in the H_2O_2 solution. Pre-formulated neutralizing solutions may also be labeled for use as a rinsing and storage solution for contact lenses. A neutralizer is generally considered to be a component of the whole H_2O_2 disinfecting system.

c. Lens Vial: In addition, the H_2O_2 system may also contain a specially-designed contact lens vial that acts as a lens case to store lenses during the H_2O_2 disinfection process. Many of the currently marketed H_2O_2 systems are uniquely designed to use only those components identified in the labeling for safe and effective use of the system.

3. Conditioning Solution: A conditioning solution is a solution that may contain multiple active ingredients (e.g., preservative and ophthalmic demulcents) in sufficient concentration to enhance the wettability of hydrophobic lenses (i.e., RGP and PMMA) prior to insertion and to destroy harmful microorganisms on the surface of the lens during the recommended soaking time.

   A conditioning solution should meet, at a minimum, the performance criteria of the regimen procedure. A conditioning solution may be recommended for use with a specific daily cleaner as part of a lens care regimen for soaking and storage of RGP lenses prior to wear. Because of the multiple claims for this type of solution, information should be submitted in a 510(k) to support all claims identified in the labeling for a conditioning solution. These products may also be used to lubricate and rewet RGP lenses prior to insertion in the eye.

Manufacturers who wish to provide eye care practitioners with separate instructions for in-office chemical disinfection and storage of trial lenses should submit a new 510(k) for the additional labeling. These instructions should be intended for reprocessing of trial lenses included as part of a manufacturer's trial lens fitting set or for individual lenses maintained in the practitioner's inventory for reuse between patients. Because there are increased risks associated with the reuse of trial lenses between patients, disinfection and storage claims should be supported by anti-microbial efficacy data, including virucidal efficacy (e.g., H. simplex, Adenovirus).

Manufacturers should include the following in their instructions to eye care practitioners:

- To record the initial storage date and the end of the storage period
- Reminder that disinfecting solutions remain within their expiration date during the entire trial lens storage period
- A visual check for turbidity in storage solution that would indicate contamination
- Instructions for proper care of storage vial to prevent biofilm

At this time, no harmonized industry standards address the issues associated with in-office disinfection and storage of trial lenses. Professional associations such as the American Optometric Association and the American Academy of Ophthalmology publish guidance for practitioners on hygienic management of trial lenses and in-office disinfection. FDA is currently working with the International Standards Organization (ISO) to develop a standardized method to address efficacy criteria and labeling recommendations regarding the disinfection and storage of trial lenses. Additional guidance will be provided as it becomes available.

TESTING MATRIX FOR SOAKING SOLUTIONS FOR DISINFECTION

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	X	X	X	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Disinfection Efficacy	X	X	X	X
Microbial Limits Test (Dry Products/Tablets)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		30 subj/1 mo		60 subj/3 mo

TESTING MATRIX FOR NEUTRALIZING PRODUCTS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Microbial Limits Test (Dry Products/Tablets)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		30 subj/1 mo	FOOTNOTE B	60 subj/3 mo

FOOTNOTE A: **If the spent solution has a pH of 7.2 $\pm$ 0.2 and tonicity of 290-320 mOsm/kg, manufacturers are not required, in most instances, to submit compatibility data.**

FOOTNOTE B: **Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected. If necessary, a 30 subject/1 month clinical study should be conducted.**

TESTING MATRIX FOR CONDITIONING SOLUTIONS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
Wetting Angle	X	X	X	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Disinfection Efficacy	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		30 subj/1 mo		60 subj/3 mo

FOOTNOTE A: **If the conditioning solution has a pH of 6.6-7.8 and tonicity of 290-320 mOsm/kg, manufacturers are not required, in most instances, to submit compatibility data.**

Chemistry:

In addition to the information listed in Section II (General Manufacturing Information) and as outlined in the testing matrices in this section, the following should be provided, when appropriate:

For conditioning solutions:

1. wetting angle of hydrophobic lenses in conditioning solution as a function of soaking time; and

2. the pH, tonicity and viscosity of the conditioning solution.

For chemical disinfection solutions:

pH and tonicity of the chemical disinfection solution used for hydrophilic contact lenses.

For H_2O_2 systems:

1. the pH and tonicity for the H_2O_2 and neutralization solutions;

2. the pH, tonicity and residual H_2O_2 of the spent solution following neutralization for a H_2O_2 disinfecting system;

3. for neutralization solution, tablets, or disks, a neutralization profile under the recommended care regimen should be provided:

   a. if a disk is used, manufacturers should establish a discard date based upon the maximum number of effective uses of the neutralization disk; and

   b. if a time-delayed tablet is used for a disinfecting/neutralization system, the following additional information is needed:

      (1) materials for coating the tablet (e.g., nature of polymer, average molecular weight, molecular weight distribution, and swelling); and

      (2) QA/QC procedures and sampling plan for time-delayed release tablet.

Microbiology:

See Section II (General Manufacturing Information), the applicable testing matrices for Soaking Solutions for Disinfection, Neutralizing Solutions, and Conditioning Solutions, and Section VI (Recommended Test Methods) Micro--Appendices A-B for guidance on recommended microbiology tests for including in the 510(k).

The disinfection efficacy of a disinfecting solution, system, or a conditioning solution should be evaluated by the stand-alone procedure [see Section VI (Recommended Test Methods) Micro--Appendix B, Part 1]. If the

product does not meet the primary criteria, but does meet the secondary criteria, the product should then be evaluated by the regimen procedure (Micro--Appendix B, Part 2).

Toxicology:

See Testing Matrices for Soaking Solutions for Disinfection, Neutralizing Solutions, and Conditioning Solutions and Section VI (Recommended Test Methods) Tox--Appendices A-B.

For H_2O_2 disinfection systems, toxicology testing should be performed on the neutralized disinfection solution (i.e., spent solution).

Clinical:

See applicable Testing Matrices for Soaking Solutions for Disinfection, Neutralizing Solutions, and Conditioning Solutions for guidance on recommended size and scope of clinical trials. Further guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

D. MULTI-PURPOSE SOLUTION

A multi-purpose solution is generally defined as a single contact lens care solution that contains multiple active ingredients in sufficient concentrations to perform the functions of daily cleaning, chemical disinfection, rinsing and storage of contact lenses. Because of the multiple uses claimed for this individual solution, information should be submitted in a 510(k) to support all claims identified in the labeling. In addition, strict attention should be paid to the labeling for this product to assure that adequate directions for use (e.g., rubbing and rinsing times for daily cleaning, soak times for disinfection, and maximum storage times following disinfection) are provided for all intended uses identified above.

A contact lens solution that cannot perform all of the functions identified above should not be labeled as a multi-purpose contact lens care solution [see Labeling section for multi-purpose solutions below and Section V (Labeling) for further guidance on labeling for multi-purpose contact lens solutions].

Chemistry:

See applicable testing matrices and Section VI (Recommended Test Methods) for the recommended manufacturing/chemistry tests for the applicable indications (e.g., daily cleaning and disinfection solutions).

Microbiology:

See Section II (General Manufacturing Information), applicable testing matrices, and Section VI (Recommended Test Methods) for the recommended microbiology tests for the applicable indications (e.g., daily cleaning and disinfection solutions).

Toxicology:

See applicable testing matrices and Section VI (Recommended Test Methods) for the recommended toxicology tests for the applicable indications (e.g., daily cleaning and disinfection solutions).

Clinical:

See applicable testing matrices for guidance on size and scope of a clinical trial for the applicable indications (e.g., daily cleaning and disinfection solutions). Further clinical guidance on protocol development is available in the Section VI (Recommended Test Methods) Clin--Appendices A-E.

Labeling:

Policy for Multi-Purpose Solutions:

Applicants are advised that a multi-purpose solution should not be labeled as an ALL-IN-ONE solution. CDRH believes that an ALL-IN-ONE claim can be misleading for these products because lubricating

and rewetting drops as well as enzyme treatment are utilized for complete lens care.

Multi-purpose products are usually labeled for cleaning and disinfecting. It is potentially unsafe to label a product intended for cleaning and disinfecting for in-eye use as well since consumers may inappropriately use other cleaners and disinfecting solutions that are not compatible with in-eye use. A multi-purpose solution should not be labeled for lubricating and rewetting lenses during wear even if the chemical compositions of the multi-purpose solution and lubricating and rewetting drops are identical.

CDRH maintains a working policy that lubricating and rewetting drops should be packaged in bottle sizes not to exceed 30 ml in order to minimize the risks of contamination and possible eye infections and facilitate ease of use.

Therefore, based on concerns for contamination during use and consumer misuse and confusion, it is CDRH's policy to discourage manufacturers from labeling multi-purpose solutions for in-eye indications for use. CDRH believes that a policy of limiting indications for in-eye use solutions to that single intended use enhances product safety and encourages consumer compliance with safe lens care practices.

See Section V (Labeling) for general guidance for developing labeling for contact lens care products. In addition, predicate device labeling should also be used as general guidance for labeling new multi-purpose solutions.

E. IN-EYE CONTACT LENS SOLUTIONS (Lubricating and/or Rewetting Drops)

An in-eye solution for use with contact lenses (e.g., lubricating and/or rewetting drops) is generally defined as a contact lens care solution containing one or more active ingredients (e.g., ophthalmic demulcents) in sufficient concentration to alleviate symptoms of discomfort from contact lens wear by a physical means as opposed to a pharmacological action generally associated with OTC in-eye solutions regulated as drugs. A preparation labeled for use with contact lenses which contains an ophthalmic demulcent, as listed in 21 CFR 349.12, will qualify as a lubricating drop based on formulation. All predicate lubricants to date contain a demulcent. If a preparation does not contain a demulcent (e.g., a small volume unit-dose saline), it would qualify as a rewetting drop, not as a lubricating drop. Predicate device labeling should be used as a comparison for intended use.

The devices in this category of products, generally referred to as lubricating and/or rewetting lens drops, are intended for direct instillation in the eye while wearing contact lenses to achieve the intended purpose. These products may also be used to lubricate and/or rewet lenses prior to insertion in the eye.

Policy for Multi-Dose In-Eye Contact Lens Solutions:

CDRH believes that lubricating and rewetting drops should be packaged in bottle sizes not to exceed 30 ml in order to minimize the risks of contamination and possible eye infections and facilitate ease of use. The risk of contamination with multi-dose in-eye contact lens solutions should be further minimized by formulating the product to contain one or more suitable harmless substances such as a preservative, that will inhibit the growth of microorganisms. Alternatively, in-eye contact lens solutions may be packaged as to volume and type of container and appropriately labeled to afford adequate protection and minimize the hazard of injury resulting from contamination during use (e.g., unpreserved in unit-dose containers).

CDRH recognizes that a solution manufacturer that produces a product with an identical formulation to that of an in-eye lens solution, such as a saline or conditioning solution, which is marketed in a size larger than 30 ml will be discouraged by this policy from labeling the solution for in-eye use. Also, the Policy for Multi-Purpose Contact Lens Solutions (see Section III D, Multi-Purpose Solution) would discourage labeling certain products for in-eye use indications.

In addition, it is encouraged that labeling for multi-dose in-eye contact lens solutions include instructions to discard the solution after a specified period after opening. If a discard date is proposed, it should be based on the package size, projected number of uses, and frequency of use.

CDRH believes that a policy of limiting indications for in-eye use solutions to that single intended use enhances product safety and encourages consumer compliance with safe lens care practices.

TESTING MATRIX FOR IN-EYE CONTACT LENS PRODUCTS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study	30 subj/1 mo	30 subj/1 mo	30 subj/1 mo	60 subj/3 mo

FOOTNOTE A: **If the in-eye contact lens solution has a pH of 6.6-7.8 and tonicity of 290-320 mOsm/kg, manufacturers are not required, in most instances, to submit compatibility data.**

Chemistry:

See Section II (General Manufacturing Information) Testing Matrix for In-Eye Contact Lens Solutions, and Section VI (Recommended Test Methods) Chem--Appendices A and C, for guidance on recommended tests for including in a 510(k).

In addition, for lubricating solutions, manufacturers should identify and characterize the ophthalmic demulcent as listed in 21 CFR 349.12 and provide pH, tonicity, and viscosity.

Microbiology:

See Section II (General Manufacturing Information), Testing Matrix for In-Eye Solutions, and Section VI (Recommended Test Methods) Micro--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Toxicology:

See Testing Matrix for In-Eye Solutions and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

See Testing Matrix for In-Eye Solutions for guidance on size and scope of a clinical trial. Further clinical guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

Applicants are reminded that FDA generally considers clinical studies of certain solutions intended to be used directly in the eye to be significant risk investigations which require both IRB and FDA review and approval prior to initiating clinical studies. Applicants should refer to the "Introduction" section for guidance concerning significant risk clinical studies.

F. HEAT DISINFECTION UNITS

A heat disinfection unit is a contact lens care product intended to disinfect soft (hydrophilic) contact lenses by means of heat. Heat disinfection units act by transferring sufficient heat to a contact lens case containing the lenses and saline solution for a specified period of time to destroy harmful microorganisms on the lenses.

Manufacturing/Chemistry:

The following manufacturing/chemistry guidance should be used when submitting a 510(k) for a heat disinfection unit:

A positive function/failure indicator should be installed in the heat unit circuitry. Any 510(k) for a heat unit without a positive function/failure indicator should have an acceptable justification for not having the indicator. A positive function/failure indicator is one that:

- indicates that the unit is heating or on only when heat is being generated or electrical current is flowing through the heat element; and

- indicates that the unit is cool or off only when the temperature has dropped towards room temperature or when no current is flowing in the heat unit.

Units that meet this definition would include:

- electrically timed or thermostatically controlled units in which a light emitting indicator is effectively in series with the heater; and

- units that use a temperature sensing element that changes color or provides a similar distinct indication between room temperature and elevated temperature.

A 510(k) for a heat disinfection unit should contain:

1. time-temperature curves from a statistically significant sample of units which demonstrate that the lower three standard deviation points of the distribution of time-temperature curves is greater than the minimum time-temperature necessary for effective heat disinfection;

2. electric circuitry and safety features;

3. certification that the heat disinfection unit conforms to the requirements of applicable electrical safety standards [e.g., Underwriters Laboratories (UL) 1431 entitled "Personal Hygiene and Health Care Appliances"].

4. QA/QC procedures and sampling techniques (e.g., Military Standard 105E) for critical components;

5. QA/QC procedures and sampling techniques (e.g., Military Standard 105E) for final device; and

6. 30-cycle lens compatibility under the recommended care regimen.

Microbiology:

Microbiology data are generally not required for heat disinfection units provided the heat disinfection cycle time and temperature are equivalent to those of the predicate device (e.g., 80°C for 10 minutes).

If an alternative heat disinfection cycle is proposed, microbicidal efficacy should be demonstrated by a microbial challenge test utilizing at least 10 units and 20 lenses each from lens groups I and IV. The following procedure is recommended:

> Inoculate lenses with approximately 1 X 10^6 organisms Enterococcus faecalis (formerly Streptococcus faecalis) (recommended strain: Ward's Natural Science Establishment #85 W 1100) in organic soil, and expose to the proposed heat disinfection cycle. Prepare the organic soil inoculum as described in Section VI (Recommended Test Methods) Micro--Appendix B, Part 2:III.B and an inoculum control as described in Micro--Appendix B, Part 2:D.1. After heat disinfection, culture lenses as described in Micro-Appendix B, Part 2:III.C.3. If a preserved saline is used in the heat disinfection process, use a recovery medium that contains one or more neutralizing agents. Validate the recovery medium as described in Micro--Appendix B, Part 2:D.2.
>
> All lens and test filter combinations should show no growth.

Toxicology:

Toxicology data are generally not required for heat disinfection units provided the heat disinfection unit is essentially identical to the predicate device unless the heat unit is also designed for use as a lens case. In the latter situation, toxicology information similar to that for lens cases should be provided.

Clinical:

Clinical data are not generally required for heat disinfection units provided the specifications for the heat disinfection unit are substantially equivalent to the predicate device.

G. CONTACT LENS CASES

A contact lens case is a lens care product to be used by the contact lens wearer or practitioner for storing contact lenses while not being worn. Contact lens cases are especially designed for use in chemical, heat or H_2O_2 disinfecting systems. Not included in this definition are lens cases intended by the manufacturer only for shipping the lenses in a dry state.

Manufacturing/Chemistry:

The following manufacturing/chemistry information should be provided in the 510(k):

1. Engineering drawing and a brief description of polymeric materials used.

2. Physical and chemical data of polymeric materials used and name and address of the manufacturer.

3. If the lens case is used in heat disinfection, the applicant should provide proof that the lens case can withstand repeated heat disinfection. Physical and chemical data of polymeric material (e.g., heat distortion temperature or glass transition temperature may be used to substantiate this indication). In general, a lens case used in heat disinfection should contain a rubber gasket.

4. The volume capacity of the lens case (e.g., should be of sufficient volume to assure that the lens remains completely immersed under conditions of use).

5. Certification that colorants used in the manufacture of the lens case are insoluble in water [this information is often found in the material safety data sheet (MSDS)].

Microbiology:

Microbiology testing requirements for lens cases are dependent upon claims made in the labeling. In general, microbiology issues pertaining to contact lens cases are covered by the warning recommended in the labeling [see Section V (Labeling)].

Toxicology:

Toxicology data from the following tests conducted on both the plastic and gasket materials should be provided:

1. Systemic Toxicity Test (see USP/NF XXII for methodology)

2. Acute Ocular Irritation Test

3. In-Vitro Cytotoxicity Test

See Section VI (Recommended Test Methods) Tox--Appendices A-B for guidance.

CDRH is aware that suppliers of plastic and other materials generally provide MSDSs to manufacturers of devices using their materials. Manufacturers are encouraged to carefully scrutinize the information provided in these MSDSs to determine if they contain the needed toxicology information before initiating the recommended tests. If the information is included on the MSDS, the MSDS may be provided in lieu of toxicology data. MSDSs should be provided in 510(k)s.

Clinical:

Clinical data are generally not required to be submitted in a 510(k) for lens cases. However, manufacturers should consider the impact of design, materials and intended use on need for clinical performance data.

H. CONTACT LENS ACCESSORIES (e.g., Mechanical Cleaning Aids and Accessory Cleaning Pads)

Contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads) are devices used as cleaning aids in conjunction with contact lens cleaning solutions.

1. Mechanical Cleaning Aid: A mechanical cleaning aid may be available as a hand or battery-operated or electrical device that aids in cleaning contact lenses by generating ultrasound, tumbling motions, or vibrations for the cleaning solution while it cleans. It may also act as a receptacle during the rinsing or chemical disinfecting steps in the lens care regimen.

   Although the mechanical cleaning aid has not been officially classified, in the past CDRH has evaluated requests for marketing such devices through the 510(k) process. With the availability of this special controls document, it is our present intention to allow manufacturers of SE mechanical cleaning aids to label their devices for use as accessories to approved contact lens cleaning solutions.

   Applicants are advised that if the new device contains a new technology, performance data (e.g., cleaning effectiveness) may be required to demonstrate substantial equivalence. DOD should be contacted concerning protocol development for performance data for 510(k)s for devices containing new technology (telephone number at the end of Introduction section).

   Manufacturing/Chemistry:

   The following information should be provided in the 510(k) for the mechanical cleaning aids (as applicable):

   a. a detailed description of the device and engineering drawings;

   b. a mode of action (e.g., ultrasound);

   c. electric circuitry and safety features if applicable [e.g., for all electrical devices, certification that they conform to the requirements of applicable electrical safety standards (e.g., UL 1431 entitled, "Personal Hygiene and Health Care Appliances")]; and

   d. if the device generates heat when used according to the directions in the labeling, an assessment of this affect on the lens parameters and durability.

Microbiology:

Microbiology testing requirements for mechanical cleaning aids are dependent upon claims made in the labeling. In general, sufficient microbiology data should be submitted to support all claims being made in the labeling.

Toxicology:

Toxicology data from the following tests conducted on the materials (e.g., gaskets, plastics, etc.) that come in contact with the solutions should be provided:

a. Systemic Toxicity Test (see USP/NF XXII for methodology)

b. Acute Ocular Irritation Test

c. In-Vitro Cytotoxicity Test

See Section VI (Recommended Test Methods) Tox--Appendices A-B for guidance.

CDRH is aware that suppliers of plastic and other materials generally provide MSDSs to manufacturers of devices using their materials. Manufacturers are encouraged to carefully scrutinize the information provided in these MSDSs to determine if they contain the needed toxicology information before initiating the recommended tests. If the information is included on the MSDS, the MSDS may be provided in lieu of toxicology data. MSDSs should be provided in 510(k)s.

Clinical:

Clinical data are generally not required to be submitted in a 510(k) for mechanical cleaning aids. However, manufacturers should consider the impact of design, materials and intended use on need for clinical performance data in order to provide adequate directions for use of the device.

2. Accessory Cleaning Pads: Accessory cleaning pads are made of materials that generally contain mildly abrasive surfaces. The pads are intended to be used in conjunction with contact lens cleaning solutions to aid in lens cleaning by minimizing direct contact with the hands.

Manufacturing/Chemistry:

The following manufacturing/chemistry information should be provided in the 510(k):

a. compatibility data that demonstrate the cleaning pad will not damage (e.g., scratch) the lenses; and

b. a detailed description of the chemical components of the device.

Microbiology:

The applicant should identify and provide information to address all potential microbial concerns raised by reuse of the pad, if the pads are to be reused, in which case cleaning instructions for the pad should be provided. In addition, appropriate lens cleaning instructions, warnings, and precautions should be included in the labeling.

Toxicology:

The following toxicology information should be provided in the 510(k):

> Data demonstrating that any materials coming in contact with the cleaning solutions are not eye irritants. This information may be provided in an MSDS or from testing conducted in accordance with the Acute Ocular Irritation Test found in Section VI (Recommended Test Methods) Tox--Appendix-A.

Clinical:

Clinical data are not generally required to be submitted in a 510(k) for accessory cleaning pads. However, manufacturers should consider the impact of design, materials and intended use on need for clinical performance data.

IV. MODIFICATIONS OF APPROVED CONTACT LENS CARE PRODUCTS REQUIRING A 510(k):

A. A manufacturer with a PMA or a 510(k) for a contact lens care product may, for a variety of reasons, want to modify the device. Based on our knowledge and experience with contact lens care products, CDRH has listed the following changes to approved care products that could significantly affect safety and effectiveness of the device and thus require 510(k) clearance under 21 CFR 807.81(a). These changes include, but are not necessarily limited to, the following:

1. a change in an active ingredient or concentration of the active ingredient;

   NOTE: Although this guidance document focuses primarily on active ingredients, manufacturers should also assess the effects of inactive ingredients (e.g., buffering agents and tablet coatings) on such factors as pH, tonicity, preservative effectiveness, solution compatibility with lenses, and preservative uptake/release to determine if the change significantly affects safety and effectiveness of the device and, therefore, requires submission of a 510(k).

