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MICROBIOLOGY

I. Introduction:

The following section includes microbiological requirements and guidance for daily wear soft (hydrophilic), and hydrophobic (e.g., RGP) contact lenses submitted under the 510(k) review process. General guidance and procedures are outlined for:

A. sterilization procedures and sterilization process changes;

B. establishment and/or extension of shelf-life requirements (expiration dating) for sterile lenses;

C. manufacture, shipping and labeling of non-sterile RGP lenses packaged in the dry state; and

D. adequate labeling of manufacturer recommendations for lens cleaning and disinfection by the consumer.

II. Sterilization of Hydrophilic Lenses:

Sterilization of hydrophilic contact lenses is required because hydrophilic lenses absorb significant amounts of water and can support microbial growth. Steam under pressure (autoclaving) is the sterilization method generally used for hydrophilic contact lenses. Manufacturers should:

1. validate the sterilization system and cycle; and

2. demonstrate the efficacy of the sterilization system and its suitability for use with the lens being sterilized.

For general information and references dealing with the development and validation of sterilization cycles, refer to USP XXII, <1211>, Sterilization and Sterility Assurance/General Information.

A. Validation of the Sterilizing System:

In accordance with Office of Device Evaluation (ODE) 510(k) Blue Book Memorandum #K90-1 dated February 12, 1990, contact lenses which are sterilized using traditional sterilization methods, such as steam under pressure, should provide the following information in the 510(k) submission:

1. the sterilization method that will be used;

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

3. the sterility assurance level (SAL) for the device which the firm intends to meet; (an SAL of 10^{-6} is expected for hydrophilic contact lenses);

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

5. if sterilization involves ethylene oxide (ETO), the maximum levels of residues of ETO, ethylene chlorhydrin, and ethylene glycol which remain on the device; and

6. the radiation dose, if radiation sterilization will be used. For purposes of this guidance document, traditional sterilization by radiation is that conducted in accordance with the most recent update of the Process Control Guidelines for Gamma Radiation Sterilization of Medical Devices as approved by the Association for the Advancement of Medical Instrumentation (AAMI).

B. Efficacy of the Sterilizing System:

A description of the quality assurance procedures and methods used for sterility testing to provide routine sterility assurance of each batch of lenses should be provided in the 510(k) submission.

C. Sterilization Process Changes:

A manufacturer holding an SE 510(k) for a class II daily wear contact lens may elect to modify the sterilization process and carefully evaluate modifications for potential effects on safety and effectiveness of the device. For contact lens manufacturing, sterilization changes may include, but are not limited to:

1. change in sterilization method (e.g., ETO to radiation);

2. change to parametric release (steam); and

3. changes in the packaging that could significantly affect the ability of the sterilization process to adequately sterilize the device. (Refer to the "PROCEDURE FOR IMPLEMENTING CHANGES IN PACKAGING MATERIALS" section for additional guidance regarding 510(k) submissions for packaging changes).

After the sterilization cycle has been validated with packaged product inoculated either with biological indicators or bacterial spore suspension, the routine release of product through use of any form of appropriately validated bioindicators alone is acceptable. For process changes such as conversion to parametric release, where average bioburden levels are evaluated, an average lens bioburden of less than 20 spores and less than 1000 vegetative organisms per lens, with an F_o of 10 delivered to the product (based on a Z function of 10°C) are recommended. To demonstrate that bioburdens are representative of routine manufacturing conditions, a minimum of 20 lenses taken from 3 lots should be reported and averaged for each sampling interval. Lots

for each of the 3 sampling intervals should be manufactured at least 1 month apart. The average total bioburden should be determined from sampling for mesophilic aerobes, fungi, and spores. After conversion to process changes such as parametric release, quality control measures should be implemented for continued bioburden monitoring, and periodic sterility re-checks according to USP test methods should be performed.

Manufacturers may follow referenced parametric release protocols and procedures from a previously approved PMA/PMA supplement or from an SE 510(k) submission for a hydrophilic contact lens and maintain all data supporting the process change on file.

Manufacturers who lack prior clearance from FDA (e.g., approved PMA, PMA supplement or SE 510(k)) for parametric release protocols and procedures should submit a 510(k) demonstrating that manufacturer's ability to satisfactorily release product based on process control release.

Regardless of whether or not the change is submitted under the 510(k) process, all validation data supporting the sterilization process change should be maintained on file since demonstration of process effectiveness and the adequacy of the quality assurance (QA) checks used for finished device release are GMP requirements.