2. addition of a new ingredient for ophthalmic use;

3. a change in preservative or preservative concentration in solutions;

4. a major change or modification in the product specific intended use of the device or indication for use (e.g., addition of performance information in the labeling that implies that the device can be used for previously unmentioned product specific use such as adding a cleaning claim to a disinfecting solution to create a multi-purpose solution or claiming that the device can be used for a different type of lens such as hydrophobic when previously hydrophilic was indicated);

5. changes in the directions for use affecting product performance (e.g., decreased soak times for disinfecting solutions or periodic cleaners);

6. a change in the type of container/closure and delivery systems of a contact lens solution [e.g., changing from a plastic bottle to an aerosol can or changing from a chemical preservative system to a physical barrier (e.g., filters) preservative system for contact lens solution];

7. changes in dosage form (e.g., adding tablet coatings for time release or changing from a liquid to tablet preparation of the active agents); and

8. addition or deletion of a contraindication:

   NOTE: Manufacturers should submit a Special 510(k)--Changes Being Effected to add a contraindication. Applicants should refer to existing FDA policy for guidance on deciding when to submit a 510(k) for a labeling change to an existing device. Deletion of a contraindication would be expected to change the intended use and would, therefore, require submission of a new 510(k).

B. Listed below are some examples of changes that should not require a 510(k) to be submitted provided the change adheres to current FDA policies and is adequately documented:

1. addition of private label distributors who are not manufacturing the product;

2. extension of the expiration date according to a cleared/approved protocol;

3. a change to a smaller or larger size container made from identical materials provided stability studies are done according to a cleared/approved protocol and product specifications remain unchanged. If the new container is no more than 8 times larger than the smallest size container for which stability/sterility testing data have previously been evaluated, no additional stability studies are necessary. In accordance with 21 CFR 800.10(b), contact lens solutions should be so packaged as to volume and type of container to minimize contamination during use. The largest size product container currently marketed is a 16 fl. oz size. [See Section VI (Recommended Test Methods, Shelf-Life Protocol) in the Appendices];

4. changes in packaging material (e.g., high density polyethylene to low density polyethylene) provided: (1) the new materials meet USP requirements (Containers for Ophthalmics Plastics--Biological Test Procedures) and leachables do not cause eye irritation, (2) the new materials do not compromise sterility package integrity, and (3) shelf-life is re-established according to a cleared/approved protocol.

5. changes in container shapes;

6. changes in trade name provided the new trade name does not misbrand the device;

7. adding a new manufacturing site without changing the manufacturing processes;

8. reformatting or editorial changes in labeling;

9. changes from one traditional sterilization method utilized for the sterilization of the final product, raw materials or packaging materials to another traditional method (e.g., from ETO to gamma radiation) provided: (1) the new method meets an acceptable SAL (10^{-6} for terminal sterilization and 10^{-3} for aseptic processing) and does not change the product performance specifications and (2) shelf-life is re-established according to a cleared/approved protocol;

10. documented changes in manufacturing process that could not significantly affect the safety or effectiveness of the device and are implemented in accordance with GMP requirements; and

11. adding or strengthening precautions or warnings in accordance with existing FDA policy.

    NOTE: Manufacturers should monitor device usage and periodically revise their warnings and precautions sections based on use experience. A 510(k) for such a change in precautions or warnings generally does not require submission of a 510(k) unless the change results in a new intended use. However, manufacturers should document these changes in their files.

If after reviewing the above changes specifically identified in this product specific guidance document as needing a new 510(k), applicants are unable to determine whether a 510(k) is required for a proposed modification to a contact lens care product, they may consult existing FDA policy (e.g., Blue Book Memorandums) on modifications needing a 510(k).

V. LABELING

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V. LABELING

A. Introduction:

This section of the guidance provides general information on the applicable regulations and requirements for labeling of contact lens care products, what information should be submitted for review of a 510(k) for these devices, and guidance on preparing labeling for contact lens care products [e.g., contact lens solutions and tablets, lens cases, heat disinfection units, salt tablets/capsules, and contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads)] respectively.

Contact lens care products are subject to the general labeling requirements for all medical devices outlined in 21 CFR 801. Contact lens solutions are further subject to 21 CFR 800.10, Contact Lens Solutions; Sterility and 21 CFR 800.12, Contact Lens Solutions and Tablets; Tamper-resistant Packaging.

CDRH considers adequate labeling to be an important safeguard (special control) for assuring that new contact lens care products are substantially equivalent in terms of safety and effectiveness to legally marketed devices. Applicants are encouraged to provide predicate device labeling in their 510(k) submissions.

B. Labeling Information Required in an Original 510(k) or 510(k) for a Modification:

Under 21 CFR 807.87(e), a 510(k) applicant is required to submit proposed labels, labeling, and advertisements sufficient to describe the device (composition), its intended use (i.e., indications for use), and the directions for its use. This basic information is required before CDRH can render a substantial equivalence determination for either an original 510(k) or for a 510(k) that includes modifications (e.g., changes in device description, intended use, or directions for use) if the modification significantly affects safety or effectiveness of the device. In addition, manufacturers should submit a 510(k) before making a change such as adding or deleting a contraindication (see Section IV).

C. Regulatory Guidance:

Information that generally accompanies the sale and distribution of contact lens care products can include, but is not limited to, such printed matter as outer carton labeling, bottle or device label, and (for solutions) a package insert. CDRH considers such printed matter to be labeling as described in Section 201(m) of the act, which also provides general guidance as to the type of information that should be included in contact lens care product labeling. Because labeling is not approved when 510(k) clearance is granted, the manufacturer should be advised that once the device is marketed, the device is required to be labeled in accordance with applicable regulations which include, among other things, prohibition against misbranding and including false and misleading information in the labeling. In order to avoid violating the labeling regulations, applicants should scrutinize their labeling in

draft for words or phrases that are exaggerated, potentially ambiguous, or subjective as well as unsubstantiated statements, claims, or puffery. Such words or phrases in labeling may be considered false or misleading, and if marketed with false or misleading claims, could cause the manufacturer to be subject to regulatory action. CDRH urges applicants to carefully adhere to pertinent labeling regulations and DO NOT PRINT LABELING IN FINAL FORM until a substantial equivalency letter is received.

Pertinent Labeling Regulations:

- Definitions of "label" and "labeling" [Sections 201(k) and 201(m) of the act].
- Information required in a premarket notification submission pertaining to labeling (21 CFR 807.87(e)).
- General Labeling Provisions (21 CFR 80l); Contact Lens Solutions; Sterility (21 CFR 800.10); and Contact Lens Solutions and Tablets; Tamper-resistant Packaging (21 CFR 800.12).
- Explanation of what causes a device to be misbranded and false and misleading labeling (Section 502 of the Act, 21 CFR 80l.6, 807.39, and 807.97).

The following references or their most recent revisions may be consulted for further guidance:

1. Labeling Regulatory Requirements for Medical Devices. This publication discusses such areas as advertising material considered labeling, what is false and misleading labeling, adequate directions for use, and provides examples of ways that device manufacturers can comply with labeling requirements. Copies of this publication can be obtained by contacting DSMA (fax and telephone numbers are at the end of the Introduction section).

2. Device Labeling Guidance #G91-1 (Office of Device Evaluation Blue Book Memorandum). This guidance provides detailed interpretations of applicable labeling regulations, and can be obtained from DSMA (fax and telephone numbers are at the end of the Introduction section).

3. Human Factors Principles of Medical Device Labeling. This guidance pertains to labeling for all medical devices. It contains basic principles for the effective design of instruction booklets for medical device use. Along with the principles are selected examples (graphics, cleaning steps, etc.) abstracted from a generic model booklet. These examples do not contain all elements required by 21 CFR 80l, but they embody human factors principles and may be used, along with predicate labeling, as a guide in writing your labeling. This guidance is available by contacting DSMA (fax and telephone numbers are at the end of the Introduction section).

D. Labeling Examples:

An outline and specific device information that should be included in pre-formulated solution and tablet labeling based upon predicate device labeling is provided in Labeling--Appendix A.

Labeling--Appendix A also includes an example of a package insert for aerosol saline solution that incorporates principles taken from labeling entitled, "Improved Patient Instructions for Care of Soft Contact Lenses," that was prepared by a CDRH focus group based upon a study using consumers and Write-It-Right principles (Write-It-Right booklet is available by contacting DSMA (fax and telephone numbers are at the end of the Introduction section).

Applicants are advised that although it is not required that they use the exact wording in the product specific contraindications, warnings, precautions, etc., provided in this outline, FDA recommends the basic content not be changed. Thus, to avoid the potential for changes in meaning, we encourage applicants to exercise care.

An applicant may follow the format using Write-It-Right principles or follow the format in the most recently marketed predicate device labeling.

In cases where individual devices require unique warnings, precautions, contraindications, etc., in addition to those recommended in the specific device information sections, applicants should provide sufficient information in the 510(k) to support the inclusion of these unique statements in their labeling.

Labeling--Appendices B-F contain examples of labeling for lens cases, heat disinfecting units, salt tablets/capsules systems, and contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads), respectively.

If further labeling guidance is required, applicants may contact DOD (fax and telephone numbers are at the end of the Introduction section).

LABELING--APPENDIX A

Package Insert for Pre-Formulated Solutions and Tablets

Labeling--Appendix A includes (1) an outline and specific device information that should be included in a package insert for pre-formulated solutions and tablets, (2) an outline of specific device information that should be included on the outer carton and bottle labeling for these devices, and (3) an example of a package insert for aerosol saline using Write-It-Right principles.

In preparing labeling, applicants should fill in the brackets by including specific information pertaining to the device in the 510(k). Predicate device labeling, the outline below, and the example provided in this section may be used as further guidance.

SAMPLE PACKAGE INSERT

PLEASE READ CAREFULLY AND KEEP THIS PACKAGE INSERT FOR FUTURE USE.

DESCRIPTION:

[Include "sterile" if it is a solution; list active ingredients and quantitate the preservative(s) 00.0%] [optional, list inactive ingredients]. When applicable, include the following additional descriptive information:

isotonic
buffered
preserved/unpreserved
propellants
enzyme
tablet, disk, or [describe]]

ACTIONS:

[Include a concise description of the function of the device (i.e., how the device works in relation to the contact lens). When applicable, the actions may be listed with the indications (i.e., INDICATIONS/ACTIONS)].

INDICATIONS (USES):

[Include a description of the proper use of the device. NOTE: The indications should be essentially the same as the predicate device.]

CONTRAINDICATIONS:

Contraindications describe situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. If there are no contraindications, include the statement: "There are no known contraindications for use of this product." Include all contraindications specific to your device. Listed below is a general contraindication.

For all contact lens pre-formulated solutions:

- If you are allergic to any ingredient in this product, DO NOT use.
- Add additional contraindications if applicable to specific device.

WARNINGS:

Warnings include serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. Listed below are (1) general warnings that pertain to all pre-formulated solutions and tablets and (2) product specific warnings. Include those general and specific warnings that apply to the device in the 510(k).

General Warnings:

- To avoid contamination, DO NOT touch tip of container to any surface. Replace cap after using.
- To avoid contaminating your solution, DO NOT transfer to other bottles or containers.
- Add additional warnings if applicable to specific device.

Product Specific Warnings:

Saline Solutions: Add the following specific warnings following heat disinfection (when applicable):

- To minimize the risk of contamination, keep lenses in the unopened case until ready to wear.

1. Aerosol Salines

   - Contents under pressure, DO NOT spray directly into the eye as serious injury to the eye may result.
   - DO NOT puncture or incinerate can.
   - DO NOT store at temperature above 120^{o}F.
   - Always spray a small amount of solution into the sink to clear the nozzle of contaminants before spraying the saline onto your lenses.

2. Unpreserved Saline

   - To minimize the risk of eye infection DO NOT use this solution beyond the recommended discard date.

3. Unit Dose Saline

- This product is provided in a single dose package that does not contain preservatives. To minimize the risk of contamination and possible eye infection, DO NOT save and reuse any unused saline. Discard the package immediately after use.

Daily Cleaners:

- DO NOT use directly in the eye. Solution may cause severe irritation, burning and stinging.

Periodic Cleaners:

- DO NOT dissolve enzyme tablets in distilled or tap water. Distilled water and tap water are non-sterile. Use of non-sterile products may lead to microbial contamination of lenses which can cause serious eye infections.

- After cleaning with enzyme cleaner, your lenses should be cleaned with a daily cleaner, rinsed and disinfected. Failure to do so may result in eye irritation, burning, or stinging.

- DO NOT put solution directly in the eye as severe irritation, burning and stinging may result.

Chemical Disinfecting Solutions/Systems and Conditioning Solution:

NOTE: No individual product within a chemical disinfection regimen should be labeled as the "disinfecting solution" unless it can meet the primary criteria of the stand-alone microbiology disinfection test (as referenced in Section VI, Recommended Test Methods, Micro--Appendix B Part 1). Chemical disinfection regimens which meet the regimen procedure criteria may be labeled, for example, as having a starting solution and a finishing solution or as having a cleaning solution and a soaking solution, but no individual product should be labeled as the disinfecting solution.

- DO NOT use with heat (thermal) disinfection unless specifically indicated in labeling.

Warnings for Hydrogen Peroxide Disinfecting Solutions:

- KEEP [TN] disinfecting solution (hydrogen peroxide) OUT OF THE EYES. ALWAYS USE [TN] (neutralizer) with [TN] disinfecting solution to NEUTRALIZE YOUR LENSES BEFORE APPLYING THEM TO YOUR EYES. If [TN] disinfecting solution accidentally comes in contact with the eyes, it may cause burning, stinging or redness. Remove your lens(es) immediately and flush your eyes with a large amount of water or sterile saline. If burning or irritation continues, seek professional assistance.

- Keep [TN] disinfecting solution (hydrogen peroxide) out of the reach of children. If accidentally swallowed, an upset stomach and vomiting may result. Seek immediate professional medical assistance or contact a poison control center.

- Not for use with heat (thermal) disinfection because [state reason].

Warnings for Neutralizing Products (when applicable):

- This tablet is not to be taken internally. If accidentally swallowed, an upset stomach and vomiting may result. Seek immediate professional medical assistance or contact a poison control center.

- DO NOT crush the [TN] Neutralizing Tablet. If a crack occurs in the coating, the tablet may begin to neutralize the [TN] Disinfecting Solution before adequate disinfection occurs.

- DO NOT use [TN] Neutralizer disk for more than XXX uses or XX months of daily use. [**Note:** Uses and time period to be determined by testing data.]

Warnings for Conditioning Solutions:

- DO NOT use with soft (hydrophilic) contact lenses. Soft (hydrophilic) contact lenses can absorb solution components that may cause severe irritation, burning and stinging of the eyes.

In-Eye Contact Lens Solutions:

- To minimize the risk of contamination and eye infection, DO NOT use beyond the discard date on the bottle label (if applicable).

The following non-product specific warnings have been included in predicate device labeling (as applicable) as a "public service" announcement:

Warnings for Hydrophilic Contact Lens Products:

Warnings: PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN SERIOUS INJURY TO THE EYE. Follow your eye care practitioner's directions and all labeling instructions for proper use and care of your lenses and lens care products, including the lens case. Eye problems, including corneal ulcers, can develop rapidly and lead to loss of vision. Daily wear lenses are not indicated for overnight wear and should not be worn while sleeping. Clinical studies have shown the risk of serious adverse reactions is increased when these lenses are worn overnight. Extended wear lenses should be regularly removed for cleaning and

disinfection or for disposal and replacement on the schedule prescribed by your eye care practitioner. Clinical studies have shown that there is an increased incidence of serious adverse reactions in extended wear contact lens users as compared to daily wear contact lens users. Studies have also shown that the risk of serious adverse reactions increases the longer extended wear lenses are worn before removal for cleaning and disinfection or for disposal and replacement. Studies have also shown that smokers have a higher incidence of adverse reactions. If you experience eye discomfort, excessive tearing, vision changes, or redness of the eye, immediately remove your lenses and promptly contact your eye care practitioner. All contact lens wearers should see their eye care practitioner as directed.

Warnings for Hydrophobic Contact Lens Products:

Warnings: PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN SERIOUS INJURY TO THE EYE. Follow your eye care practitioner's directions and all labeling instructions for proper use and care of your lenses and lens care products, including the lens case. Eye problems, including corneal ulcers, can develop rapidly and lead to loss of vision. Daily wear lenses are not indicated for overnight wear and should not be worn while sleeping. If you experience eye discomfort, excessive tearing, vision changes, redness of the eye, immediately remove your lenses and promptly contact your eye care practitioner. All contact lens wearers should see their eye care practitioner as directed.

Listed below is a general warning taken from the Write-It-Right example that applies to both soft (hydrophilic) and rigid gas permeable contact lenses:

Warning: Serious injury to the eye and loss of vision may result from problems with contact lenses and lens care solutions. Eye problems, including corneal ulcers and infections, can develop rapidly. Immediately remove your lenses and call or visit your eye care practitioner if you experience any adverse reactions such as: eye discomfort, excessive tearing, vision changes, pain, unusual eye discharge, sensitivity to light, or redness of the eye.

PRECAUTIONS:

Precautions include information regarding any special care to be exercised by the user for the safe and effective use of the device. Listed below are (1) general precautions that pertain to all pre-formulated solutions and tablets and (2) product specific precautions. Include those general and specific precautions that pertain to the device in the 510(k).

General Precautions:

- Never reuse this solution.

- Keep the bottle tightly closed when not in use.

Special Storage Conditions.

- Use before the expiration date marked on the [carton] [bottle] and [label] (use applicable).
- Keep out of the reach of children.
- Store at room temperature (if applicable).

Specific Precautions:

Daily Cleaners:

- Lenses should never be placed directly in the eyes from the cleaning solution. Always rinse and disinfect lenses after cleaning.

Periodic Cleaners:

- Tablets are not to be taken internally. If accidentally swallowed, [describe what may occur and measures to be taken].
- DO NOT use tablets that are broken or discolored.
- DO NOT use tablets from packages that are torn or punctured.
- Use only the special vials recommended for use with [TN].
- Use only freshly prepared enzymatic cleaning solution and discard immediately after use.
- DO NOT soak lenses for more than XX hours because [state reason as determined by test data (if applicable)].
- The enzymatic cleaning cycle is not a substitute for regular cleaning or disinfecting of your contact lenses.

Chemical Disinfecting Solutions/Systems:

Hydrogen Peroxide Systems:

- DO NOT USE OVER-THE-COUNTER GENERIC HYDROGEN PEROXIDE because [state reason].

Neutralizing Products:

- DO NOT use tablets that appear to be broken, chipped, or discolored.
- DO NOT use tablets from packages which are torn or punctured.

- DO NOT substitute [TN] Neutralizer components;
- DO NOT use neutralizing tablets in a heat disinfection unit.

In-Eye Contact Lens Solutions (Lubricating/Rewetting Drops):

- Add precautions that are specific to the device in the 510(k).

ADVERSE REACTIONS (Problems and what to do):

Adverse reactions include undesirable effects, reasonably associated with the use of the device, that may occur as part of the effect of the device or may be unpredictable in their occurrence.

[Include the following, as applicable to the device in the 510(k).]

The following problems may occur: eyes sting, burn or itch(irritation),comfort is less than when lens was first placed on the eye, feeling of something in the eye (foreign body, scratched area), excessive watering (tearing) of the eye, unusual eye secretions, redness of the eye, reduced sharpness of vision (poor visual acuity), blurred vision, rainbows or halos around objects, sensitivity to light (photophobia), or dry eyes.

If you notice any of the above:

IMMEDIATELY REMOVE YOUR LENSES.

- If the discomfort or problem stops, then look closely at the lens.
- If the lens is in any way damaged, DO NOT put the lens back on your eye. Place the lens in the storage case and contact your eye care practitioner.
- If the lens has dirt, an eyelash, or other foreign body on it, or the problem stops and the lens appears undamaged, thoroughly clean, rinse and disinfect the lens, then reinsert it.
- If the problem continues, IMMEDIATELY remove the lens and consult your eye care practitioner.

If any of the above symptoms occur, a serious condition such as infection, corneal ulcer, neovascularization or iritis may be present. Seek immediate professional identification of the problem and prompt treatment to avoid serious eye damage.

All adverse reactions observed while using [TN] should be reported to:

Name of Company
Address

 1-800-[phone number] 

[Insert information from predicate device labeling and any other information that is specific to the device in the 510(k).]

DIRECTIONS FOR USE:

General Instructions:

Always wash and rinse your hands before handling your lenses. This will help to prevent eye infections by removing dirt and oils that could get on the lenses.

Use only the solutions recommended by your eye care practitioner. Seek advice from your eye care practitioner before making any changes to your care regimen to ensure compatibility with lenses.

Always follow the directions for use in the labeling included with each solution as instructions may be different for each solution.

Specific Instructions: [Include specific Directions for Use (e.g., directions for a disinfecting regimen should describe all steps in the regimen using non-descriptive headings such as Step 1, Step 2, Step 3...), Directions for a disinfecting product (stand-alone) may describe the specific steps in the regimen using descriptive headings (e.g., Cleaning, Disinfection, Rinsing...]

HOW SUPPLIED:

[Describe how device is packaged for distribution (e.g., quantity of contents, sterile, packaged in bottle/aerosol can, and marked with lot number and expiration date).]

MANUFACTURER OR DISTRIBUTOR NAME AND ADDRESS:

Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code.

Printed [Month and Year]

Note: **MULTI-PURPOSE SOLUTIONS**

Labeling for multi-purpose solutions should combine the Description, Actions, Indications (Uses), Precautions, Warnings, and Directions for Use statements for each applicable indication (e.g., saline, disinfecting solution, cleaner). Duplicate words or phrases can be eliminated so that the resulting information is clear and understandable. Strict attention should be paid to the labeling for this product to assure that adequate directions for use (e.g., rubbing and rinsing times for daily cleaning, soak times for disinfection, and maximum storage times following disinfection) are provided for all intended uses identified above. A contact lens solution that cannot perform all of the functions indicated in the labeling should not be labeled as a multi-purpose contact lens care solution.

APPENDIX A (CONTINUED)

Bottle/Can Label:

Front:

- Product Trade Name
- Actions and Indications (e.g., cleans, disinfects, etc.)*
- Lens Statement [i.e., the type of lenses for which the device may be used (e.g., RGP or soft (hydrophilic) lenses)]
- Net Quantity Contents**
- Sterile

Side or Back:

- [Date Opened_____/or Discard Date_____] (when applicable)•Tamper-Resistant Statement***
- Description (i.e., Contents)
- SEE PACKAGE INSERT FOR... IMPORTANT SAFETY INFORMATION.
- Directions for Use
- Special Storage Conditions (e.g., store at room temperature)
- Keep out of Reach of Children
- Product Specific Warnings
- Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot Number
- Expiration Date

___

* 21 CFR 801.61
** 21 CFR 801.62
*** 21 CFR 800.12

APPENDIX A (CONTINUED)

Carton:

Principal Display Panel*:

- Product Trade Name
- Actions and Indications** (e.g., cleans, disinfects, etc.)
- Lens Statement (i.e., the type of lenses for which the device may be used)
- Net Quantity Contents***
- Sterile

Outer Carton Panels:

- Description (i.e., Contents)
- Contraindications:
  - If you are allergic to any ingredient in this device, DO NOT use.
  - Any additional known contraindications for specific device.
- Directions for Use (or reference Package Insert)
- Special Storage Conditions (e.g., store at room temperature)
- SEE PACKAGE INSERT FOR... IMPORTANT SAFETY INFORMATION.
- Keep out of Reach of Children
- Tamper-Resistant Statement****
- Product Specific Warnings
- Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot Number
- Expiration Date

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* 21 CFR 801.60
** 21 CFR 801.61
*** 21 CFR 801.62
**** 21 CFR 800.12

APPENDIX A (CONTINUED)

Package Insert Using Write-it-Right Principles

Included below is an example of a package insert for aerosol saline solution. This example incorporates principles taken from labeling entitled, "Improved Patient Instructions for Care of Soft Contact Lenses," that was prepared by a CDRH focus group based upon a study using consumers and Write-It-Right principles. This example differs somewhat in format from predicate device package inserts in that some sections have been rearranged, while others have been combined in an effort to eliminate duplication. In writing this package insert, icons were used to focus on various information. Warnings and precautions were boxed and strategically placed throughout the package insert to highlight the consumer's awareness to special considerations. Applicants developing new labeling or needing to bring their labeling up to date may choose to follow this sample package insert format or follow the format in predicate device labeling.

SAMPLE PACKAGE INSERT FOR MULTI-DOSE UNPRESERVED SALINE
(packaged in aerosol container)

IMPORTANT: Please read carefully and keep this information for future use.

[Trade Name (TN)]

WARNING

Serious injury to the eye and loss of vision may result from problems with contact lenses and lens care solutions. Eye problems, including corneal ulcers and infections, can develop rapidly. Immediately remove your lenses and call or visit your eye care practitioner if you experience any adverse reactions such as: eye discomfort, excessive tearing, vision changes, pain, unusual eye discharge, sensitivity to light, or redness of the eye.

[Note: Use only those indications included in the labeling that have been approved in a PMA or cleared in a 510(k).]

INDICATIONS/ACTIONS:

[TN] saline is indicated for use with (specify type) contact lenses for rinsing after cleaning to remove loosened debris and cleaning solution, rinsing prior to lens insertion, keeping lenses wet during heat disinfection, storage after disinfection, as a diluent for dissolving lens care tablets (e.g., enzyme or disinfecting tablets), and as a diluent for use in hydrogen peroxide disinfection systems (limited use).

DIRECTIONS FOR USE:

General Instructions:

Always wash and rinse your hands before handling your lenses. This will help to prevent eye infections by removing dirt and oils that could get on the lenses.

Use only the solutions recommended by your eye care practitioner. Seek advice from your eye care practitioner before making any changes to your care regimen to ensure compatibility with lenses.

Always follow the directions for use in the labeling included with each solution as instructions may be different for each solution.

WARNING

To avoid contaminating your solution or your lenses:

- DO NOT transfer this solution into other bottles or containers.
- DO NOT touch nozzle tip of the can to any surface.

STEP 1. RINSE

WARNING

- Contents under pressure, DO NOT spray directly into the eye, as serious injury to the eye may result.
- Always spray a small amount into the sink to clear the nozzle of contaminants before spraying the saline onto your lenses.

☞ Rinse the lens thoroughly with fresh saline solution. Direct a stream of saline on both sides of the lens for at least 10 seconds.

STEP 2. HEAT DISINFECTION

☞ Place each lens in the appropriate chamber of the storage case.

☞ Fill each chamber with enough [TN] to completely cover the lenses.

☞ Close the lens case tightly so that the lens will not dry out.

☞ Place the lens storage case in your heat disinfection unit.

☞ Follow the instructions that come with your heat disinfection unit.

☞ Keep the lenses in the unopened lens case until you are ready to wear them.

CAUTION
• Never reuse the solution • Store at room temperature • Keep out of reach of children • Use before expiration date marked on the container

WARNING
• To minimize the risk of contamination, DO NOT store lenses in saline that has not been heat disinfected.

WARNING CONTENTS UNDER PRESSURE
• DO NOT puncture or incinerate can. • DO NOT store at temperatures above 120^{o}F.

NOTE: This product may be used to dissolve enzyme tablets or as a neutralizing solution in some hydrogen peroxide systems. Follow the Directions for Use in the labeling accompanying your enzyme tablets or hydrogen peroxide system.

All contact lens wearers should see their eye care practitioner as often as directed. If your lenses are for extended wear, your eye care practitioner may prescribe more frequent visits to carefully monitor your ocular health.

DESCRIPTION/CONTENTS:

[TN] is a sterile isotonic [the following as applicable: buffered/ unpreserved] solution containing [list all ingredients including any propellant(s)].

CONTRAINDICATIONS:

There are no known contraindications for use of this product OR

If you are allergic to any ingredient in [TN], DO NOT use.

ADVERSE REACTIONS:

All adverse reactions observed while using [TN] should be reported to:

Name of Company
Address

 1-800-[phone number] 

HOW SUPPLIED:

[TN] is supplied sterile in [] fl. oz. aerosol cans. Each can is marked with the lot number and expiration date.

Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code

Printed [Month and Year]

LABELING--APPENDIX B

Lens Cases

[Include applicable information under the following headings. Applicants should use predicate device labeling as guidance].

TRADE NAME:

INDICATIONS: For storage of [soft (hydrophilic)/rigid gas permeable/and hard] contact lenses during [heat disinfection/heat or chemical disinfection (use applicable)].

Include additional limiting information (if applicable):

- For storage only - not for use as a container for heat or chemical disinfection.
- Use for storage during chemical disinfection only. DO NOT USE WITH HEAT.

DIRECTIONS FOR USE:

General Instructions: [Include preparing the lens case for use and how to care for the lens case daily.]

Specific Instructions: [Include step-by-step instructions for use.]

WARNINGS:

Warning for All Lens Cases:

- Lens cases can be a significant source of microbial contamination. To help prevent eye infections, lens cases should be cleaned, rinsed and air dried every day; and replaced frequently (as recommended by the manufacturer).

Warning for Lens Cases Indicated for Use in Chemical Disinfection Only:

- Use of this lens case with heat may cause warpage. USE FOR STORAGE DURING CHEMICAL DISINFECTION ONLY. DO NOT USE WITH HEAT.

ENDING:

- Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot No.
- Printed [Month and Year]

LABELING--APPENDIX C

Heat Disinfection Units

Applicants should follow the format of predicate device labeling for heat disinfection units.

The heat disinfection unit labeling should comply with 21 CFR 801.15, "Medical devices; prominence of required label statements," and 21 CFR 801.60, "Principal display panel."

Heat disinfection labeling should contain explanatory labeling of the heat indicator function. Listed below are models of what should be minimal acceptable labeling pertaining to indicator and heater function for contact lens heat disinfection units that utilize either a thermostat or electronic timer to automatically control the disinfection cycle. The applicant should pick the appropriate indicator information and integrate it into the labeling. Alternate wording may be used, but the meaning of all labeling statements should be unchanged. Emphasis shown in the model labeling by use of uppercase lettering is considered to be essential. Both carton and user instruction paragraphs should be located and emphasized by use of bold faced type or contrasting color so as to elicit the attention of the user.

1. MODEL LABELING FOR UNITS WITH LIGHT FOR POSITIVE FUNCTION/FAILURE INDICATOR

Package Labeling:

Principal Display Panel:

HEATER INDICATOR LIGHT - This unit uses a light to indicate the start and finish of the disinfection cycle.

READ USER INSTRUCTIONS CAREFULLY

Any Panel:

THE UNIT HAS A LIGHT TO INDICATE THE START AND FINISH OF THE DISINFECTION CYCLE THAT ONLY LIGHTS WHEN THE HEATER IS ON. ALLOW ___ MINUTES COOLING TIME AFTER THE LIGHT GOES OFF BEFORE REMOVING LENSES.

User Instructions:

CAUTION: Observe the light indicator to confirm that the unit is operating correctly. It must turn on when the unit is started and turn off after ___ to ___ minutes. REPLACE THE UNIT if the light does not turn on when the unit is started or does not turn off within ____ minutes after being started.

2. MODEL LABELING FOR UNITS WITH A TEMPERATURE SENSOR (NON-LIGHT) INDICATOR FOR POSITIVE FUNCTION/FAILURE INDICATOR

Package Labeling:

Principal Display Panel:

HEAT SENSOR - This unit uses a heat sensor to indicate the start and finish of the disinfection cycle by (describe how).

READ USER INSTRUCTIONS CAREFULLY

Any Panel:

THE UNIT HAS A HEAT SENSITIVE INDICATOR THAT TELLS WHEN DISINFECTION STARTS BY CHANGING FROM _____ TO _____ AND TELLS WHEN THE UNIT IS COOL ENOUGH TO REMOVE LENSES SAFELY BY CHANGING FROM _____ TO _____.

User Instructions:

CAUTION: Observe the heat sensor to confirm that the unit is operating correctly. It must change from ____ to ____ after starting the disinfection cycle. Observe the heat sensor again after completion of the disinfection cycle and prior to unplugging the unit. It must change back from ____ to ____. REPLACE THE UNIT if the heat sensor does not change.

Carton Label:

TRADE NAME:

INDICATIONS:

DIRECTIONS FOR USE:

Before First Use: [Provide necessary instructions.]

Heat (Thermal) Disinfection: [Provide step-by-step instructions for disinfecting lenses.]

Maintenance of Your Heat Disinfection Unit [Provide necessary maintenance instructions.]

CONTRAINDICATIONS: [DO NOT use with rigid gas permeable or hard contact lenses.]

WARNINGS:

General Warnings:

- DO NOT IMMERSE OR RINSE UNIT IN TAP WATER. IF SALINE, WATER, OR OTHER LIQUIDS COME IN CONTACT WITH THE EXTERIOR OF THE UNIT, _____, AND _____, IMMEDIATELY WIPE DRY BEFORE USING.

- [Include other general warnings as applicable.]

Warnings for Electrical Device (as applicable):

SAVE THESE INSTRUCTIONS:

To reduce the risk of electrocution:

- DO NOT operate your [TN] if the unit is wet. Dry exterior surfaces before using.

- DO NOT touch the [TN] or the removable electrical plug with wet hands.

- Always unplug this product immediately after using.

- DO NOT use while bathing.

- DO NOT place or store product where it can fall or be pulled into a bath or sink.

- DO NOT place in or drop into water or other liquid.

To reduce the risk of burns, electrocution, fire or injury:

- Close supervision is necessary when this product is used by, on, or near children or invalids. This is not a toy for children.

- Never operate this product if it has a damaged cord or plug, if it is not working properly, if it has been dropped or damaged, or dropped into water.

- DO NOT use outdoors or operate where aerosol products are being used or where oxygen is being administered.

- Electrical shock can occur if the unit is wet or if the electrical plug is not completely engaged in the receptacle.

DESCRIPTION: [Include description of device, including indicator and how it works.]

ENDING: Include the information that expresses the facts:

- [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot or Serial No.
- Printed [Month and Year]

LABELING--APPENDIX D

Salt Tablets/Capsules Systems:

On September 21, 1987, CDRH sent a letter to salt tablet PMA owners and interested persons advising them that specific directions for use and warnings should be used in salt tablet labeling to ensure safe and effective use of homemade saline from salt tablets. PMA owners subsequently revised their labeling in accordance with CDRH's letter. No changes have been made in CDRH's policy since the September 21 letter issued. The letter advised PMA owners that CDRH believes that there is sufficient scientific evidence to demonstrate that (1) salt tablets/capsules saline should NOT be used in conjunction with chemical disinfection systems for contact lens care and (2) the continued use of salt tablets/capsules saline in conjunction with heat disinfection requires greater consumer awareness that salt tablets/capsules saline should NEVER be used FOLLOWING heat disinfection. The letter further stated that the following labeling (Warnings and Indications for Use) should be used for salt tablets/capsules system labeling to provide continuing safety and effectiveness of the device for its intended use. All labeling for salt tablets/capsules systems should follow the format of predicate device labeling that has been revised after the September 21, 1987 letter issued and include the information listed below:

1. Carton Labeling

   The front panel of the salt tablets/capsules carton should prominently display the following warning:

   WARNING: USE THIS PRODUCT EXACTLY AS DIRECTED. The package insert for this product contains WARNINGS and SAFETY INFORMATION. PLEASE READ IT CAREFULLY.

2. INDICATIONS: The Indications for Use statement should read as follows:

   For rinsing and for use during heat disinfection and storage of soft (hydrophilic) contact lenses.

   Rinsing PRIOR to heat disinfection only.

   Storage DURING heat disinfection only.

3. Package Insert

   General Warning Statements - The package insert for this product should prominently display the following warnings:

   SALT TABLETS/CAPSULES

   WARNINGS: AN ASSOCIATION HAS BEEN ESTABLISHED BETWEEN IMPROPER USE OF SALT TABLETS/CAPSULES SALINE AND SERIOUS EYE INFECTIONS THAT MAY RESULT IN LOSS OF SIGHT.

   DISTILLED WATER IS A NON-STERILE PRODUCT. THE USE OF NON-STERILE PRODUCTS IN THE PREPARATION OF CONTACT LENS

SOLUTIONS MAY LEAD TO CONTAMINATION OF LENSES BY MICROORGANISMS INCLUDING ACANTHAMOEBA WHICH CAN CAUSE SERIOUS EYE INFECTIONS AND RESULT IN PERMANENT VISUAL LOSS.

WHILE CHEMICAL DISINFECTION SOLUTIONS, INCLUDING HYDROGEN PEROXIDE, ARE EFFECTIVE IN KILLING MICROORGANISMS THAT COMMONLY PRODUCE EYE INFECTIONS, THEY MAY NOT BE EFFECTIVE AGAINST THE ACANTHAMOEBA ORGANISM. FOLLOW THESE REVISED INSTRUCTIONS CAREFULLY, OR DISCONTINUE USE OF SALT TABLETS/CAPSULES SALINE.

- NEVER USE SALT TABLETS/CAPSULES SALINE SOLUTION WITH CHEMICAL OR HYDROGEN PEROXIDE DISINFECTION OF CONTACT LENSES.
- NEVER USE SALT TABLETS/CAPSULES SALINE SOLUTION AS A RINSE AFTER ANY DISINFECTION (use only a commercially prepared sterile saline solution for rinsing after disinfection).
- NEVER USE SALT TABLETS/CAPSULES SALINE SOLUTION DIRECTLY IN THE EYE.

DIRECTIONS FOR USE:

DESCRIPTION/CONTENTS:

PRECAUTIONS:

CONTRAINDICATIONS:

ADVERSE REACTIONS:

HOW SUPPLIED:

ENDING:

- Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot Number
- Expiration Date
- Printed [Month and Year]

LABELING--APPENDIX E

Contact Lens Accessories (Mechanical Cleaning Aids)

[Include applicable information under the following headings. Applicants should use predicate device labeling as guidance].

TRADE NAME:

INDICATIONS/ACTIONS: [Include specific indications (e.g., [TN] is indicated for use with contact lens cleaning solutions to aid in cleaning by minimizing hand contact with lenses.)]

CONTRAINDICATIONS: [If there are no known contraindications, add the statement: "There are no known contraindications associated with the use of this device." If there are contraindications, list them.]

DIRECTIONS FOR USE: [Include step-by-step directions for use including what products can be used with the device.]

WARNINGS: [Include warnings applicable to the device in the 510(k).]

Warnings for Electrical Device: [Include the information from the labeling example for Heat Disinfection Units (Labeling--Appendix C), if applicable].

PRECAUTIONS:

- To avoid damage to lenses, follow precautions in the contact lens solution labeling.
- [Additional precautions specific to the device in the 510(k).]

ADVERSE REACTIONS:

ENDING:

- Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot or Serial No.
- Printed [Month and Year]

LABELING--APPENDIX F

Contact Lens Accessories (Accessory Cleaning Pads)

[Include applicable information under the following headings. Applicants should use predicate device labeling as guidance].

TRADE NAME:

INDICATIONS/ACTIONS: [Include specific indications (e.g., [TN] is indicated for use with contact lens cleaning solutions to aid in cleaning by minimizing hand contact with lenses).]

CONTRAINDICATIONS: [If there are no known contraindications, add the statement: "There are no known contraindications associated with the use of this device." If there are contraindications, list them.]

DIRECTIONS FOR USE: [Include step-by-step directions for use, including how to clean the pad, and how often to replace it.]

WARNINGS:

- [Add for pads that are to be reused.] To help avoid contamination and eye infection, clean and air-dry pad every day; replace pad every (insert number) day(s).
- [Add for pads that are disposable (i.e., use once and throw away).] To help avoid contamination and eye infection, discard pad after each use.
- [Additional warnings applicable to the device in the 510(k).]

PRECAUTIONS:

- To avoid damage to lenses, use exactly as instructed in the contact lens solution labeling.
- [Additional precautions specific to the device in the 510(k).]

ADVERSE REACTIONS:

ENDING:

- Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot No.
- Printed [Month and Year]

VI. RECOMMENDED TEST METHODS

Page

INTRODUCTION

This section of the guidance includes recommended preclinical and clinical test methods designed to provide data to assess substantial equivalence of contact lens care products to legally marketed devices. Whenever possible, the guidance references applicable standards that have been finalized and have been found acceptable for use by CDRH.

CDRH is actively working on the development of contact lens product standards with the American National Standards Institute (ANSI) and the International Organization of Standards (ISO) in an effort to harmonize our requirements and recommended test methods with voluntary standards being developed nationally and internationally. Although some contact lens care product standards have been completed and published for use, a number of important standards are currently under development and have not been completed or adopted at this time. For those standards currently under development, CDRH has attempted to harmonize our requirements and recommended test methods, to the extent possible, with standards being drafted at this time. For purposes of harmonization, elements of those draft standards that CDRH finds acceptable have been incorporated into the appropriate sections of this guidance or into the recommended test methods included in this section.

CHEM--APPENDIX A

PRESERVATIVE UPTAKE/RELEASE TEST PROCEDURES

The purpose of this test is to determine preservative uptake/release in solutions containing new preservatives for contact lens use. The results of these test data will be used to predict the potential for a preservative related toxicity, as well as the potential for inducing a sensitivity/allergic response associated with the contact lens care products.

The test procedures outlined here have been accepted by CDRH for the quantitative analysis of the uptake/release of preservatives, such as thimerosal, chlorhexidine, and benzalkonium chloride, in contact lenses. It is the responsibility of the applicant to select a validated chemical method for the quantitative analysis of the uptake/release of the preservative from the lens, whether it be thimerosal, chlorhexidine, benzalkonium chloride or other newer agents.

In general, a thermodynamically defined "plateau" of total* accumulation of preservative on the lens should be demonstrated for the recommended lens care regimen. Alternatively, the preservative uptake/release studies through equilibration studies can substitute cycling studies (e.g., each lens is soaked in 100 ml care solution at room temperature for 4 days, 8 days, and 12 days or longer).

At least three data points, each separated by at least 20 cycles under the recommended lens care regimen, should be submitted. Each data point should be expressed in terms of the average value, standard deviation, and number of measurements. A statistical analysis should be performed to ensure that it reaches a plateau area. For hydrophilic contact lenses, it should be expressed as µg preservative/mg dry lens; however, for hydrophobic contact lenses, it should be expressed as µg preservative/surface area of lens in cm^2.

A. Thimerosal Uptake/Release Studies of Hydrophilic and Hydrophobic Lens Materials by Atomic Absorption Spectrometry:

1. Sample Preparations

Each lens, after cycling under the recommended care regimen or after a reasonable soaking time in the thimerosal preserved care solution, is placed in a borosilicate vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens is removed from the vial, blot-dried, and placed in another borosilicate vial which is used for the preservative uptake study.

2. Preservative Uptake Study

Five ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing the lens. The vial is heated, gently

*Total accumulation of preservative on the lens is a sum of preservative uptake and preservative release data.

**2:l by volume for hydrophilic plastic lenses.

at first on a hot plate until the lens is decomposed. Care should be taken during heating to avoid charring. The vial is then heated strongly to remove all traces of nitric acid, which is determined visually by the presence of white vapor instead of brown vapor (nitrous oxide) inside the vial. If charring occurs, a few drops of concentrated nitric acid are added and the sample reheated.

The entire sample is employed for the mercury determination using cold vapor atomic absorption spectrometry. Two control lenses, which have been soaked in an isotonic pH = 7.0 buffered saline solution for the duration of the study (35°C for 15 hours), are decomposed and treated as the test lens. Absorbance values for the sample lenses are corrected by subtracting the absorbance value of the control lens.

3. Preservative Release Study

Five ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing lens leachate. The solution is treated as the test lens. A control solution (an isotonic pH = 7.0 buffered saline solution) is also treated as the test lens. Absorbance values for the lens leachates are corrected by subtracting the absorbance value of the control solution.

4. Standard Curve

Five ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing a known concentration of thimerosal standard. The standard solution is treated as the test lens. A reagent blank (concentrated sulfuric:nitric acid = 3.1 by volume) is also treated as the test lens. Absorbance values for the standard solutions are corrected by subtracting the absorbance value of the reagent blank.

B. Chlorhexidine Uptake/Release Studies of Hydrophilic and Hydrophobic Lens Materials by ^{14}C-Labeled Technique:

The procedure for chlorhexidine (CHG) can be used for any preservative which can be tagged with a non-labile radioactive label.

CHG accumulation by contact lenses is assessed by ^{14}C counting of radiolabeled CHG associated with the lens after the recommended care regimen. The modified procedure of MacKeen and Green*** specifically designed for preservative determination in contact lenses is briefly described as follows:

***MacKeen, D.L. and Green, K.: Chlorhexidine Kinetics of Hydrophilic Contact Lenses; J. Pharm. Pharmacol., 30: 578-682, 1978. MacKeen, D.L. and Green, K.: Chlorhexidine Kinetics in Hard Contact Lenses; J. Pharm. Pharmacol., 31: 714-716, 1979.

1. Sample Preparations

Radiolabeled ^{14}C-CHG is added to the care solution containing CHG. Each lens after cycling under the recommended care regimen containing ^{14}C-CHG or after a reasonable soaking time in ^{14}C-CHG preserved care solution is placed in a scintillation vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35^{o}C for 15 hours (preservative release study). The lens is removed from the vial, blot-dried, and placed in another scintillation vial which is used for the preservative uptake study.

2. Preservative Uptake Study

Three ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing the lens. The vial is heated to boiling. After cooling to room temperature, duplicate 100 µl samples are taken of the resultant solution, mixed with 1 ml of deionized water and 10 ml of Aquasol (New England Nuclear Corporation) with vigorous agitation. After cooling, the samples are counted. The control lens, just removed from the shipping container, is solubilized and treated as the test lens. The counts for the test lenses are corrected by subtracting the counts of the control lens.

3. Preservative Release Study

Three ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing lens leachate. The vial is heated to boiling. After cooling to room temperature, duplicate 100 µl are mixed with 1 ml of deionized water and 10 ml of Aquasol and counted. Duplicate 100 µl of a control solution (an isotonic pH = 7.0 buffered saline solution) are also treated in the same way. The counts for lens leachate are corrected by subtracting the counts of the control solution.

4. Standard

Three ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the scintillation vial containing 100 µl of ^{14}C-CHG standard solution. The vial is heated to boiling. After cooling to room temperature, duplicate 100 µl samples are taken of the resultant solution, mixed with 1 ml deionized water and 10 ml of Aquasol with vigorous agitation. After cooling, the samples are counted.

C. Chlorhexidine Uptake/Release Studies of Hydrophilic Lens Materials by High Pressure Liquid Chromatography (HPLC)

This procedure for chlorhexidine uptake/release studies can be used for hydrophilic lens materials which show a strong absorption and adsorption to CHG through electrostatic interactions.

The modified procedure of Stevens et al[+] specifically designed for preservative determination in hydrophilic lens materials is briefly described as follows.

Lenses are soaked in a minimum volume of care solution at room temperature for 4 days, 8 days, and 12 days or longer. The CHG accumulation by hydrophilic lens materials is assessed by a difference in concentrations of CHG in the care solution before and after lens soaking. After soaking, the lens is removed and placed in 1 ml isotonic pH = 7.0 buffered solution at 35°C for 15 hours (preservative release study). The CHG concentrations in both soaking and elution solutions are determined by injecting sample aliquots of 20 µl directly onto the HPLC column and calculating from the standard. The detection limit, reproducibility, and reliability should be assessed compared to preservative uptake/release studies to ensure the suitability of this method.

D. Benzalkonium Chloride (BAK) Uptake/Release Studies of Hydrophobic Lens Materials by Laser Fluorescence Spectroscopy++

1. Sample Preparation

After cycling under the recommended care regimen or after a reasonable soaking time in BAK preserved care solution, each lens is placed in a vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens that is removed from the vial and air-dried is used for the preservative uptake study.

2. Preservative Uptake Study

Adsorbed BAK is measured by laser fluorescence spectroscopy with an argon laser. The excitation intensity is on the order of 4×10^{-6} Einsteins/second, providing a fluorescence spectrum level of 10^3 counts/second at the phototube. For detection, a Hammamatsu photomultiplier tube biased with a Keithley microammeter/high voltage power is used. Monochromators are double JY 0.5 meter holographic gratings.

3. Preservative Release Study

Total adsorbed BAK on the lens is also measured by laser fluorescence spectroscopy. The difference between total adsorbed BAK and adsorbed BAK is the value for preservative release study.

+Stevens, L.E., Durrwachter, J.R., and Helton, D.O.: Analysis of Chlorhexidine Sorption in Soft Contact Lenses by Catalytic Oxidation of ^{14}C-Chlorhexidine and by Liquid Chromatography: J. Pharm. Sci., 75: 83-86, 1986.

++Wong, M.P., Dziabo, A.J., and Kiral, R.M.: Dynamics of BAK Adsorption by Silicone Acrylate Lenses; Contact Lens Spectrum, November. 49-53, 1986.

CHEM--APPENDIX B

CLEANING EFFECTIVENESS

Determination of the Critical Micelle Concentration of a Surfactant (or Surfactant System) in a Lens Care Product Having a Cleaning Claim

In an aqueous solution of a surfactant, the surfactant is molecularly dispersed at low concentrations. At higher concentrations, however, when a certain critical concentration is reached, the molecules form micelles. These micelles are in equilibrium with the free surfactant molecules. The concentration that must be reached in order that micelles are formed is called the critical micelle concentration. Adequate cleaning effectiveness of a daily cleaner can be demonstrated in vitro by determining that the concentration of a surfactant (or surfactants) in a daily cleaner are higher than the critical micelle concentration of surfactant (or surfactants).

Many physical properties of the surfactant solution when plotted against the concentration show more or less sudden changes at the critical micelle concentration. By measuring such properties as electrical conductivity, interfacial tension, surface tension, refractive index, viscosity, and light scattering as a function of the concentration of the surfactant, the critical micelle concentration is determined as the concentration at which the property versus concentration curve shows a change in slope. The hydrophobic part of the surfactant molecule is situated at the inside of the micelle, the hydrophilic part at the outside. Inside the micelles lipophilic substances may be solubilized.

The purpose of a daily cleaner is to remove loosely held lens deposits on the lens surface. Generally, a daily cleaner contains at least a surfactant which lowers surface tension of the solution to facilitate removal of loosely held lens deposits on the lens surface in conjunction with mechanical means (e.g., fingers). The concentration of a surfactant (or surfactants) in a daily cleaner should be sufficient enough to be higher than the critical micelle concentration of surfactant (or surfactants). The critical micelle concentration of surfactant may be significantly affected by pH, tonicity, and other inactive ingredients in the daily cleaner.

The purpose of this appendix is not intended to list all methods to determine the critical micelle concentration of surfactant (or surfactants). Rather, we are providing a simple method such as measuring surface tension of a surfactant (or surfactants) in a device medium to determine the critical micelle concentration.

1. Solution 1: Prepare the daily cleaner medium (i.e., the daily cleaner without surfactants).

2. Solution 2: Prepare a reasonable concentration of the surfactant system (if more than one surfactant is in the daily cleaner, the weight or mole ratio of the surfactant system should be the same as the one in the daily cleaner).

3. Solution 3: Prepare varying concentrations of the surfactant system in the daily cleaner medium by diluting Solution 2 with Solution 1.

4. Measure surface tension of Solution 3 by the Tensiometer.

5. Plot surface tension versus log concentration of surfactant system in the daily cleaner medium (Solution 3) and perform least square linear regressions to determine the critical micelle concentration.

CHEM--APPENDIX C

SOLUTION COMPATIBILITY TEST PROTOCOL

The purpose of this test is to assess the effect of a contact lens solution on contact lens parameters and solution compatibility under the recommended care regimen. CDRH does not believe that data will ordinarily be required to be submitted in the 510(k) if the solution is essentially identical to the predicate device in terms of active and inactive ingredients. For purpose of this guidance, our focus is on active ingredients. However, manufacturers should also assess the effects of inactive ingredients on such factors as pH and tonicity, which could significantly affect solution compatibility. For hydrophilic contact lenses, CDRH considers tinted contact lenses to represent the worst case. The following is a suggested protocol:

1. Number of Cycles:

   30 cycles for heat disinfection regimen
   30 cycles for chemical or hydrogen peroxide disinfection regimen

2. Number of Lenses:

   For hydrophilic contact lenses
   Group I: at least 10 lenses with low powers
   Group IV: at least 10 lenses with low powers

   For hydrophobic contact lenses
   Number of lenses should be equally divided between the lens groups for which the solution is indicated, for a total of 20 lenses

3. Parameters Monitored:

   Optical parameters: power, base curve, and diameter
   Physical appearance: discoloration and clarity
   Chemical parameters: tint (if applicable)
   ultraviolet absorption (if applicable)

4. Test Method:

   a. Record optical, physical, and chemical parameters before cycling.

   b. Flex lenses in a manner to simulate removal of the lens from the eye (not applicable for hydrophobic lenses).

   c. Clean, rinse, and disinfect lenses (including handling procedures) as required in the labeling for the recommended care regimen.

   d. Repeat (b) if applicable and (c) for each cycle up to 30 cycles with the appropriate heat disinfection, chemical disinfection, and hydrogen peroxide regimen.

   e. Record optical, physical, and chemical parameters after cycling.

   f. Summarize and discuss the test results.

MICRO--APPENDIX A

PRESERVATIVE EFFICACY OF MULTI-DOSE PRESERVED CONTACT LENS CARE PRODUCTS

I. PRINCIPLE

The antimicrobial activity test uses a standard inoculum of a representative range of microorganisms to challenge a preserved product and establishes the extent of viability loss at predetermined time intervals. The size of the microbial challenge chosen in this test is not intended to be representative of the likely challenge in practice but to provide countable numbers from which estimation of the rate and extent of viability loss can be determined. The capability of the product to prevent microbial growth is evaluated.

In carrying out the test for antimicrobial activity the qualitative and quantitative composition of the product at the time of testing should be known by either analytical testing or extrapolation.

Appropriate measures should be taken to inactivate or remove residual antimicrobial agents during recovery of survivors, and the effectiveness of these measures should be demonstrated.

Three lots of product should be tested. Each lot of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS & REAGENTS

A. Test Organisms

Pseudomonas aeruginosa	NCIMB 8626	ATCC 9027
Staphylococcus aureus	NCTC 10788	ATCC 6538
Escherichia coli	NCIB 8245	ATCC 8739
Candida albicans	NCPF 3179	ATCC 10231
Aspergillus niger	IMI 149007	ATCC 16404

B. Test Media

Tryptone Soya Broth (TSB), Tryptone Soya Agar (TSA), Sabouraud Dextrose Agar (SDA), Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/l KCl, 200 mg/l KH_2PO_4, 8000 mg/l NaCl, and 2,160 mg/l $Na_2HPO_4 \bullet 7H_2O$ or suitable diluent; Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or suitable diluent
Validated neutralizing agents/media as required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, 100 X 20 mm petri dishes, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Product samples to be tested should be representative of the product to be marketed. Aliquots should be taken directly from the final product container immediately prior to testing.

III. TEST METHOD

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than 5 passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository).

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured on agar as in Table 1.

Table 1: Media & Incubation Conditions for Growth of Challenge Organisms

Organism	Medium	Incubation Temp ^{o}C	Time
Pseudomonas aeruginosa	TSA	30-35	18-24h
Staphylococcus aureus	TSA	30-35	18-24h
Escherichia coli	TSA	30-35	18-24h
Candida albicans	SDA SDA	20-25 30-35	42-48 or 18-24h
Aspergillus niger	SDA	20-25	7 days

To harvest all cultures, use sterile DPBST or a suitable diluent, washing the surface growth and transfer to a suitable vessel. The spore suspensions may be filtered through sterile glass wool, cotton gauze, or cheese cloth to remove hyphal fragments.

After harvesting, the cultured organisms may be washed using centrifugation. If centrifugation is used, each centrifugation should be conducted at 2-25^{o}C for no longer than 10 minutes at 4000 x g or less. The bacterial suspensions may be filtered (e.g., 3 - 5 μm pore size) to produce a single cell dispersion.

All challenge cell suspensions should then be adjusted with DPBST or other suitable diluent to 1 X 10^{7} - 1 X 10^{8} colony forming units (cfu)/ml. The approximate cell concentration may be estimated by measuring the turbidity of the suspension or a

dilution of the suspension using a spectrophotometer. The actual concentration of cfu/ml should be determined for each suspension by the plate count method at the time of the test.

Bacterial and yeast cell suspensions should be used on the day of preparation. Bacterial and yeast cells may lose viability and resistance if not used on the day of preparation. Spore suspensions may be used up to 7 days following preparation by storage under refrigeration (Avg. 4±2°C).

C. Test Procedure

1. Prepare one tube containing a minimum of 10 ml of test solution per challenge organism. Inoculate the sample tube of the product to be tested with a suspension of test organisms sufficient to provide a final count of 1.0×10^5 - 1.0×10^6 cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing.

2. Store inoculated product at 20-25°C. Temperature should be monitored using a calibrated device and documented. If sensitive to light the product should be protected during the period of the test.

3. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 7 days and 14 days.

4. Each sample is rechallenged as in III.C.1 on day 14 after taking the 14-day sample. Use an inoculum level of 1.0×10^4 - 1.0×10^5 cfu/ml.

5. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 21 and 28 days.

6. Subject 1.0 ml aliquots removed at the specified time intervals to a suitable series of decimal dilutions in validated neutralizing media. Mix suspension well by vortexing vigorously and incubate for a suitable period of time to allow for neutralization.

   If the antimicrobial agent(s) in the formulation cannot be adequately inactivated or neutralized it may be eliminated using a validated membrane filtration procedure (Micro--Appendix D).

7. Determine the viable count of organisms in appropriate dilutions by preparation of triplicate plates (unless otherwise justified) of suitable recovery medium (e.g., TSA for bacteria and SDA for mold and yeast). The agar for pour plates should be kept between 40-50°C prior to pouring. The agar media used for determination of viable counts may also contain antimicrobial inactivators or neutralizers if required. Where membrane filtration has been employed to remove/neutralize antimicrobial agents, membranes should be cultured on these media as appropriate.

8. Incubate bacterial recovery plates at 30-35°C for 2-4 days. Incubate yeast at 20-25°C or 30-35°C for 3-5 days and mold recovery plates at 20-25°C for 3-7 days.

9. Determine the average number of cfu on countable plates and record. Countable plates refer to 30-300 cfu/plate for bacteria and yeast, and 8-80 cfu/plate for mold except when colonies are observed only for 10^0 or 10^{-1} dilution plates. Calculate microbial reduction at the specified time points.

10. The concentration of survivors is calculated at each time point. The concentration of viable organisms following the 14-day rechallenge is the sum of the rechallenge inoculum concentration and the 14-day survivor concentration.

D. Controls

1. Inoculum Controls

The initial and rechallenge inoculum concentrations are calculated by dispersing an identical aliquot of the inoculum into the same volume of a suitable diluent (e.g., DPBST) as used in III.C.1 to achieve a final concentration of 1.0×10^5 - $l.0 \times 10^6$ cfu/ml for the initial inoculum or 1.0×10^4 - 1.0×10^5 cfu/ml for the rechallenge inoculum. Ensure dispersion of the inoculum by adequate mixing. This control sample should be evaluated within 1 hour of its preparation using the same procedure used for the inoculated product. This serves to demonstrate the suitability of the medium used for growth of the test organism and provides an estimate of the initial (rechallenge) inoculum concentration.

2. Recovery Medium Control

Qualify the neutralizing agent/medium for the product initially and periodically thereafter. Prepare a 1/10 dilution of the preserved product in the validated neutralizing broth (1 ml into 9 ml). If a greater dilution of the test solution is required to achieve neutralization, the latter dilution should be used. Prepare a second control tube with 10 ml of a suitable diluent (e.g., TSB). Inoculate the tubes with sufficient inoculum to result in 10 - 100 cfu of challenge organism per plate. Incubate for an appropriate period of time at ambient temperature. Plate the appropriate aliquot from each tube onto the recovery agar plates in triplicate unless otherwise justified. The recovery in the neutralizer broth should be at least 50% of the recovery in the second control tube. This control is to be performed for each challenge organism.

IV. PERFORMANCE CRITERIA

A. Bacteria

The number of organisms recovered per ml is reduced by a mean value of not less than 3.0 logs at 14 days. After the rechallenge at day 14, the concentration of bacteria should be reduced by at least a mean value of 3.0 logs by day 28.

B. Molds and Yeasts

The number of organisms recovered per ml remain at or below the initial concentrations within an experimental error of ±0.5 logs within 14 days. At day 28, the concentration of mold and yeast should remain at or below the concentrations after the rechallenge within an experimental error of ±0.5 logs.

C. Products should be capable of meeting these criteria throughout their labeled shelf-life.

MICRO--APPENDIX B

DISINFECTION EFFICACY TESTING

PART 1. STAND-ALONE PROCEDURE FOR DISINFECTING PRODUCTS

I. PRINCIPLE

The stand-alone test challenges a disinfecting product with a standard inoculum of a representative range of microorganisms and establishes the extent of viability loss at pre-determined time intervals comparable with those during which the product may be used. The size of the microbial challenge chosen in this test is not intended to be representative of the likely challenge in practice, but to provide countable numbers from which estimation of the rate and extent of viability loss can be determined.

In carrying out the test for antimicrobial activity, the qualitative composition of the product should be known at the time of testing by either analytical testing or extrapolation.

Appropriate measures should be taken to inactivate or remove residual antimicrobial agents during culturing and counting of survivors and the effectiveness of these measures should be validated and the action of this process during the test should be demonstrated by the construction of suitable controls.

Three batches of product should be tested. Each batch of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS AND REAGENTS

A. Test Organisms

Pseudomonas aeruginosa	NCIMB 8626	ATCC 9027
Staphylococcus aureus	NCTC 10788	ATCC 6538
Serratia marcescens	NCTC 10211	ATCC 13880
Candida albicans	NCTC 3179	ATCC 10231
Fusarium solani		ATCC 36031

B. Test Media

Potato Dextrose Agar (PDA)
Tryptone Soya Broth (TSB)
Tryptone Soya Agar (TSA)
Sabouraud Dextrose Agar (SDA)
Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/L KCl, 200 mg/L KH_2PO_4, 8000 mg/L NaCl, and 2,160 mg/L $Na_2HPO_4 \bullet 7H_20$ or a suitable diluent.
Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or a suitable diluent.
Validated neutralizing agents/media required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, 100 X 20 mm petri dishes, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Product samples to be tested should be representative of the product to be marketed. Aliquots should be taken directly from the final product container immediately prior to testing.

III. TEST METHOD

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than five passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository.)

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured on agar as in Table 1.

Table 1

Media and Incubation Conditions for Growth of Challenge Organisms

Organism	Medium	Temp(^{0}C)	Incubation Time
P. aeruginosa	TSA	30-35	18-24 hrs
S. aureus	TSA	30-35	18-24 hrs
S. marcescens	TSA	30-35	18-24 hrs
C. albicans	SDA	20-25	42-48 hrs or
	SDA	30-35	18-24 hrs
F. solani	PDA	20-25	10-14 days

To harvest all cultures, use sterile DPBST or a suitable diluent, washing the surface growth and transfer to a suitable vessel. The spore suspensions may be filtered through sterile glass wool, cotton gauze or cheese cloth to remove hyphal fragments.

After harvesting, the cultured organisms may be washed using centrifugation. If centrifugation is used, each centrifugation should be conducted at 2-25^{o}C for no longer than 10 minutes at 4000 x g or less. The bacterial suspensions may be filtered (e.g., 3 - 5 µm pore size) to produce a single cell dispersion. All challenge cell suspensions should then be adjusted with DPBST or other suitable diluent to 1 X 10^{7} - 10^{8} cfu/ml. The approximate cell concentration may be estimated by measuring the turbidity of the suspension or a dilution of the suspension using a spectrophotometer. The actual concentration of cfu/ml should be determined for each suspension by the plate count method at the time of the test.

Bacterial and yeast cell suspensions should be used on the day of preparation. Bacterial and yeast cell may lose viability and resistance if not used on day of preparation. Spore suspensions may be used up to 7 days following preparation by storage under refrigeration (Avg. $4\pm2^{0}C$).

C. Test Procedure

1. Prepare one tube containing a minimum of 10 ml of test solution per challenge organism. Inoculate the sample tube of the product to be tested with a suspension of test organisms sufficient to provide a final count of 1.0×10^{5} - 1.0×10^{6} cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing.

2. Store inoculated product at $20\text{-}25^{0}C$. Temperature should be monitored using a calibrated device and documented. If sensitive to light the product should be protected during the period of the test.

3. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 25%, 50%, 75% and 100% of the minimum recommended disinfection time for all organisms, and, in addition, at not less than 4 times the minimum recommended disinfection time for yeast and mold. Where overnight disinfection is recommended, disinfection time is taken to be 8 hours.

4. Subject 1.0 ml aliquots removed at the specified time intervals to a suitable series of decimal dilutions in validated neutralizing media. Mix suspension well by vortexing vigorously and incubate for a suitable period of time to allow for neutralization.

   If the antimicrobial agent(s) in the formulation cannot be adequately inactivated or neutralized it may be eliminated using a validated membrane filtration procedure (e.g., Micro--Appendix D).

5. Determine the viable count of organisms in appropriate dilutions by preparation of triplicate plates (unless otherwise justified) of a suitable recovery medium (e.g., TSA for bacteria and SDA for mold and yeast).

   Where membrane filtration has been employed to remove/neutralize antimicrobial agents, membranes should be cultured on these media as appropriate. The agar for pour plates should be kept between $40\text{-}50^{0}C$ prior to pouring. The agar media used for determination of viable counts may also contain antimicrobial inactivators or neutralizers if required.

6. Incubate bacterial recovery plates at $30\text{-}35^{0}C$ for 2-4 days. Incubate yeast at $20\text{-}25^{0}C$ or $30\text{-}35^{0}C$ for 3-5 days and mold recovery plates at $20\text{-}25^{0}C$ for 3-7 days.

7. Determine the average number of cfu on countable plates. Countable plates refer to 30 to 300 cfu/plate for bacteria and yeast, and 8 to 80 cfu/plate for mold except when colonies are observed only for the 10^0 or 10^{-1} dilution plates. Calculate microbial reduction at the specified time points.

D. Controls

1. Inoculum Control

An inoculum count is made by dispersing an identical aliquot of the inoculum into the same volume of suitable diluent (e.g., DPBST) as used in Part 1:III.C.1 to achieve a final concentration of 1.0×10^5 - 1.0×10^6 cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing. This control sample should be evaluated for cfu/ml at the beginning of the test. This serves to demonstrate the suitability of the medium used for growth of the test organism and provides an estimate of the initial inoculum concentration.

2. Recovery medium control

Prepare a 1/10 dilution of the disinfecting solution in the validated neutralizing broth (1 ml into 9 ml). If a greater dilution of the test solution is required to achieve neutralization, the latter dilution should be used. Prepare a second control tube with 10 ml of a suitable diluent (e.g., TSB). Inoculate the tubes with sufficient inoculum to result in 10-100 cfu of challenge organism per plate. Incubate for an appropriate period of time at ambient temperature. Plate the appropriate aliquot from each tube onto the recovery agar plates in triplicate unless otherwise justified.

The recovery in the neutralizer broth should be at least 50% of the recovery in the second control tube. This control should be performed for each challenge organism.

IV. PERFORMANCE REQUIREMENT

A. Control Specification

If any control value falls out of specification, the associated test is invalid and should be repeated.

B. Primary Criteria (See Part 2, Table 2)

1. Bacteria

The number of organisms recovered per ml should be reduced by a mean value of not less than 3.0 logs within the minimum recommended disinfection period.

2. Molds and Yeasts

The number of organisms recovered per ml should be reduced by a mean value of not less than 1.0 log within the minimum recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time.

C. Secondary Criteria (See Part 2, Table 2)

Products failing to meet the criteria in Part I:IV.B.1 or Part 1:IV.B.2 may be evaluated by the regimen test procedure described below, provided there is a combined log reduction for the means of all bacteria of not less than 5.0 within the recommended disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0. Stasis for the yeast and mold (within an experimental error of ± 0.5 log) should be observed for the recommended disinfection period.

PART 2. REGIMEN PROCEDURE FOR DISINFECTING REGIMENS

I. PRINCIPLE

This procedure is applicable to multi-functional disinfection regimens which may include the steps of cleaning, rinsing, and soaking. In carrying out the regimen test procedure, the products should be used in the manner and quantity recommended in product labeling and/or patient instructions. The test challenges the proposed disinfection regimen with a standard inoculum of a representative range of microorganisms. The inoculum is carried through the various stages of the regimen by preliminary application to contact lenses.

The disinfecting stage of any proposed contact lens disinfection regimen evaluated by this test should have demonstrated minimum antimicrobial activity by the Stand-Alone Procedure as indicated for Regimen Qualification.

In carrying out the test, qualitative and quantitative composition of all products used in the test regimen should be known at the time of testing, either by analytical testing or extrapolation.

Appropriate measures should be taken to inactivate or remove residual antimicrobial agents during culturing and counting of the challenge organism and the effectiveness of these measures should be demonstrated by the construction of suitable controls.

A minimum of three lots of product should be tested. Each lot of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS AND REAGENTS

A. Test Organisms

Pseudomonas aeruginosa	NCIMB	8626	ATCC 9027
Staphylococcus aureus	NCTC	10788	ATCC 6538
Serratia marcescens	NCTC	10211	ATCC 13880
Candida albicans	NCPF	3179	ATCC 10231
Fusarium solani			ATCC 36031

B. Test Media

Tryptone Soya Broth (TSB)
Tryptone Soya Agar (TSA)
Sabouraud Dextrose Agar (SDA)
Potato-Dextrose Agar (PDA)
Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/L KCl, 200 mg/L KH_2PO_4, 8000 mg/L NaCl, and 2,160 mg/L $Na_2HPO_4 \bullet 7H_20$ or suitable diluent.
Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or suitable diluent. Validated neutralizing agents/media as required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, filters, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Test product samples to be tested should be representative of the product to be marketed. Aliquots should be taken directly from the final product container immediately prior to testing. All regimen items, including cases, lenses, cleaning devices, etc., should be new and unused. If the test regimen results will be directly compared with results for a predicate device, then a predicate device from the same product category should be used for the comparison (e.g., a hydrogen peroxide product should be compared to a predicate hydrogen peroxide system and a multi-purpose product should be compared to a predicate multi-purpose product). Refer to Part 2:IV (PERFORMANCE REQUIREMENT).

III. TEST METHODS

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than 5 passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository).

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured and harvested as in Part 1:III.B.

After harvesting, organic soil consisting of heat killed yeast cells and heat inactivated serum, should be combined with the test organism to result in an initial concentration of $1 \times 10^7 - 10^8$ cfu/ml.

Prepare organic soil as follows. Culture S. cerevisiae on SDA at 20-25°C for 48 hrs. Harvest as in Part 1:III.B. Heat kill the suspension at 100 ±2°C for 10 minutes. Centrifuge at no more than 5000 X g for a maximum of 30 minutes. Resuspend in bovine serum which has been heated at 56°C for 30 minutes to inactivate complement. The concentration of S. cerevisiae in serum should be $1 \times 10^7 - 10^8$.

Centrifuge test organism suspension. Resuspend in organic soil to a concentration $1 \times 10^7 - 10^8$ cfu/ml. This is the inoculum to be used in the following procedure.

C. Test Procedure

1. Lens Inoculation

The test should be conducted with lens types representative of those with which the regimen is intended to be used (e.g., low water non-ionic, high water ionic, silicone acrylate, etc.).

Inoculate eight lenses per lot of test product per microbial species tested; to qualify for all hydrophilic lenses use four (4) non-ionic low water lenses and four (4) ionic high water lenses. For hydrophobic lenses, use four (4) silicone-acrylate and four (4) fluorosilicone-acrylate lenses.

Organism 1	Hydrophilic Lenses	
	Group I Material	Group IV Material
Lot 1 of Test Product	4 lenses	4 lenses
Lot 2 of Test Product	4 lenses	4 lenses
Lot 3 of Test Product	4 lenses	4 lenses
	12 lenses	12 lenses

Organism 1	Hydrophobic Lenses	
	Silicone-Acrylate	Fluorosilicone-Acrylate
Lot 1 of Test Product	4 lenses	4 lenses
Lot 2 of Test Product	4 lenses	4 lenses
Lot 3 of Test Product	4 lenses	4 lenses
	12 lenses	12 lenses

For hydrophilic or hydrophobic lenses, a total of 120 lenses (24 for each organism/60 lenses in each representative lens material) will be needed to test all 5 organisms.

Place test and control lenses, concave surface uppermost in a sterile petri dish.

Inoculate each lens by placing 0.01 ml of inoculum on the under surface of the lens at the point of contact between the petri dish and the lens, and 0.01 ml of inoculum on the top surface of the lens.

Allow the inoculum to absorb to each lens for 5-10 min. at 20-25^{0}C.

2. Lens Treatment

After inoculum absorption, treat lenses as described in the manufacturer's consumer instructions for lens disinfection, including all steps of cleaning, rinsing and soaking specified by the manufacturer. Cleaning and rinsing

procedures (e.g., rubbing and rinsing times and rinse volumes) should be performed in identical fashion for the predicate device and the test sample, unless otherwise stated in the manufacturer's consumer instructions for lens care. Test protocols should specify these parameters.

3. Recovery of Surviving Challenge Organisms (e.g., Micro--Appendix D Membrane Filtration Procedure)

   a. Dispense suitable volume of validated neutralizing medium into filtration apparatus.

   b. Transfer entire content of each test lens case (lens and solution) into the neutralizing medium in the filtration apparatus. The neutralization exposure time prior to filtration should be determined in the validation study.

   c. Apply vacuum and filter solution. Rinse the filter two additional times with the neutralizing medium.

   d. Aseptically transfer the lens onto a bed of agar medium appropriate for recovery of the test organism. Pour 40-50^{0}C agar medium (same as bed agar above) over the lens to cast it.

   e. Apply the test filter to the surface of a plate of appropriate solid media (could be the same as used in Part 2:III.C.3.d).

   f. Incubate bacterial recovery plates at 30-35^{0}C for 2-4 days. Incubate yeast recovery plates at 20-25^{0}C or 30-35^{o}C for 3-5 days and mold recovery plates at 20-25°C for 3-7 days.

D. Controls

1. Lens Inoculation Control

   For each microbial species tested transfer 3 inoculated lenses to tubes of TSB (for bacteria and yeasts) or SDB (for fungi) as appropriate. Vortex for 30 seconds. Serially dilute and plate out appropriate dilutions to permit a count of viable cells present.

   This count confirms that the number of organisms on the lens at the time of regimen challenge is adequate. The mean of the 3 counts should be not less than 2.0 X 10^{5}.

2. Neutralization and Recovery Control

Prepare filtration apparatus in triplicate (unless otherwise justified) as in Part 2:III.C.3 with suitable volumes of neutralizing medium and disinfecting solution. Add 5 to 50 cfu of challenge organism, filter and cultivate as outlined in Part 2:III.C.3.

Confirm inoculum on suitable medium in triplicate unless otherwise justified.

The recovery in the neutralizer broth should be at least 50% of the inoculum.

IV. PERFORMANCE REQUIREMENT

Bacteria, molds and yeast (See Table 2)

Less than or equal to 10 cfu recovered from each lens and test filter combination for each test organism. Alternatively, the average number of surviving organisms recovered on the lens and the respective test filter should be shown to be substantially equivalent to results obtained for the predicate device(s) when tested according to this regimen procedure. Organism counts (average for each organism) may be considered to be substantially equivalent if the difference between the subject device and the predicate device is less than or equal to 0.5 log.

Table 2

SUMMARY OF RECOMMENDED PERFORMANCE

CRITERIA FOR CONTACT LENS DISINFECTION PROCEDURES

PRODUCT	MEAN LOG REDUCTION AT DISINFECTION TIME				
	FUNGI		BACTERIA		
	FS[a]	CA	SM	PA	SA
Stand-Alone Criteria	1	1	3	3	3
Regimen Qualification	b	b	c	c	c
Regimen Criteria	d	d	d	d	d

a FS = F. solani ATCC 36031,
CA = C. albicans ATCC 10231,
SM = S. marcescens ATCC 13880,
PA = P. aeruginosa ATCC 9027,
SA = S. aureus ATCC 6538

b Stasis with an experimental error of $\pm$0.5 log at the disinfection time.

c The minimum acceptable log reduction for the mean value of all 3 bacteria combined should be 5.0. The minimum acceptable log reduction for any single bacterial type should be 1.0.

d Less than or equal to 10 cfu per lens and test filter combination from 0.01 ml of 1 X 10^7 to 1 X 10^8 inoculum OR

The average combined number of surviving organisms recovered on the lens and the respective test filter must be shown to be substantially equivalent to the predicate device(s).

MICRO--APPENDIX C

BACTERIOSTASIS TEST

I. PRINCIPLE

Bacteriostasis testing is performed for multi-dose saline products which do not contain conventional preservatives, yet do contain bacteriostatic agents (e.g., borate, boric acid, potassium sorbate, and EDTA). For these products, which do not meet the preservative efficacy criteria described in Micro--Appendix A, a discard date should be determined on the basis of the product's bacteriostatic activity. The bacteriostasis test is a modification of the preservative efficacy test procedure.

Three lots of product should be tested. Each lot of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS & REAGENTS

A. Test Organisms

Pseudomonas aeruginosa	NCIMB 8626	ATCC 9027
Staphylococcus aureus	NCTC 10788	ATCC 6538
Escherichia coli	NCIB 8245	ATCC 8739
Candida albicans	NCPF 3179	ATCC 10231
Aspergillus niger	IMI 149007	ATCC 16404

B. Test Media

Tryptone Soya Broth (TSB), Tryptone Soya Agar (TSA), Sabouraud Dextrose Agar (SDA), Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/l KCl, 200 mg/l KH_2PO_4, 8000 mg/l NaCl, and 2,160 mg/l $Na_2HPO_4 \bullet 7H_2O$ or suitable diluent
Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or suitable diluent
Validated neutralizing agents/media as required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, 100 X 20 mm petri dishes, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Product samples to be tested should be representative of the product to be marketed. Prepare one tube containing a minimum of 10 ml of test solution per challenge organism. The largest container size proposed for the product should be used.

III. TEST METHOD

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than 5 passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository).

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured on agar as in Table 1.

Table 1: Media & Incubation Conditions for Growth of Challenge Organisms

Organism	Medium	Incubation Temp °C	Incubation Time
Pseudomonas aeruginosa	TSA	30-35	18-24h
Staphylococcus aureus	TSA	30-35	18-24h
Escherichia coli	TSA	30-35	18-24h
Candida albicans	SDA SDA	20-25 30-35	42-48 or 18-24h
Aspergillus niger	SDA	20-25	7 days

To harvest all cultures, use sterile DPBST or a suitable diluent, washing the surface growth and transfer to a suitable vessel. The spore suspensions may be filtered through sterile glass wool, cotton gauze or cheese cloth to remove hyphal fragments.

After harvesting, the cultured organisms may be washed using centrifugation. If centrifugation is used, each centrifugation should be conducted at 2-25°C for no longer than 10 minutes at 4000 x g or less. The bacterial suspensions may be filtered (e.g., 3 - 5 µm pore size) to produce a single cell dispersion. All challenge cell suspensions should then be adjusted with DPBST or other suitable diluent to 1×10^7 - 1×10^8 cfu/ml or cell concentration sufficient to result in final concentration of 1×10^5 - 1×10^6 cfu/ml in the product. The approximate cell concentration may be estimated by measuring the turbidity of the suspension or a dilution of the suspension using a spectrophotometer. The actual concentration of cfu/ml should be determined for each suspension by the plate count method at the time of the test.

Bacterial and yeast cell suspensions should be used on the day of preparation. Bacterial and yeast cells may lose viability and resistance if not used on the day of preparation. Spore suspensions may be used up to 7 days following preparation by storage under refrigeration (Avg. 4 ± 2°C).

C. Test Procedure

1. Inoculate the sample product to be tested with a suspension of test organisms sufficient to provide a final count of 1.0 X 10^5 - 1.0 X 10^6 cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing.

2. Store inoculated product at 20-25°C. Temperature should be monitored using a calibrated device and documented. If sensitive to light the product should be protected during the period of the test.

3. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 7, 14, 21, and 28 days. If longer discard dates are desired, continue sampling periodically thereafter.

4. Subject 1.0 ml aliquots removed at the specified time intervals to a suitable series of decimal dilutions in validated neutralizing media. Mix suspension well by vortexing vigorously and incubate for a suitable period of time to allow for neutralization.

   If the antimicrobial agent(s) in the formulation cannot be adequately inactivated or neutralized it may be eliminated using a validated membrane filtration procedure (e.g., Micro-Appendix D).

5. Determine the viable count of organisms in appropriate dilutions by preparation of triplicate plates (unless otherwise justified) of suitable recovery medium (e.g., TSA for bacteria and SDA for mold and yeast). The agar for pour plates should be kept between 40-50°C prior to pouring. The agar media used for determination of viable counts may also contain antimicrobial inactivators or neutralizers if required. Where membrane filtration has been employed to remove/neutralize antimicrobial agents, membranes should be cultured on these media as appropriate.

6. Incubate bacterial recovery plates at 30-35°C for 2-4 days. Incubate yeast at 20-25°C or 30-35°C for 3-5 days and mold recovery plates at 20-25°C for 3-7 days.

7. Determine the average number of cfu on countable plates and record. Countable plates refer to 30-300 cfu/plate for bacteria and yeast, and 8-80 cfu/plate for mold except when colonies are observed only for 10^0 or 10^{-1} dilution plates. Calculate microbial reduction at the specified time points.

8. The concentration of survivors should be calculated at each time point.

D. Controls

1. Inoculum Controls

The initial inoculum concentration should be calculated by dispersing an identical aliquot of the inoculum into the same volume of a suitable diluent (e.g., DPBST) as used in III.C.1 to achieve a final concentration of 1.0×10^5 - 1.0×10^6 cfu/ml. Ensure dispersion of the inoculum by adequate mixing. This control sample should be evaluated at the same time as the zero time sample. This serves to demonstrate the suitability of the medium used for growth of the test organism and provides an estimate of the initial inoculum concentration.

2. Recovery Medium Control

Qualify the neutralizing agent/medium for the product initially and periodically thereafter. Prepare a 1/10 dilution of the product in the validated neutralizing broth (1 ml into 9 ml). If a greater dilution of the test solution is required to achieve neutralization, the latter dilution should be used. Prepare a second control tube with 10 ml of a suitable diluent (e.g., TSB). Inoculate the tubes with sufficient inoculum to result in 10 - 100 cfu of challenge organism per plate. Incubate for an appropriate period of time at ambient temperature. Plate the appropriate aliquot from each tube onto the recovery agar plates in triplicate unless otherwise justified. The recovery in the neutralizer broth should be at least 50% of the recovery in the second control tube. This control is to be performed for each challenge organism.

IV. PERFORMANCE CRITERIA

A. Bacteria

The concentration of each bacterial challenge organism should remain at the initial level or decrease.

B. Molds and Yeasts

The concentration of the yeast and mold should remain at initial levels or decrease within an experimental error of ± 0.5 log.

C. The product should be labeled to discard the container after it has been opened for the number of days which corresponds to time point previous to the point at which any organism shows an increase in number (see example). The container label should include a space on which to record the date opened.

Example:

(Concentration in Abbreviated Log Value)

	DAY 0	7	14	21	28	35
E. coli	10^5	10^3	<10	10^1	10^2	10^3
P. aeru.	10^5	10^3	10^3	10^2	10^3	10^4
S. aureus	10^5	<10	<10	<10	<10	<10
C. alb.	10^5	10^5	10^4	10^2	<10	<10
A. niger	10^5	10^4	10^3	10^4	10^4	10^5

Cut off point: E. coli 14 days
P. aeru. 21 days
A. niger 14 days

The use of the above hypothetical product is limited to 14 days after opening.

MICRO--APPENDIX D

MEMBRANE FILTRATION PROCEDURE

I. SUMMARY

This document provides an example of procedures and controls for membrane filtration.

II. MATERIALS AND REAGENTS

A. Test Media

Suitable diluent with or without neutralizers
Tryptone Soya Agar (TSA)
Sabouraud Dextrose Agar (SDA)
Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/L KCl, 200 mg/L KH_2PO_4, 8000 mg/L NaCl, and 2,160 mg/L $Na_2HPO_4 \bullet 7H_20$ or other suitable diluent
Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST)

B. Test Equipment

Sterile pipettes, petri dishes, containers, etc., as needed. Suitable sterile apparatus for holding the sterile membrane filter and the filtrate. Suitable equipment for creating a vacuum or pressure to cause the liquid phase of the inoculated test solution to pass through the membrane filter aseptically. The membrane filter should have a nominal pore size of not greater than 0.45 µm, a diameter of at least 47 mm and should be free of chemicals which could be toxic to microbial cells.

III. TEST METHOD

A. Moisten the sterile membrane filter in a sterile filter assembly with sterile DPBST or other suitable diluent.

B. Aseptically transfer a measured volume of the inoculated test solution into sterile DPBST or other suitable diluent.

C. Transfer the diluted solution to the membrane and filter immediately with the aid of vacuum or pressure. The sample applied to the filter should be diluted in 50-100 ml of dilution fluid and thoroughly mixed to ensure uniform distribution of the sample over the entire area of the filter. This will decrease the probability of multiple cfu being placed on the filter at the same location.

D. Wash the membrane filter with several volumes of a suitable diluent which may contain additional neutralizing agents as needed. Three volumes of a suitable diluent (100 ml each) are usually sufficient to remove and/or dilute the antimicrobial agent. The actual volume should be determined empirically for each formulation for each challenge organism.

E. The membrane filter is then aseptically incubated with appropriate media to allow growth of cfu on the surface of the filter. This may be accomplished by aseptic removal of the membrane filter from the filter assembly unit and placement of the membrane on the surface of a sterile agar plate which does not have obvious liquid on the surface or the membrane may be enclosed in an agar sandwich. Alternatively, a sterile membrane filter unit may be used which requires addition of sterile media to the sealed filter and incubation of the membrane in situ. Media should be used which are appropriate for the type of challenge organism and the specific formulation under test.

F. Determine the average number of cfu on countable membrane filters (3-100 cfu/47 mm filter for bacteria and yeast and 3-10 cfu/47 mm filter for molds). Calculate the cfu/ml of inoculated solution.

G. Controls

Neutralizer efficacy may be confirmed by transferring an aliquot of the uninoculated test solution into 50-100 ml of sterile diluting fluid using the same ratio of volume of test solution to volume of diluting fluid. Apply the entire volume to the membrane and filter using vacuum or pressure. Wash the filter with several volumes of the diluting fluid using the same volume as used for the test procedure. Transfer 10-20 cfu for bacteria and yeasts or 3-10 cfu for molds into 100 ml of diluting fluid and apply to the membrane. Incubate the membrane filter in contact with media as described in the test procedure (see section III.E).

The procedure should be repeated using diluting fluid not exposed to the test solution. Counts should be compared with those derived by the same method but using DPBST instead of test solution. The count observed for diluting fluid with test solution should be comparable with that obtained for diluting fluid. The latter count should be statistically comparable with a direct plate count on rich medium to eliminate the possibility of loss of viable cells by filtration or test medium toxicity.

TOXICOLOGY

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TOX--APPENDIX A

TOXICOLOGY

I. Introduction

This section of the guidance document discusses the toxicological considerations that CDRH believes should be addressed in order to assess substantial equivalence in terms of safety and biocompatibility of contact lens care products.

In an effort to harmonize the biological response to testing of medical devices, CDRH has issued blue book memorandum #G95-1 entitled "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing," which includes an FDA-modified matrix that delineates the type of testing recommended for various medical devices. It also includes a flow chart entitled "Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s." The tests recommended in this toxicology section are generally consistent with the studies recommended in the blue book memorandum but have been adapted for specific use with contact lens care products.

The manufacturing process and chemical formulation used to fabricate a contact lens/lens care product should dictate, in general, the extent of the toxicology testing necessary to establish substantial equivalence in terms of its safety and effectiveness. It is the applicant's responsibility to develop an appropriate toxicology and biocompatibility profile for the specific lens material/lens care product in order to demonstrate that the device is substantially equivalent in terms of safety and effectiveness to the predicate device. Any test suggested in this toxicology section may be replaced by a suitable alternative if the alternative test has been validated or can be justified for use as an alternative. All nonclinical laboratory studies should include a statement that each study was conducted in compliance with the GLP Regulation for Nonclinical Laboratory Studies. If the study was not conducted in compliance with the GLP Regulation, a justification of the noncompliance should be submitted.

CDRH is aware of the ongoing research efforts to achieve the goal of eventual substitution of in vitro tests for certain biological tests utilizing animals*. However, at present, in vitro alternatives to animal testing have not been sufficiently developed or validated for use. Therefore, CDRH regrets that toxicology tests involving animals will continue to be used at this time in order to adequately assess risks and evaluate safety of ocular products prior to 510(k) clearance. CDRH will continue to monitor the developments of alternatives to animal testing and will recommend their use once such studies have been validated.

*Goldberg, A.M., et al. Framework for Validation and Implementation of In Vitro Toxicity Test: Report of the Validation and Technology Transfer Committee of the Johns Hopkins Center for Alternatives to Animal Testing. J. Am. Coll. Tox. 1993: 12:23-30.

The toxicology studies recommended below are generally consistent with the applicable studies recommended in normative standards and/or USP/NF 23.

NOTE: In addition to the recommended tests listed, CDRH believes that the material safety data sheet (MSDS) should be submitted in order to establish a toxicology profile for active ingredients and/or new chemical components incorporated into the finished contact lens care product (i.e., preservative, tablet, etc.). CDRH is aware that additional safety and toxicology data are generally included in the MSDS which can be obtained from the supplier of the chemical constituent, in lieu of performing additional or repetitive toxicology testing. The MSDS should be included in the 510(k) submission.

II. Minimum Recommended Toxicology Test Procedures for Contact Lens Care Products (i.e., Solutions/Tablets)

A. In-Vitro Cytotoxicity, USP/NF 23

The purpose of this study is to evaluate the potential for toxicity of residual chemicals leaching from the lens into the care products (i.e., solution(s)/solubilized tablets). In addition, this test may be used to detect potential toxic carryover from uptake/release of the solution by the lens. The effects are assessed in vitro using cytotoxicity studies (i.e., Tissue Culture-Agar Diffusion Test, Direct Contact Test and/or Elution Test) or a suitable validated alternative method.

B. Acute Ocular Irritation, USP/NF XXII

The purpose of the study is to evaluate the potential for ocular irritation resulting from residual chemical leachables from the finished device which may be extracted in the care products (i.e., solution(s)/solubilized tablets). This method is also used to detect the potential for ocular irritation due to carryover from uptake/release of the solution by the lens and from direct instillation of an in-eye solution. This test should not be needed in cases where formulations contain known ocular irritants. In such cases, an appropriate warning should be required on the label for products known to cause ocular irritation (i.e., daily cleaners/periodic cleaners) in lieu of performing this test.

C. Acute Oral Toxicity

The purpose of this study is to assess the potential of the contact lens care product (i.e., solution(s)/tablet(s)) to produce a toxic response as a result of deliberate or accidental ingestion of the device by adults or children. These data will be used to determine the need for additional warnings or precautions in the labeling of the product for the purpose of consumer protection. For rodent testing, the maximum volume of an aqueous solution generally should not exceed 2 ml/100 g body weight. This single large dose is referred to as the maximum tolerable dose (MTD). However, should signs of toxicity be demonstrated at this MTD,

further testing consistent with accepted toxicological practices is recommended in order for CDRH to complete its risk/benefit assessment of the device. See Tox--Appendix B for the suggested test method.

III. Additional Recommended Testing

Data from the following tests should be submitted if a manufacturer is using a new preservative or an active ingredient/chemical component not previously used in a currently marketed contact lens care product.

A. Sensitization (Guinea Pig Maximization Test*):

The purpose of this test is to grade or rank chemical constituents on a scale of I through V as to their potential for inducing sensitivity response in the guinea pig model. The grades of rankings are based on the number of animals sensitized, and results are classified on an ascending scale from a weak sensitizing agent (grade I) to an extreme sensitizing agent (grade V).

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*Magnusson, B. and Kligman, A.M. The Identification of Contact Allergens by Animal Assay. The Guinea Pig Maximization Test. J. Invest. Dermatol. 1969; 52.

B. In-Vivo Ocular Biocompatibility (ISO 9394-1994):

This test method entitled, "Optics and optical instruments--Determination of biological compatibility of contact lens material --Testing of the contact lens system by ocular study with rabbit eyes," is published as an international standard by ISO. This ISO standard has been evaluated by CDRH, and we believe it should be acceptable in its entirety to address preclinical ocular biocompatibility of contact lens products.

IV. Toxicology Tests for Containers

The purpose of these testing requirements is to indirectly or directly assess the potential toxicity of constituent(s) that may leach from the container when the solution comes in contact with the container for a prolonged period of time. The following in vitro and in vivo test procedures are recommended by CDRH and are consistent with the procedures listed in USP/NF XXII, Containers for Ophthalmics--Plastics (Biological Test Procedures).

A. Systemic Injection Test, USP/NF XXII

B. Acute Ocular Irritation

C. In-Vitro Cytotoxicity

TOX--APPENDIX B

ACUTE ORAL TOXICITY

The following is a generalized test protocol that may be used as guidance in assessing a contact lens solution for acute oral toxicity. Specific test procedures may vary for each individual laboratory but generally should follow the outline given below.

Purpose of the Study:

The objective of the study is to evaluate the potential oral toxicity of a designated test material following a single oral dose at 15 g/kg of body weight.

This study should be conducted in accordance with the requirements of the Good Laboratory Practice (GLP) Regulations (21 CFR 58).

Control Article:

No control article should be employed in this study, since dose response during the study may serve as an internal control.

Test System and Justification:

Ten albino rats of the Sprague-Dawley strain (five male, five female), obtained from a commercial supplier, should be selected from the stock colony after a minimum 5-day acclimation period. Prior to overnight food deprivation, animal weights should range from 200 to 300 g. Rats should be identified by ear punch and housed, according to sex, up to five per suspended cage.

The rat has been historically used to establish relative LD_{50} data. The oral route of dosing is selected as the strongest challenge for materials that could be accidentally ingested. A 15 g/kg dose is generally regarded as nontoxic (Gleason, et al, 1969).

Animal Management:

Animal husbandry and environmental conditions should conform to specifications based on the "Guide for the Care and Use of Laboratory Animals," National Institutes of Health (NIH) Publication No. 85-23. Rats should receive a commercial rodent food on a daily basis; tap water should be freely available. No contaminants are suspected to be present in the food or water that would affect the results of this study.

No sedation, analgesia or anesthesia should be necessary in this procedure. In the unlikely event that an animal should become injured, ill, or moribund, euthanasia or veterinary care should be conducted in accordance with current veterinary medical practice.

Test Article Preparation:

Density (g/ml) of the liquid should be determined prior to dosing.

As far as practical, composition of the test substance should be known. Information should include the name and quantities of all major components, known contaminants and impurities, and the percentage of unidentifiable materials to account for 100% of the test substance. Ideally, the lot of the substances tested should be the same throughout the study. The test sample should be stored under conditions that maintain its stability, strength, quality, and purity from the date of its productions until the tests are complete.

Methods and Route of Administration:

Food should be withheld overnight (16-20 hours). Each rat should then be gavaged with a single 15 g/kg dose of the test material via stainless steel blunt tipped cannula attached to a disposable syringe. The maximum dose volume should not exceed 2 ml/100 g body weight. The rats should be weighed at dosing, at observation day 7, and at day 14 of the study. Animals should be observed for clinical signs of toxicity immediately after dosing, at 4 hours after dosing and daily for 14 days. Food should be returned following the immediate observation. Rats found dead during the study and those euthanatized should be subjected to a macroscopic examination of the viscera. A complete gross necropsy should be performed on all animals that die during the course of the study.

Evaluations and Statistics:

Mean body weights should be calculated for all animals at dosing (day 0) and for survivors at days 7 and 14. Statistical manipulation of data is not applicable to this study.

Should 80% of the animals survive, the test material preparation should not be considered orally toxic. Greater than 20% mortality may warrant additional investigation.

Report:

The report should contain a description of the methods employed, data accumulated in tabular form and a summary of results.

Quality Assurance:

Inspections should be conducted at the major phases of the study (e.g., test article preparation, dosing, and necropsy). The final report should also be inspected for conformance to Subpart J of the GLP Regulations (21 CFR 58.185). A Certificate of Quality Assurance Inspections should be provided with the final report.

Records:

Test article preparation, animal weights, observations for adverse clinical signs, macroscopic necropsy findings, and dates of relevant activities (e.g., study initiation and completion) should be recorded.

All raw data pertaining to this study and a copy of the final report should be retained in the designated archive files of the testing laboratory/sponsor.

References:

21 CFR 58 (GLP Regulations)

Gleason, M.N., et al. 1969. Clinical Toxicology of Commercial Products (Third Ed.). The Williams & Wilkins Co., Baltimore, MD.

CLIN--APPENDIX A

CLINICAL

I. Introduction:

This section of the guidance is designed to assist manufacturers in developing clinical performance data necessary to demonstrate substantial equivalence to a class II lens care product. Whenever possible, CDRH has provided manufacturers with guidance on when to submit clinical performance data and recommended minimum numbers for the size and duration of a clinical study for a new or modified lens care product. When clinical performance data are needed, however, it is the overall responsibility of the manufacturer to design the clinical study with an appropriate number of subjects and sufficient duration to provide adequate data to demonstrate substantial equivalence.

The means for collecting clinical performance data should be designed and conducted in a manner that will provide data constituting valid scientific evidence within the meaning of 21 CFR 860.7. It is not merely a compilation of available subject records. Monitoring of the study, accountability of all subjects, and details of complications or discontinuations are all essential elements.

It is important to note that while CDRH has recommended the appropriate use of controlled studies, such as randomized controlled trials, as a means of minimizing study biases, it also recognizes that some devices with well documented clinical experience may be studied with no control group. This will allow the sponsor to gain experience with the use of the device as well as to confirm safety as predicted from the preclinical data developed for the device.

The recommended preclinical testing is heavily weighted toward demonstrating substantial equivalency to a predicate device. The clinical testing is generally considered as additional confirmatory information to supplement the preclinical data. This is particularly true for "me-too" types of products which are within the marketed concentrations for the active ingredients of the predicate device.

Study protocol suggestions are provided in Clin--Appendix B. It is recommended that the study involve evaluable (completed) subjects divided evenly between independent investigators when applicable. In order to maximize the subjects' exposure to the products during the clinical study, a daily wear schedule should be followed for most products. However, a study of a periodic cleaner, used on weekly intervals, may provide more valuable clinical data concerning efficacy when extended wear subjects are enrolled than a similar study with daily wear subjects.

Clinical study designs may take on a variety of appearances. Concurrent control groups either of equal number to the test group, or utilizing an approximate 2:1 ratio of test to control subject ratio (see table 1) are but two examples. A cross-over study design may also be appropriate in some cases. The use of intrapatient controls in a solution study may

not be feasible for some products, but may be utilized if the sponsor desires and determines it to be appropriate.

Historical data may also serve as a control for products with available literature information, or from a manufacturer's previous clinical database, when an adequate justification is provided. If historical controls are used instead of interpatient controls, the historical control group should be defined and adequately characterized for comparison to the test group. When literature information is utilized, a review of applicable published studies along with comparative analysis of the study design, subject populations and outcome measures should be provided. Simply citing references would not be appropriate as a control.

For a clinical study of hydrophilic lenses, the study may be designed with subjects divided as equally as possible between Group I and Group IV lenses. Subjects in clinical studies with RGP lenses should be divided as equally as possible between RGP lens groups requested for 510(k) clearance (currently there are four). If the manufacturer of a lens care solution wishes to recommend its use with a specific type of lens in the labeling, the compatibility with the lens type should be confirmed preclinically and/or during the clinical trial.

Any lens care product study resulting in more than one adverse reaction should include adequate justification in order to establish substantial equivalence to the predicate device in terms of safety and effectiveness. The clinical sample sizes are calculated to be reasonably assured of obtaining at least one complication, as a function of the expected complication rate (5% for a 60 subject group, 10% with a 30 subject group), with a probability of greater than 95%. Therefore, in a subject group of 30 evaluable (completed) subjects exposed to a short term duration of a test product, an adverse event occurrence in 2 to 3 subjects will raise questions as to biocompatibility and fundamental safety of the product.

The clinical protocol for non-significant risk studies requires IRB clearance prior to beginning the study. Applicants should provide the complete protocol along with the study report in their application. FDA recommends the protocol study design, at a minimum, address the following:

1. Statement of the specific study objective(s)
2. Study duration
3. Sample size and selection criteria
4. Number of investigators and selection criteria
5. Methods of reducing study biases (control, etc.)
6. Study materials (lenses and care regimen)
7. Follow-up visit schedule

8. Methods of data collection, monitoring, and analysis

When questions remain concerning the protocol or content and format of a 510(k), sponsors should consult with DOD prior to finalizing their clinical protocol and initiating the investigation.

A “Modified” Trend Analysis Profile (TAP) form should be completed for all clinical studies and included in the clinical report section of the 510(k). The TAP helps identify trends in clinical data which assist the manufacturer and CDRH reviewers in evaluating the substantial equivalence of a device to a legally marketed device. This equivalence is based on whether any differences between the devices would affect safety and effectiveness.

Note that in small clinical studies of short duration (i.e., 30 subjects for 1 month duration), the TAP in addition to a written summary of the clinical trial results may be considered as sufficient documentation for submission. More extensive clinical study submissions should be supported by a TAP as well as a complete clinical report to include the summary reporting tables (Clin--Appendix D).

A sample TAP form is available in Clin--Appendix E. The sample form establishes the basic format that should be presented; however, it should be expanded to include all slit lamp parameters measured as well as visual acuity results and lens replacements. This is especially important when the TAP is provided for the short duration studies without the summary reporting tables. Sponsors with questions concerning the TAP should contact DOD staff for clarification.

Table 1

Example of Distribution of Completed Subjects for Hydrophilic Lens Study with 2:1 Ratio of Test to Control

60-Subject Study

Lens Material	Test Group	Control Group	Total
Group IV	20	10	30
Group I	20	10	30
Subtotal	40	20	60

30-Subject Study

Lens Material	Test Group	Control Group	Total
Group IV	10	5	15
Group I	10	5	15
Subtotal	20	10	30

CLINICAL TESTING MATRIX FOR CLASS II CONTACT LENS CARE PRODUCTS

Product	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients in Lower Concentrations Than Marketed Products	New Ingredients For Ophthalmic Use or Different Active Ingredient
Saline Solutions				60 subj/1 mo
Daily Cleaner		Footnote A	Footnote B	60 subj/3 mo
Periodic Cleaner		Footnote A	30 subj/1 mo	60 subj/3 mo
Soaking Solution for Disinfection		30 subj/1 mo		60 subj/3 mo
Neutralizer		30 subj/1 mo	Footnote A	60 subj/3 mo
Conditioning Solution		30 subj/1 mo		60 subj/3 mo
In-Eye Solution	30 subj/1 mo	30 subj/1 mo	30 subj/1 mo	60 subj/3 mo

Footnote A: Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected (i.e., a higher concentration of the active cleaning ingredient in a multi-purpose solution may require submission of clinical data while an increase in concentration of the active ingredient in a periodic cleaner may not unless it is used in conjunction with the disinfection regimen). If necessary, a 30 subject/1 month study should be conducted.

Footnote B: If active ingredient is a surfactant, the sponsor may use either appropriate in vitro tests or conduct a clinical test with 60 subjects/3 months to establish the efficacy of the lower concentration of active ingredient.

In the absence of validated in vitro data, such as non-surfactant cleaning studies, at present a cross-over design with additional in-vitro analysis of worn lenses is an example of one method to demonstrate substantial equivalence to the predicate device. While it may not always be necessary to consult with DOD prior to developing a test protocol, sponsors should note that additional discussion and guidance will be provided if requested.

II. Necessity for Clinical Performance Data and Study Size and Duration Recommendations:

A. Claim of Substantial Equivalence for a Lens Care Product Based Upon Same Active Ingredients:

1. Claims of substantial equivalence for a lens care product based upon the same active and inactive ingredients within marketed concentrations and the same manufacturing processes will not need clinical performance data provided that the preclinical testing (i.e., physical/chemical, microbiological and toxicological data) supports the claim.

   This pertains to an identical "me-too" product for the same product specific intended use and indication as the predicate device. In some cases, the applicant may have obtained referencing rights to predicate device data.

2. Claims of substantial equivalence for a lens care product based upon the same active ingredients within marketed concentrations but different inactive ingredients in some cases require clinical performance data, in addition to physical/chemical, microbiological and toxicological data, to support the claim. This "me-too" product may not be identical to the predicate device since the inactive ingredients in the predicate device may not be identified.

   If any of preclinical characteristics differ from the predicate device (data outside the range of the test method) the sponsor should justify why this characteristic difference will not impact upon the safety and effectiveness or supply supporting clinical performance data.

   When clinical performance data are necessary, such as for in-eye solutions, it is recommended that this study involve at least thirty (30) evaluable subjects followed for at least 1 month.

3. Claim of substantial equivalence based upon same active ingredients in higher or lower concentrations than marketed products generally require clinical performance data to be submitted depending on the physical/chemical, microbiological and toxicological data collected to support the claim.

   When clinical performance data are necessary it is recommended that this study involve at least 30 evaluable subjects followed for at least 1 month.

B. Claim of Substantial Equivalence for a Lens Care Product with New Ingredients for Ophthalmic Use or Different Active Ingredient:

Claims of substantial equivalence for a lens care product with new ingredients for ophthalmic use or different active ingredient require submission of clinical performance data, in addition to physical/chemical, microbiological and toxicological data, to support the claims. It is recommended that this clinical study involve at least sixty (60) evaluable (completed) subjects followed for at least 3 months.

C. Labeling Claims with Additional Indications:

The sponsor should design the study to collect data demonstrating the substantial equivalence of the lens care product to a legally marketed device in terms of the safety and effectiveness of the device. Additional indications could include use of the product with a different lens material [e.g., rigid gas permeable lenses (hydrophobic) when previously indicated for soft hydrophilic lenses, or an additional product specific intended use such as saline solution repackaged and relabeled as a rewetting drop].

Applicants should select an appropriate predicate device for comparisons and determination of substantial equivalence. The appropriate clinical testing matrix for the additional claim(s) should be referred to for guidance. Applicants may also contact DOD prior to initiating studies if they have questions.

III. Study Summary

For the purpose of ease in the submission of clinical performance data in support of a claim of substantial equivalence, DOD recommends that the following outline be utilized:

A. Introduction

1. Purpose
2. Statement of compliance
3. List of investigators to include number of eyes enrolled by each; control and trial, completed and discontinued

B. Materials and Methods

1. Study materials; to include lens(es) utilized and any solutions in addition to the study solution for both test and control subjects
2. Study design and procedures; to include randomization procedures, if utilized
3. Data analysis

C. Subjects

1. Demographic data
2. Completed and discontinued for both control and trial groups

D. Data to support substantial equivalence - sample tables included in Clin--Appendix D (data for control eyes should be reported separately from data for the trial eyes)

1. Adverse Reactions
2. Slit Lamp Examination
3. Symptoms/Problems/Complaints
4. Visual Acuity
5. Average Wear Time
6. Discontinued Eyes
7. Lens Replacements

Note: *Keratometric changes and refractive changes have been deleted as any event severe enough to cause these types of changes in experienced lens wearers would manifest itself in other categories*

E. “Modified” Trend Analysis Profile - Clin--Appendix E

F. Conclusion

CLIN--APPENDIX B

CLINICAL PROTOCOL SUGGESTIONS

OUTLINE

I. ALL STUDY DESIGNS

II. LENS CARE PRODUCT STUDIES

A. PROTOCOL CONSIDERATIONS

1. Statement of Specific Study Objective(s)
2. Sample Size and Study Duration
3. Sample Selection Criteria (a-e)
4. Investigator Selection Criteria
5. Methods of Study Control
6. Adjunct Solutions
7. Visit Schedule
   a. General Information
   b. Follow-up Schedules
8. Monitoring and Accountability
   a. Enrollment/Accountability
   b. Visit Forms
   c. Monitoring Responsibilities
   d. Methods of Analysis

B. METHODS OF DATA COLLECTION AND ANALYSIS

1. Adverse Reaction Data
2. Slit Lamp Findings
3. Symptoms/Problems/Complaints
4. Visual Acuity
5. Average Wear Time
6. Discontinuation
7. Lens Replacements

III. PROBLEMS/QUESTIONS

I. ALL STUDY DESIGNS:

It is important that the means for collecting clinical performance data be designed and conducted in a manner that will provide data constituting valid scientific evidence within the meaning of 21 CFR 860.7. In that section, the essentials of a well-controlled clinical investigation are discussed. During the design of a study the impact of the protocol on final product labeling should be kept in mind.

II. LENS CARE PRODUCT STUDIES:

A. Protocol Considerations:

The clinical protocol should, at a minimum, address the following:

1. Statement of the Specific Study Objective(s)

2. Sample Size (interpatient controls) and Study Duration--is dependent upon the basis for the claim of substantial equivalence and formulation.

a. At least 60 evaluable subjects (one evaluable subject is defined as two completed eyes) for a minimum of 3 months for a claim of substantial equivalence based upon the same intended use, but composed of new ingredients for ophthalmic use or different active ingredient.

b. At least 30 evaluable subjects for a minimum of 1 month for a claim of substantial equivalence based upon the same intended use, composed of the same active ingredients as the predicate product, a "me-too" product (refer to matrix).

3. Sample Selection Criteria

The following definitions should be used when reading this section.

Normal: a set of clinical findings which would not prevent a subject from contact lens wear. For example, a small corneal scar located off the visual axis which is long-standing may not preclude the use of cosmetic contact lenses.

Abnormal: a finding which would preclude a subject from consideration as an acceptable lens candidate.

a. Subjects should have worn contact lenses successfully previously (so as to not add another variable to the study).

b. Subject selection for entry into the study should meet the entry criteria established in the protocol.

c. In appropriately randomized, controlled studies, the subjects should be randomly assigned to either the control or the test group and the sponsor should detail the randomization procedure.

d. Subjects should have normal eyes and use no ocular medications. A normal eye is defined as having the following characteristics:

(1) no anterior segment infection, inflammation or abnormality;

(2) no other active ocular or systemic disease that would contraindicate contact lens wear; and

(3) no medications that would contraindicate contact lens wear.

e. Subjects with normal eyes not correctable to 20/40 with spectacles may be enrolled, but should be analyzed separately.

A minor positive finding should not disqualify a subject from participating in a clinical study if the investigator determines that the finding does not interfere with contact lens wear or cause the eye to become compromised from contact lens wear. The investigator should use clinical judgment to determine a subject's eligibility based on any trace pre-fitting observations and the study protocol as designed by the monitor and sponsor.

4. Investigator Selection Criteria

The sponsor should select an appropriate number of investigators to minimize biases. The training, experience, and objectivity of investigators should also be considered when attempting to reduce study biases.

As an example, a ratio of evenly assigning enough subjects to each investigator to allow for an evaluation of trends between investigators would be two (2) or three (3) investigators for a 30 subject study, and three (3) or four (4) investigators in a 60 subject study. The targeted minimum number of subjects per site would then be 10 to 15 in a small study, and 15 to 20 in the large study. These numbers also allow for the poolability of data for analysis.

5. Methods of Study Control

The sponsor should address those features of the study design which have been devised to minimize biases. CDRH suggests protocols which incorporate the appropriate use of controlled studies as a means of minimizing biases in clinical data. Randomized controlled clinical trials (RCT) may be appropriate in some cases, but not in all cases, refer to the Introduction section of Clinical (Clin--Appendix A). If the sponsor chooses to use historical controls instead of interpatient controls, the historical control group should be defined and adequately characterized for comparison to the test group.

For further information refer to texts such as:

Friedman, L.M. et al. Fundamentals of Clinical Trials. John Wright-PSG Inc., Boston, MA, 1982.

Meinert, C.L. and S. Tonascia. Clinical Trials - Design, Conduct and Analysis. Oxford University Press, New York, NY 1986.

6. Adjunct Solutions

All lens care products used in the study should be specified. The surface quality of the lenses should also be assessed for such findings as deposits, cracking or crazing. CDRH recommends the use of grading systems to standardize such findings. One example of a grading system for deposits is the modified Rudko Method which is discussed in an article by R.A. Hathaway and G.E. Lowther in the Journal of the American Optometric Association, 49 (3) 259-266, 1978.

Another grading scale is as follows:

Lens Surface Characteristics

Front Surface Wettability:

0 = a smooth uniformly reflecting surface
1 = a coarse hazy surface which seems resolved momentarily with each blink and becomes exacerbated with staring
2 = a stable dry (non-wetting) area of some magnitude
3 = gross crystalline or amorphous deposits

Front Surface Deposits:

0 = absent, clean surface
1 = very slight, only visible after tear film drying
2 = slight, visible deposits easily removed
3 = moderate, deposits adherent and not removable
4 = severe, non-removable deposits and comfort affected

Findings of an increase in the frequency of use for lubricants, in-office cleanings, or need for enzyme use should be evaluated and addressed by the applicant.

7. Visit Schedule

a. General Information

All subjects in a study should be on the same follow-up schedule. In the event an ocular abnormality is observed at any visit, the investigator should see the subject as frequently thereafter as necessary to treat and eliminate the abnormality. (Documentation of abnormalities will be discussed later.) The reason for each unscheduled visit should be reported in the 510(k).

b. Follow-up Schedules (after the initial dispensing of new lenses and lens care products)

The following schedule contains target dates, rather than absolute dates for follow-up. In most cases, the sponsor may assign acceptable windows around each target date to further clarify the visit schedule for the investigator:

One Month Study: 1 week, 2 weeks, 4 weeks.

Three Month Study: 1 week, 4 week, then monthly through study.

Any subject reporting for an unscheduled visit should be documented on the reporting tables under "Unscheduled Visit."

8. Monitoring and Accountability

(Reference 21 CFR 812 Subparts C and E)

a. Enrollment/Accountability

A subject should be considered enrolled when he or she signs the informed consent form. This form should be signed prior to dispensing of any lens care products. All subjects enrolled should be accounted for even if they are not dispensed lens care products. Once enrolled, a subject is considered "active" and should be accounted for at every visit until completion of, or discontinuation from, the study.

b. Visit Forms

A visit form should be filled out and signed by the investigator performing the examination at the time of the scheduled or unscheduled visit. Adverse reaction reports must be completed in accordance with 21 CFR 812.46(b) and submitted to CDRH.

c. Monitoring Responsibilities

If an investigator is not complying with the signed agreement, the investigational plan or other conditions imposed by the IRB or CDRH, the sponsor should either secure compliance or discontinue shipments of the device to the investigator and end his or her participation in the study.

d. Methods of Analysis

The sponsor should summarize the methods of analysis including any appropriate statistical methods of evaluating the data.

B. Methods of Data Collection and Analysis:

This section discusses the data which are provided to support the claim of substantial equivalence. The Summary Reporting Tables (Clin-Appendix D) may be used by sponsors as a basis for developing clinical reporting forms.

1. Adverse Reaction Data

CDRH believes an "adverse reaction" would include, but not be limited to a hazardous, sight-threatening condition such as: corneal ulcers, severe corneal abrasion > 2 mm in diameter, iritis, other ocular infections or inflammations, corneal scarring, or permanent loss of vision.

Photodocumentation or detailed drawings that detail the size, location and depth of the adverse reaction should be provided. Infections should be cultured.

The sponsor should detail the events of all adverse reactions including all treatment(s) and diagnoses through the resolution of the event.

Events which are not sight-threatening should be graded and reported as significant findings in the appropriate category such as slit lamp findings or the symptoms/problems/complaint section.

Non-sight-threatening events may include, but are not limited to, the following: giant papillary conjunctivitis, epiphora, dry eyes, and irritation.

2. Slit Lamp Findings

Slit lamp examinations should be performed at each visit. The investigator should record all positive and negative (grade 0) findings, not only those which are considered to be clinically significant. The results should be tabulated, and all findings over grade 2 should be explained in the 510(k).

An example of a SLIT LAMP FINDINGS CLASSIFICATION SCALE is included in Clin--Appendix C. Other suitable well defined classification scales can be found in the FDA PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES or the ISO standard, Optics and Optical Instruments - Contact Lens and Contact Lens Care Products - Guidelines for Clinical Investigations, ISO/DIS 11980.

3. Symptoms/Problems/Complaints

Subjective data should be collected at each visit and tabulated in the 510(k). These data are used in conjunction with objective findings in the assessment of safety and effectiveness.

Additionally, the following information may be submitted:

Subjective Acceptance

Below are samples of acceptable grading scales for a limited number of parameters. Please refer to Table 5 of Clin--Appendix D, Informative Summary Reporting Tables, for additional sample parameters.

Other suitable well defined scales, such as that found in the ISO standard, Optics and Optical Instruments - Contact Lens and Contact Lens Care Products - Guidelines for Clinical Investigations, ISO/DIS 11980, may also be used. Sponsors may also consider utilizing an alternative to the numeric rating scale, such as a visual analog scale, provided the method is appropriate for collection and analysis of the data.

Comfort:

0 = Excellent, cannot be felt
1 = Very comfortable, just felt occasionally
2 = Comfortable, noticeable but not irritating
3 = Slightly uncomfortable, just irritating or annoying
4 = Very uncomfortable, very irritating or annoying
5 = Causes pain, lens cannot be tolerated

Vision:

0 = Excellent, cannot notice any visual loss
1 = Very good, just noticeable and very occasional reduction
2 = Good, occasional noticeable but acceptable reduction
3 = Poor, noticeable but acceptable reduction
4 = Very poor, marked and unacceptable reduction
5 = Unacceptable, lens cannot be worn

Handling:

0 = excellent, no problems with lens insertion and removal
1 = Very good, occasional difficulty with lens insertion and removal
2 = Good, some problems but insertion and removal usually successful
3 = Poor, difficult and very occasional unsuccessful insertion/removal
4 = Very poor, difficult and occasional unsuccessful insertion/removal
5 = Unmanageable, lenses impossible to handle

4. Visual Acuity (VA) Data

Distance VA should be taken at each visit. Although other acceptable scales such as Snellen Acuity are available, the use of logMAR progression VA charts with equal steps between successive lines is recommended.

For purposes of submission, the initial VA (best corrected with the contact lens) should be compared to the VA results with the contact lens at the final visit. VA decreases of 2 or more lines should be reported with explanations. Investigator comments and explanations for all decreases of 2 or more lines at final visit compared to initial visit should be included. Additionally, a similar decrease in VA during the course of the study should be reported and explained.

5. Average Wear Time (AWT)

The lens AWT should be recorded at each visit. A tabulated report of AWT in hours, or days as appropriate, by visit should be provided to assess trends during the

study. When data are collected for both daily lens wearers and extended lens wearers, these data should be analyzed separately.

6. Discontinuations

Complete data should be provided on all discontinued subjects including the reason for discontinuation and visual status at the final visit. If problems persist, the subject should be followed until resolution of the problem. All data which would normally be collected at the final study visit should also be collected at the discontinued subject's last visit. Copies of subject report forms for all discontinued subjects should be provided in the submission.

7. Lens Replacements

The reason for each replacement should be tabulated in a manner which allows for trend analysis during the course of the study. Lens replacements for the following reasons should be further explained: discoloration, response to physiological problems, slit lamp findings, or "other."

III. PROBLEMS/QUESTIONS:

When questions remain concerning the protocol or content and format of a 510(k), sponsors should consult with DOD prior to finalizing their clinical protocol and initiating the investigation.

CLIN--APPENDIX C

SLIT LAMP FINDINGS CLASSIFICATION SCALE

A. EDEMA

Corneal edema should be classified according to the haziness of the epithelium, the number of microcysts observed, and the clouding of the stroma.

EPITHELIAL EDEMA

0 - NONE:	None: No epithelial or sub-epithelial haziness. Normal transparency
1 - TRACE:	Barely discernible localized epithelial or subepithelial haziness
2 - MILD:	Faint but definite localized or generalized haziness
3 - MODERATE:	Significant localized or generalized haziness
4 - SEVERE:	Definite widespread, epithelial cloudiness giving dull glass appearance to cornea, or numerous coalescent bullae (Note the number and location of bullae)

EPITHELIAL MICROCYSTS

0 - NONE:	No microcysts
1 - TRACE:	1 to 20 microcysts
2 - MILD:	21 to 50 microcysts
3 - MODERATE:	51 to 100 microcysts
4 - SEVERE:	> 100 microcysts or bullae

The presence/absence of vacuole or bullae should be documented along with their numbers. The presence of bullae should be considered as reportable grade 4 severe epithelial edema.

STROMAL EDEMA

0 - NONE:	None: No stromal cloudiness. Normal transparency
1 - TRACE:	Barely discernible localized stromal cloudiness
2 - MILD:	Faint but definite localized or generalized stromal cloudiness
3 - MODERATE:	Significant localized or generalized stromal cloudiness
4 - SEVERE:	Definite widespread, stromal cloudiness, or numerous striae. (Note the number and location of striae)

B. CORNEAL NEOVASCULARIZATION

Maximal corneal vascularization should be reported according to the following scale:

0 - NONE:	No vessel penetration
1 - TRACE:	< 1.0 mm vessel penetration
2 - MILD:	1.0 mm - 1.5 mm vessel penetration
3 - MODERATE:	1.5 mm - 2.0 mm vessel penetration
4 - SEVERE:	Vessel penetration > 2.0 mm.

Optionally the depth and location of vessel penetration can also be reported as follows:

Depth

a. superficial
b. stromal

Location

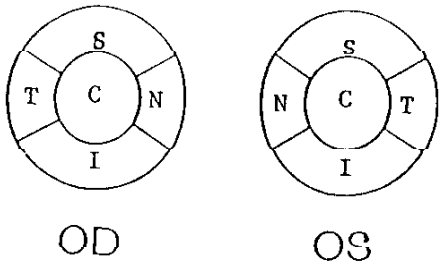
N	Nasal	T	Temporal
I	Inferior	S	Superior
C	Circumferential	X	Other (describe)

c. CORNEAL STAINING

It is recommended that sponsors design data collection forms to obtain information concerning the location of corneal staining so that peripheral staining can be differentiated from central staining.

Maximal corneal staining should be recorded according to the following scale:

0 - NONE:	No staining
1 - TRACE:	Minimal superficial staining or stippling a. Dimpling, discrete dot staining, OR b. Trace superficial lens insertion marks or foreign body tracks
2 - MILD:	Regional or diffuse punctate staining a. Central or generalized, OR b. Peripheral including 3 9 o'clock staining, OR c. Mild abrasion or foreign body tracks
3 - MODERATE:	Dense coalesced staining up to 2 mm diameter a. Corneal abrasion b. Foreign body track
4 - SEVERE:	Dense coalescent staining greater than 2 mm in diameter or full thickness abrasion .
Location:	N - Nasal, T - Temporal, I - Inferior, S - Superior, C - Central



OD OS

D. BULBAR HYPEREMIA

Maximal limbal and bulbar hyperemia should each be recorded on a 5 point scale as follows:

0 - NONE:	No hyperemia present
1 - TRACE:	Slight regional hyperemia
2 - MILD:	Diffuse hyperemia
3 - MODERATE:	Marked regional or diffuse hyperemia
4 - SEVERE:	Diffuse episcleral or scleral hyperemia

E. PALPEBRAL CONJUNCTIVAL OBSERVATIONS

The location of maximal conjunctival response should be documented according to the following scale:

0 - NONE:	Uniform satin appearance of conjunctiva
1 - TRACE:	Slight conjunctival injection without texture
2 - MILD:	Mild or scattered papillae/follicles less than 1 mm in diameter
3 - MODERATE:	a. Significant papillae/follicles less than 1 mm in diameter, and/or marked conjunctival injection b. Staining of the top of one papilla
4 - SEVERE:	a. Localized or generalized papillae/follicles 1 mm or more in diameter b. Staining of the top of more than 1 papilla

Optionally, the conjunctival response can also be recorded for each of the four lid areas:

Upper lid

1 - Superior tarsal conjunctiva
2 - Middle tarsal conjunctiva
3 - Inferior (lid margin region) tarsal conjunctiva

Lower lid

4 - Palpebral conjunctiva of lower lid

F. OTHER COMPLICATIONS (List all reports by specific finding and grade by severity)

This section is intended to capture less commonly observed clinical entities such as corneal infiltrates, conjunctival infection, EKC, corneal ulcers, iritis, lens adhesions and recurrent erosion. The complication should be identified and described according to the following generic scale.

Example provided for infiltrates, but the concept is applicable to all findings:

0 - NONE:	No other significant biomicroscopic findings
1 - TRACE:	Minimal finding such as one faint peripheral infiltrate which does not stain
2 - MILD:	Mild findings such as a few faint infiltrates
3 - MODERATE:	Significant findings such as multiple, dense infiltrates
4 - SEVERE:	Severe finding such as marked infiltrates with overlying staining

CLIN--APPENDIX D

INFORMATIVE SUMMARY REPORTING TABLES
(Provided for reference)

Table 1 Notes:

TITLE: Accountability of Eyes Enrolled and Distribution by Status

PURPOSE: To ensure a complete accounting of all eyes enrolled in the investigation.

General: Six status subgroups are identified and defined below. In all cases status is as of the cutoff date of the study at which time data were tabulated for submission.

Enrolled Dispensed: All subjects who signed an informed consent form prior to having lens care product(s) dispensed to them.

Completed Eyes: Eyes which used the lens care product(s) for the prescribed investigational period and for which a final visit form was completed and submitted.

Active Eyes: Eyes which were using the lens care product(s) but had not completed the prescribed investigational period.

Discontinued Eyes: Eyes which had ceased using the lens care product(s) prior to completion of the prescribed investigational period.

Incomplete Eyes: Eyes which have completed the prescribed investigation period but for which a final visit report has not been received by the sponsor.

Enrolled But Not Dispensed: Eyes considered enrolled because the subject had signed an informed consent form, but for which lens care product(s) had not been dispensed.

TABLE 1
ACCOUNTABILITY BY EYES ENROLLED IN THE STUDY
AND DISTRIBUTION BY STATUS

Status		Number of Eyes		
Enrolled Dispensed				
Completed			C/T	
Active	(Visit Completed)			
	Dispensing	C/T		
	1st follow up	C/T		
	2nd follow up	C/T		
(list through)	nth follow up	C/T		
Total Active			C/T	
Discontinued			C/T	
Incomplete			C/T	
Total Dispensed				C/T
Enrolled Not Dispensed				C/T
Total Enrolled				C/T

C = # control eyes
T = # trial eyes

Table 2 Notes:

TITLE: Demographics

PURPOSE: To provide demographic data.

TABLE 2
DEMOGRAPHICS

Age of Subjects: From _____ To _____, Average _____.

Sex: Female _____, Male _____, Ratio _____.

Table 3 Notes:

TITLE: Adverse Reactions (3A), SLFs Requiring Treatment (3B), SPCs Requiring Treatment (3C)

PURPOSE: To provide a detailed accounting of any condition occurring in any eye in the study requiring treatment to ensure ocular health.

DEFINITIONS:

Adverse Reaction: Considered to include, but not be limited to a hazardous, sight-threatening condition such as: corneal ulcers, iritis, other ocular infections or inflammations, corneal scarring, or permanent loss of vision.

SLFs Requiring Treatment: Any slit lamp finding in any examination, scheduled or unscheduled, that requires treatment, including temporary discontinuation of lens wear, to maintain normal ocular health. This does not include SLFs that are corrected by refitting of lenses without discontinuation of wear or by retraining subjects in proper lens care.

SPCs Requiring Treatment: Any symptom, problem or complaint that requires treatment, including temporary discontinuation of lens wear, to maintain normal ocular health. This does not include SPCs that are corrected by refitting of lenses without discontinuation of wear or by retraining of subjects in proper lens care.

GENERAL: Outcome should include cause of condition, treatment required, resolution including VA, damage to the eye if any, and whether or not discontinued from the study.

TABLE 3
ADVERSE REACTIONS (3A)

ADVERSE REACTION	TIME IN INVESTIGATION	OUTCOME
1.		
2.		
3.		
4.		
etc.		

Total eyes with adverse reactions____.

SLFs Requiring Treatment (3B)

SLF	TIME IN INVESTIGATION	OUTCOME
1.		
2.		
3.		
4.		
etc.		

Total eyes with SLFs requiring treatment _____.

SPCs Requiring Treatment (3C)

SPC	TIME IN INVESTIGATION	OUTCOME
1.		
2.		
3.		
4.		
etc.		

Total eyes with SPCs requiring treatment____.

Table 4 Notes:

TITLE: Slit Lamp Findings By Visit, Tabulated By Eyes and Incidence Rate

PURPOSE: To provide comprehensive tabulation of SLF data by visit (time in study) and completeness of recording.

GENERAL:

Separate tables should be prepared and clearly identified for:

- Completed Control Eyes (Table 4A)
- Completed Trial Eyes (Table 4B)
- Discontinued Control Eyes (Table 4C)
- Discontinued Trial Eyes (Table 4D)

In Tables 4A and 4B, total eyes should be the same for all visits and the same as the number of eyes completed in Table 1.

In Tables 4C and 4D, total eyes will vary by visit as a function of when subjects discontinued.

Intermediate visits should be numbered in sequence and the time in study for each sequence number should be provided in a footnote to Table 4A.

Tables 4 (A, B, C & D) should be expanded laterally as necessary to provide a data column for each intermediate visit.

For each SLF (e.g., edema, vascularization, etc.) a horizontal row should be provided for each SLF grade up through the highest grade recorded for each SLF.

Slit Lamp Findings reported between scheduled visits should be reported under "Unscheduled Visits."

Percentages should be calculated in accordance with the following formula:

= Eyes at grade of SLF or eyes not recorded

% = Incidence rate or percent eyes not recorded

$$\% \text{ Incidence Rate} = \frac{\text{Eyes at grade of SLF}}{\text{Total Eyes at visit}} \times 100$$

$$\% \text{ Eyes not recorded} = \frac{\text{Eyes not recorded}}{\text{Total eyes at visit}} \times 100$$

Any SLFs that require treatment should be listed in Table 3B.

In the "Eyes Not Recorded" row, list the number of eyes and percent not recorded for each visit.

TABLE 4
SLIT LAMP FINDINGS BY VISIT, TABULATED BY EYES
AND INCIDENCE RATE

	Initial Dispensing Visit	Intermediate Visits 1	2	3	4	Unsched.	Total
	# %	# %	# %	# %	# %	# %	# %
(Parameters reported should correspond to grading scale used in the study)							
EDEMA							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
grade 4	X X						
NEOVASCULARIZATION							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
grade 4	X X						
STAINING							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
grade 4	X X						
OTHER							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
grade 4	X X						
(Include all parameters assessed in study)							
Eyes not recorded	X X						
Total eyes	XX	XX	XX	XX	XX	XX	XX

Table 5 Notes:

TITLE: Symptoms, Problems, and Complaints by Visit, Tabulated by Eyes and Incidence Rates

PURPOSE: To provide comprehensive tabulation of data on SPC by visit (time in study).

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Control Eyes (Table 5A)
Completed Trial Eyes (Table 5B)
Discontinued Control Eyes (Table 5C)
Discontinued Trial Eyes (Table 5D)

In Tables 5A and 5B, total eyes should be the same for all visits and the same as the number of "eyes completed" in Table 1.

In Tables 5C and 5D, total eyes will vary by visit as a function of when subjects discontinued.

Intermediate visits should be numbered in sequence and the time in study for each sequence number should be provided in a footnote to Table 5A.

Tables 5 (A, B, C & D) should be expanded laterally as necessary to provide a data column for each intermediate visit.

SPCs reported between scheduled visits should be reported under "Unscheduled Visits."

Percentages should be calculated in accordance with the following formula:

= Eyes reporting that SPC

% = Incidence rate at visit

$$\% \text{ Incidence Rate} = \frac{\text{Eyes reporting SPC at final visit}}{\text{Total eyes at final visit}} \times 100$$

Any SPCs that require treatment should be listed in Table 3C.

TABLE 5
SYMPTOMS, PROBLEMS, AND COMPLAINTS BY VISIT
TABULATED BY EYES AND INCIDENCE RATES

	Initial Dispensing Visit	Intermediate Visits					Total
		1	2	3	4	Unscheduled	
Total Eyes At Visit	XX	XX	XX	XX	XX	XX	XX
	# %	# %	# %	# %	# %	# %	# %
None	X	X	X	X	X	X	XX
(The following are examples of parameters assessed. Some may not be applicable for a given study design)							
Discomfort							
Excess Tearing							
Photophobia							
Halos							
Itching							
Burning							
Spectacle Blur							
Variable Vision							
Blurred Vision							
Lens Needs Cleaning							
Lens Awareness							
Other (Specify)							
Total Positive Reports	X	X	X	X	X	X	XX

Table 6 Notes:

TITLE: Visual Acuity (VA) Results with Contact Lens at Final Visit

PURPOSE: To provide VA data for the contact lens in a concise format.

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Control Eyes (Table 6A)
Completed Trial Eyes (Table 6B)
Discontinued Control Eyes (Table 6C)
Discontinued Trial Eyes (Table 6D)

In addition to the data on the table for the final visit, the data in the "Visual Acuity Summary" should be provided. The number of eyes that had a VA of 2 or more lines on the logMAR progression scale worse than the initial best corrected VA should be provided for each visit, and an explanation should be provided for each instance in the second section of Table 6.

Number and percentage in each horizontal row of each VA column refer to the number of eyes in the best corrected column for the corresponding row. Percentage should be calculated in accordance with the formula on the table.

TABLE 6
VISUAL ACUITY RESULTS WITH CONTACT LENS
AT FINAL VISIT (EXAMPLE PROVIDED IN logMAR NOTATION

Initial Best Corrected	Number of Eyes	-0.1 # %	0.0 # %	0.1 # %	0.2 # %	0.3 . . . # %	Not Reported # %	Totals # %
-0.1	X X	X X						X X
0.0	X X	X X						X X
0.1	X X	X X						X X
0.2	X X	X X						X X
0.3	X X	X X						X X
(Continue as Needed)	X X	X X						X X
Totals	X X	X X						X X

$$\%\text{ at each VA} = \frac{\#\text{ of eyes at each VA (or total)}}{\#\text{ of eyes at initial best (or total) corrected of corresponding row}} \times 100$$

Visual Acuity Summary:

eyes with initial best corrected VA of 0.2 logMAR or better _____.
eyes with final VA with lens of 0.2 logMAR or better _____.
eyes with final VA with lens within +/- 1 logMAR progression of best corrected _____.
eyes with final VA with lens of worse than +/- 1 logMAR progression of best corrected _____.

TABLE 6 (cont.)
LISTING OF EYES THAT CHANGED 2 OR MORE LINES ON THE
VISUAL ACUITY SCALE

Investigator	Subject	Eye	Initial VA	VA at Visit	Reason
1.					
2.					
3.					
etc.					

Table 7 Notes:

TITLE: Average Wear Time per Visit

PURPOSE: To provide an accounting of wearing time by time in study.

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Control Eyes (Table 7A)
Completed Trial Eyes (Table 7B)
Discontinued Control Eyes (Table 7C)
Discontinued Trial Eyes (Table 7D)

Number and percentage refer to the number of eyes in the average wearing time column for the corresponding row. Percentage should be calculated in accordance with the following formula:

$$\%\ \text{at each time} = \frac{\#\ \text{of eyes at each time}}{\#\ \text{of total eyes}} \times 100$$

TABLE 7
AVERAGE WEAR TIME

Wearing time	Intermediate Visits 1		2		3		4		Final Unscheduled		Visit	
	#	%	#	%	#	%	#	%	#	%	#	%
0 to 6.0	X	X	X	X	X	X						
6.1 to 12.0												
12.1 to 18.0												
1 overnight												
2 overnights												
3 overnights												
4 overnights												
5 overnights												
6 overnights												
Not reported												

Wearing time
average/visit

Table 8 Notes:

TITLE: Discontinued Eyes Tabulated by Completed Visits and Reasons for Discontinued with Incidence Rates

PURPOSE: To provide comprehensive data on all discontinued eyes with reasons for discontinuation, time in study, and incidence rates.

GENERAL:

Eyes known to have discontinued between scheduled visits should be listed in the "Unscheduled Visits" column.

Total discontinuations should be provided for each intermediate visit. Aggregate discontinuations and aggregate incidence rate should be calculated for each reason and for total discontinuations.

Aggregate incidence rates should be calculated in accordance with the formula shown on the table. It is recognized that this formula will result in some error because active and incomplete eyes are not taken into account. However, this error will be small unless the discontinuation rate, number of active eyes, or number of incomplete eyes is excessive. In such cases, submission of additional data and subsequent review may be required.

Note: More than one reason may be given for discontinuation. In such a case, note only the principal reason on the table and identify the additional reasons in a footnote to the table.

TABLE 8
DISCONTINUED EYES TABULATED BY COMPLETED VISITS
AND REASONS FOR DISCONTINUED WITH INCIDENCE RATES

Reasons for Discontinuation	Eyes at (or after) Visit Completed: INITIAL	Intermediate 1	2	3	4	Unsch.	Aggre. Disc.	%
Visual acuity								
Positive SLF								
Adverse Reaction								
Lens Positioning								
Discomfort								
Handling Problem								
Disinterest								
Lost-to-Follow-up								
None Given								
Other (Specify)								
Total								

$$\% \text{ Incidence} = \frac{\text{Aggregate eyes discontinued per reason}}{\text{Total eyes completed + total eyes disc.}} \times 100$$

C = # control eyes
T = # trial eyes

Table 9 Notes:

TITLE: Lens Replacements by Visit

PURPOSE: To provide a tabulation of all lenses replaced during the study by reason for replacement.

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Subjects (Table 9A)
Discontinued Subjects (Table 9B)

Lenses replaced for visual acuity, pathology or other physiological reasons must be listed individually, with the specific reason for replacement and the visual acuity with the replacement lens.

Number and percentage refer to the number of eyes for each reason for replacement for the corresponding row. Percentage should be calculated in accordance with the following formula:

$$\% \text{ of eyes with lenses replaced} = \frac{\text{\# of eyes at each visit}}{\text{\# of total eyes}} \times 100$$

TABLE 9
LENS REPLACEMENTS BY VISIT

Reason for Replacement	INITIAL Total # %	Intermediate Visit 1 # %	2 # %	3 # %	4 # %	Unsched. # %	# %
Visual Acuity	C/T	C/T	C/T	C/T	C/T	C/T	C/T
Comfort							
Pathology							
Base Curve							
Diameter							
Lost							
Torn							
Lens Deposits							
Bad Edge							
Bad Surface							
Discoloration							
Other (Specify)							
Totals	C/T	C/T	C/T	C/T	C/T	C/T	C/T

C = # control eyes
T = # trial eyes

CLIN--APPENDIX E

"MODIFIED" TREND ANALYSIS PROFILE

The "Modified" Trend Analysis Profile (TAP) is intended to assist in the identification of trends. The TAP provides the number of events (e.g., adverse reactions), that occur at each visit of the study as well as the total number of events occurring during the study. In a sense, it is similar to a life table analysis in that it may quickly indicate the interval of time from the entry of subjects into the trial until the occurrence of specific events (e.g., adverse reactions). It may also reveal data trends that would be difficult to glean from the clinical report; however, it is not intended to replace the clinical report or a 510(k) Summary of Safety and Effectiveness.

The following directions outline the appropriate methods recommended for completing the TAP form. CDRH anticipates that the TAP form may evolve over time as CDRH and sponsors discover improved means of presenting trend data.

Item	Category	Instructions for completing TAP
1	Time in Study	This entry identifies how far the study has progressed (e.g., 1 week or 1 month into the study). (The data reported in a given column should represent only the data collected during that particular time interval. Only data in the Total column, at the far right of the table, are cumulative for the entire study.)
2	Total # of Eyes	This number includes the total number of eyes, either active or discontinued, that were examined during that time interval.
3	D/C Eyes	This number includes all the eyes discontinued during that time interval.
4	Average Wear Time	This number is the average wear time reported by all eyes, either active or discontinued, during that time interval.
5	Lens Replacements	This number is the actual number of lenses replaced during that time interval.
6	All Adverse Reactions	Each adverse reaction should be recorded only at the onset of the event. Follow-up visits for that particular event should not be recorded here.
7	All Corneal Ulcers	This is a subset of the Adverse Reactions discussed in Item 5. For this entry, each ulcer should be recorded only at the onset in the same manner that adverse reactions were reported in Item 5.

8	All Iritis	This is a subset of the Adverse Reactions discussed in Item 5. For this entry, each iritis episode should be recorded only at the onset in the same manner that adverse reactions were reported in Item 5.
9	Total Reports Staining	This number includes all staining reports which occurred during that time interval. If there are multiple reports for one eye, each report should be counted in this category.
10	Staining Reports >Gr 2	This number includes all staining reports greater than grade 2, which occurred during that time interval. If there are multiple reports > grade 2 for one eye, each report should be counted in this category.
11	Total # of Eyes Reporting Staining:	This number includes the number of eyes that had staining reports one or more times during the study. Even if there are multiple reports for one eye, only one report should be counted.
12-14	Edema Categories	The instructions for completing the edema entries correspond exactly to the instructions for completing the staining categories (Items 8-10 above). Follow the instructions for Items 8-10 substituting the word "edema" for the word "staining."
15-17	Injection Categories	The instructions for completing the injection entries correspond exactly to the instructions for completing the staining categories (Items 8-10 above). Follow the instructions for Items 8-10 substituting the word "injection" for the word "staining."
18-20	Neovasc. Categories	The instructions for completing the neovascularization entries correspond exactly to the instructions for completing the staining categories (Items 8-10 above). Follow the instructions for Items 8-10 substituting "neovascularization" for the word "staining."
21	Total Visits	This includes the total number of visits occurring during this time interval.
22	Total Missed Visits	This includes the total number of missed visits during this time interval.

CLIN--APPENDIX E

"MODIFIED" TREND ANALYSIS PROFILE (TAP)

SPONSOR/510(K) No. _____ **TRADE NAME:** _____

No. Eyes Enrolled: _____ **Generic Indication** _____

	VISIT NUMBER 1	2	3	4	5	6	TOTALS
TIME IN STUDY							
TOTAL # OF EYES							
D/C EYES							
AVERAGE WEAR TIME							
LENS REPLACEMENTS							
ALL ADVERSE REACTIONS							
ALL CORNEAL ULCERS							
ALL IRITIS							
TOTAL REPORTS STAINING							
STAINING REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING STAINING							
TOTAL REPORTS EDEMA							
EDEMA REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING EDEMA							
TOTAL REPORTS INJECTION							
INJECTION REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING INJECTION							
TOTAL REPORTS NEOVASC.							
NEOVASC. REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING NEOVASCULARIZATION							
TOTAL VISITS							
TOTAL MISSED VISITS							

SHELF-LIFE PROTOCOL

Listed below is guidance for establishing, or extension of, shelf-life (expiration date) for sterile contact lens care solutions and tablets:

A. Manufacturing/Chemistry:

The manufacturer should demonstrate the stability of the solution or tablet over time as packaged and stored under the proposed storage conditions. Manufacturers should provide their shelf-life protocol and have shelf-life data sufficient to support their labeled expiration date prior to marketing their product.

The aging of the solution in the storage containers should be initiated as soon as possible. The stability tests should include all parameters (if applicable) such as pH, tonicity, viscosity, surface tension, active ingredients, and physical appearance. Accelerated aging up to 45^{o}C may be used as supporting evidence of stability. Generally every 10^{o}C increase for tested temperature will enhance the expiration date by a factor of two compared to the normal storage temperature. Containers selected randomly from a minimum of 3 lots are required for shelf-life tests for the smallest container size. Lot number, manufacturing date, testing date, and analytical methodology for the active ingredients should be provided. Note: Manufacturers may release product with shelf-life based initially on accelerated stability data. However, the shelf-life protocol should provide for ongoing "real-time" stability data to support the accelerated data.

The size of the container tested should be the same as that intended to be marketed. Generally, if the solution is susceptible to chemical degradation via light and oxygen, 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 volume to internal surface area decreases as the container size decreases. For this reason, DOD may grant 510(k) clearance of a solution in a container larger than that used for stability testing, but usually not a container smaller than tested unless additional testing is conducted by the sponsor according to cleared/approved protocol and product specifications remain unchanged. This policy may extend to containers eight times the size tested provided the containers are constructed of the same materials. Currently, the largest size container marketed is a 16 fl. oz. container.

B. Microbiology:

Manufacturers should demonstrate the preservative effectiveness or bacteriostasis and sterility for multi-dose packaged solutions to establish shelf-life. An approved extension of shelf-life protocol permits the manufacturer to extend shelf-life up to the time designated in the protocol without submitting a new 510(k). Preservative effectiveness (Micro--Appendix A) and bacteriostasis testing (Micro-Appendix C) are conducted, as applicable.

Maintenance of sterility over a product's shelf-life may be determined by USP sterility testing or by validated package integrity testing. If sterility testing is performed, product samples should be stored at

temperatures up to 37°C. These random samples should be from 3 lots of approximately the same age. The samples should be stored in a manner that maximally tests the container/closure system (e.g., inverted).

Shelf-life can be established using "real time" data from sterility and preservative effectiveness or bacteriostasis testing. Shelf-life based on "real time" data may be given a shelf-life equal to the time which packaged solutions are stored at ambient temperature (generally 23±2°C). For example, samples stored at ambient temperature (generally 23±2°C) for 24 months may be granted a 24-month (2-year) expiration date if they have passed the microbiology stability testing and physical/chemical stability requirements outlined in the extension of shelf-life protocol.

Accelerated studies may be run for preservative effectiveness testing, bacteriostasis testing and validated package integrity testing at a maximum temperature of 45°C to establish shelf-life. Manufacturers should support the accelerated data with ongoing "real-time" data. Accelerated shelf-life estimates should be calculated using the following information:

1. Accelerated Storage Time refers to the actual storage time at elevated temperature for packaged solutions.

2. Acceleration Factor refers to the factor used to extrapolate the aging of the samples at the elevated temperature. The Acceleration Factor should be based on Q_{10} equal to 2.0 for each 10°C above ambient temperature.

Accelerated shelf-life estimates may be calculated as follows for samples stored only at the accelerated temperature:

Step 1. Calculate the Acceleration Factor based on the temperature difference between the elevated temperature and the ambient temperature. For example, based on a 15°C rise above ambient temperature, the Acceleration Factor may be calculated as $2.0^{(1.5)} = 2.83$; the Acceleration Factor based on a 20°C rise above ambient temperature is $2.0^{(2)} = 4.0$.

Step 2. Accelerated Storage Time x Acceleration Factor = Accelerated Age or Shelf-life

For samples which are stored at ambient temperature prior to being stored at the elevated temperature, the age of the sample at the start of the accelerated study can be added to the Accelerated Age when calculating shelf-life.

A product may be marketed in a container up to 8 times larger than the container tested for shelf-life (identical container and closure system). Currently, the largest size container marketed is a 16 fl. oz. container. If a product is to be marketed in a container smaller than the container previously tested for shelf-life, the manufacturer should perform the applicable shelf-life testing.

Ordinarily, FDA will not require a 510(k) for extension of shelf-life beyond the shelf-life requested in the original 510(k) provided the same protocol is followed.

FDA will consider alternative methods to sterility testing to support package integrity provided a method is adequately validated.

For multi-dose preserved contact lens care products, the labeling and instructions for use may include a statement recommending the period for which a product should be used after opening (discard date). This recommended period should be based on container size, projected number of uses, and frequency of use, as determined by the manufacturer. For bacteriostatic solutions, a discard date should be determined according to the bacteriostasis test (Micro--Appendix C).

QUESTIONS AND ANSWERS

Q1: Because this guidance document is the "special control" which is the basis for reclassification, am I required to conduct every test listed for a given product?

A1: The term "special control" refers to a variety of items such as guidance documents or product specific labeling which are available to provide reasonable assurance of safety and effectiveness within the scope of Class II regulation of a medical device. As stated in the Introduction Section, Purpose of Document, this guidance provides comprehensive directions to manufacturers for collecting and preparing data for a 510(k). The preclinical and clinical testing is that which FDA believes to be acceptable to establish substantial equivalence. Persons may choose to follow the guidance, or may follow different data collection and preparation procedures. Alternative procedures will need to be justified to CDRH's satisfaction that they are applicable to demonstrate substantial equivalence. The specific scientific items listed in the guidance represent the minimum which should be addressed to demonstrate substantial equivalence. In some cases it may be possible to address the item without conducting or repeating the specific test.

Q2: What is the difference between intended use and indication for use?

A2: The intended use of a medical device is defined in 21 CFR 801.4 and guidance is provided in CDRH Blue Book Memorandum K86-3. It refers to how a product is to be used. The GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS includes a variety of product specific intended uses as exist in 1996 with current technology. An example of a product specific intended use is an in-eye lubricating drop. The indication for use is a specific statement which includes the intended use of the device. An indication for the in-eye drop may be limited to either hydrophobic (RGP) or hydrophilic (soft) lenses, or it may include both. If a product had been legally marketed for use with soft lenses only, and later a manufacturer wants to market it for both soft and RGP lenses, this would be a change in indication, but not a change in the intended use since the product specific use remains the same. A new 510(k) application is required for either a change in intended use or a change in indication.

Q3: How do I use a product specific matrix for a "me-too" product, and for a product which isn't "me-too"?

A3: The matrices are designed to provide guidance for products with the same active ingredients as the predicate device (so called "me-too products"), as well as products which contain different active ingredients, for the various product specific intended uses. When developing a product with the same active ingredient, a manufacturer determines the concentration of the active ingredient in the formulation then refers to the appropriate column for guidance. Recommended testing may vary depending on whether the active ingredient is formulated at a higher, lower, or the same concentration as the predicate device. When a manufacturer develops a

formulation which contains a different active ingredient from the chosen predicate device, or when the active ingredients are new for ophthalmic use, the fourth column is provided for guidance.

Q4: Why is a "new ingredient for ophthalmic use" grouped in the same matrix column as a "different active ingredient" for a given product specific intended use"?

A4: As stated in Section II., General Manufacturing Information, the guidance focuses primarily on active ingredients. The active ingredient a manufacturer chooses to use to achieve the product specific intended use, (e.g. cleaner, disinfecting product, etc.) will often be the same active ingredient as found in the predicate device. Additional testing is recommended when the manufacturer uses a different active ingredient than found in the predicate device since that case generally represents the need for additional information to determine substantial equivalence.

Q5: What are the different hydrophilic and rigid gas permeable (RGP) lens groups and why are tests conducted with representative groups?

A5: The lens groups are described in detail in the PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES. There are four hydrophilic groups based on ionic surface charge and water content (Groups I, II, III, and IV). There are also four RGP groups based on material composition. However, the majority of currently marketed RGP lenses fall into only two of the four groups; silicone acrylate and fluorosilicone acrylate. The pure fluoropolymer group consists of only one polymer which currently is not marketed, and the last group represents an assortment of RGP materials which are generally no longer marketed or rarely encountered. It is primarily the solution manufacturer’s responsibility, not the lens manufacturer’s, to demonstrate compatibility with the indicated lens material groups.

Q6: If my product is already approved for use with a soft lens, do I have to do any testing to change the indication to include use with RGP lenses, or may I just revise the labeling as necessary? What about the reverse situation (i.e. going from RGP to soft lens use)?

A6: In either case, a new 510(k) will be necessary, although the content may differ. Soft lens use may be a worst case in some situations, so the recommended tests in the product specific matrix need to be considered and addressed individually. A solution for RGP lenses may prove to be incompatible with soft lenses due to lens absorption or adsorption of an ingredient. Because the manufacturer should know the product very well, characteristics of the active and inactive ingredients will dictate whether toxicology screening needs to be repeated, or if preservative uptake studies are necessary. The guidance is designed to rely on preclinical testing to answer the major part of the compatibility question. The characteristics of the product, along with the indication change, will dictate how much or how little testing is necessary and which areas may be addressed by explanation.

Q7: Why are contact lens solutions intended for chemical disinfection of lenses not generally labeled as "chemical disinfectants"?

A7. The distinction is made to differentiate contact lens disinfecting solutions from more potent chemical disinfectants used to prevent patient to patient transmission of microorganisms both on medical devices which are disinfected between patients, and on inanimate surfaces. The term "chemical disinfectant" generally applies to germicidal products demonstrating a six log reduction in microorganisms using Association of Official Analytical Chemists (AOAC) test methods. Historically contact lens solutions intended to destroy ocular pathogens have been labeled as disinfecting solutions, even though many products do not meet the same efficacy criteria as other chemical germicides. The lower recommended efficacy criteria outlined in this guidance document for contact lens disinfecting solutions are intended to minimize the risks of toxicity to ocular tissue from the contact lens care solutions while providing a regimen for effective reprocessing of contact lenses.

Q8: What is the difference between a "chemical disinfecting solution" and a "chemical disinfection system"?

A8: As defined in Micro--Appendix B, Disinfection Efficacy Testing, there are two levels of antimicrobial efficacy with performance criteria modeled after the ISO/CEN draft requirements. For both levels, cleaning is an integral part of the lens care process necessary to achieve proper lens care. A product may be labeled as "disinfecting solution" only when it meets the higher level of antimicrobial efficacy for the "Stand-Alone" test. The "Regimen" procedure evaluates the adequacy of the entire "chemical disinfection system for solutions which fail to meet the Stand-Alone efficacy criteria."

Q9: If I want to change my bottle size or the material the bottle is made from, do I need to submit a new 510(k)?

A9: In Section IV. Modifications of Approved Contact Lens Care Products requiring a 510(k), this question is addressed under Section B., examples which should not require a 510(k). As stated in the Shelf-Life Protocol Appendix, there can be greater chemical degradation in susceptible solutions when the container size is decreased since the ratio of solution volume to internal surface is decreased. For that reason, stability test data are necessary to establish a shelf-life for the smallest container. A new 510(k) should not be necessary provided the testing performed demonstrates that the product specifications remain unchanged and proper documentation is included in the device master record. Likewise, a change in packaging material should not be necessary provided the conditions noted in Section IV.B.4. are met. This packaging change guidance is a continuation of a policy in place while these products were regulated under Class III. At that time packaging changes meeting specified criteria were reportable in the Annual Report to the PMA rather than under a PMA supplement.

Q10: The Toxicology Appendix lists three minimum recommended toxicology tests under Section II., but the Acute Oral Toxicity is not recommended in all cases in the product specific matrices. What is really necessary?

A10: This is generally addressed as a labeling precaution when appropriate. If a predicate device with the same active ingredient is used, the predicate device labeling would already address this item. If a new active

ingredient is used, information on oral toxicity may already be available, so the test may not have to be actually conducted to address this item.

Q11: The statement "when clinical performance data are necessary" is somehow tied into the "physical/chemical, microbiological and toxicological data to support a claim." What does this really mean?

A11: The guidance really emphasizes preclinical testing. In many cases, a side-by-side analysis with the predicate device will go a long way to demonstrating substantial equivalence. The tests and parameters noted in Section II. General Manufacturing Information introductory paragraph and Section A, and in Section IV. Modifications of Approved Products A.1 list the primary physical/chemical preclinical comparisons. When these test data demonstrate a difference from the predicate device, additional clinical performance data are recommended.

Q12: With so many options for controls in clinical design, how do I decide which one to choose?

A12: In general, the complexity of the study design will reflect the uniqueness of the product. For example, a clinical study of a “me-too” product with the same active ingredients may be addressed without a concurrent control. If the product has different active ingredients from the predicate device, but does not contain a new ingredient for ophthalmic use, then a control group would be appropriate. When the new ingredient is also a new ingredient for ophthalmic use, randomization may be appropriate.

Q13: Do I need 510(k) clearance for separate instructions to practitioners for in-office disinfection?

A13: Yes. The additional 510(k) clearance pertains to specific instructions the manufacturer may want to develop for in-office disinfection of trial lenses. Refer to Section III. C. Chemical Disinfecting Products for current labeling and test recommendations intended to address the additional safety considerations associated with trial lens disinfection between patients.

Q14: Can I add catchy statements to my product's labeling to give it a marketing edge?

A14: When developing product labeling, the manufacturer should refer to the predicate device labeling for the product specific intended use and directions for use. The manufacturer has the responsibility for familiarity with applicable regulations to avoid misbranding his or her device. A determination of substantial equivalency will be based on the predicate device's labeling, as well as the product specific intended use and directions for use. FDA primarily reviews medical device claims which concern the safety and/or effectiveness of the device as well as those which address inherent properties of the device. Manufacturers should be aware that additional product attribute labeling claims such as comparative claims to another manufacturer’s product will usually require significant data above the minimum necessary information recommended in the GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS to determine substantial equivalency.

Q15: Why do I have to use all those boxes in my labeling from that Write-it-Right example? There's no regulation that says I have to do it that way.

A15: Yes, you are correct. There are no specific regulations concerning this model. The Write-it-Right example is included for the benefit of those manufacturers who wish to utilize that labeling model. The Write-it-Right booklet referenced is available from CDRH/DSMA. If a manufacturer uses that model, it is recommended that the concepts be followed, or a justification and explanation be provided for deviations from the model. For example, Write-it Right suggests that the labeling be geared to a seventh grade reading level. If a different reading level is used, an explanation should be provided.

Q16: Why do I need to submit a new 510(k) if I want to have my saline solution used as a rewetting agent? Do I really need a clinical study for something like that?

A16: These two questions involve more than one answer. If the saline product is already cleared for marketing, then it certainly would be possible to address the clinical study issue. Remember back to the first question? Not every test needs to be conducted if it can be adequately addressed. It's very difficult to write a guidance to clearly direct a manufacturer to each possible situation. The matrices are mainly constructed to provide guidance for a new manufacturer of a new product. In that situation, there's nothing to establish the biocompatibility of a product, even if it's a "me-too" product. That's why the toxicology screening tests are listed in the matrix. Because manufacturing processes and inactive ingredients may vary, there need to be some data to support biocompatibility, either toxicology and/or clinical data. The matrices are also to be used for guidance when legally marketed products are modified. In that situation, some of the test data already available may be applicable to address a specific item.

As for the need for a new 510(k), the change in labeling is a new indication for use of the saline and requires a 510(k). In addition, both Sections III. D. Multi-purpose Solution and E. In-eye Contact Lens Solutions address issues related to current policy for in-eye products. In order to both reduce the risk of contamination during use and to facilitate ease of use, lubricating and rewetting solutions should be packaged in bottle sizes not to exceed 30 ml. FDA believes that limiting the indications for in-eye use solutions to a single intended use (even when the chemical composition is identical to a multi-purpose solution, saline or conditioning solution) enhances product safety and encourages consumer compliance with safe lens care practices.

End of Guidance