D. Microbiology Requirements for Establishment or Extension of Shelf-Life (Expiration Date) for Sterile Lenses:

A manufacturer of sterile lenses must provide data supporting the sterility of packaged lenses for the shelf-life requested in the 510(k). To fulfill this requirement, a manufacturer may certify that shelf-life was established according to the guidance outlined below, and provide the supporting data.

The manufacturer should test 10-20 lenses that have been packaged and stored for the proposed shelf-life. These 10-20 random samples from 2 or 3 lots of approximately the same age should be tested using USP Sterility Test Methods, irrespective of the storage temperature.

An extended shelf-life can be established using "real time" data or accelerated aging data. Shelf-life based on "real time" data will be given a shelf-life equal to the time which lenses are stored at ambient temperature ($23\pm2°C$). For example, lenses stored at ambient temperature (generally $23\pm2°C$) for 12 months are granted a 12-month (1-year) expiration date if they have passed the sterility stability testing and the other (physical/chemical) stability requirements outlined in the extension of shelf-life protocol; lenses stored at ambient temperature for 36 months will be given a 36-month expiration date.

Accelerated studies may be run at a maximum temperature of 45°C to extend shelf-life. Manufacturers should support the accelerated data with on-going "real time" data and generate a minimum of 6 months ambient temperature data before marketing the product. Accelerated shelf-life estimates are calculated using the following information:

1. Accelerated Storage Time refers to the actual storage time at elevated temperature for lenses.

2. Acceleration Factor refers to the factor used to extrapolate the aging of the lens at the elevated temperature. The Acceleration Factor is based on Q_{10} equal to 1.8 for each 10°C above ambient temperature.

Accelerated shelf-life estimates may be calculated as follows for lenses 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 is calculated as $1.8^{(1.5)} = 2.4$; the Acceleration Factor based on a 20°C rise above ambient temperature is $1.8^{(2)} = 3.2$.

Step 2. Accelerated Storage Time x Acceleration Factor = Accelerated Age or Shelf-Life

For lenses which are stored at ambient temperature prior to being stored at the elevated temperature, the age of the lens at the start of the accelerated study is added to the Accelerated Age when calculating shelf-life.

Alternatively, a manufacturer may submit and/or reference approved PMA/PMA supplement or SE 510(k) data from identical contact lens packaging systems for the requested shelf-life.

No 510(k) is required 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 support package integrity provided a method is adequately validated.

III. Microbiology Requirements for Hydrophobic Contact Lenses:

In general, daily wear hydrophobic lenses that were approved for marketing through the PMA process and reclassified into class II on March 4, 1994 (i.e. RGP lenses) demonstrated that these lenses do not absorb a significant amount of water (e.g., <2% water content) and do not support the growth of microorganisms upon storage when packaged and shipped in a dry state. Therefore, RGP lenses have routinely been

packaged and shipped as non-sterile devices. However, by definition, lens materials containing <10% water content are also considered hydrophobic lenses and could qualify for packaging and shipping as a non-sterile device. Therefore, a 510(k) application for daily wear RGP lenses with water contents exceeding those that are currently on the market (e.g., lenses with ≥2% water content), labeled non-sterile and shipped in a dry state, should include the following microbiological information:

1. Studies demonstrating that the lenses do not support the growth of microorganisms as routinely manufactured, packaged, and stored. A minimum of 10 lenses/lot randomly selected from at least 2 lots manufactured at least 1 month apart should be tested.

2. Shelf-life studies using the same lots and sample sizes demonstrating that the bioburden levels remain constant or decrease upon storage at ambient conditions. Finished product specifications for the bioburden levels should not exceed bioburden levels established for currently marketed lenses (e.g., lenses with <2% water contents) without an appropriate justification.

These studies are one-time requirements that apply only to the 510(k) applicant and are not required testing for each duly-authorized independent finishing laboratory.

All manufacturers of RGP lenses holding an approved PMA or an SE 510(k) who authorize independent finishing laboratories to manufacture and distribute their lenses are responsible for assuring that each finishing laboratory is in conformance with applicable GMP requirements. From a microbiological perspective, each authorized finishing laboratory manufacturing RGP lenses and shipping them in a dry state should conform to the following minimum criteria:

1. Low bioburden levels during routine manufacture at ambient temperatures.

   An average bioburden level of <100 CFU/lens should be demonstrated using a validated bioburden test method.

   The bioburden test requirement may be satisfied by conducting tests on a minimum of any 10 currently marketed RGP lenses cleared for manufacturing under routine conditions in the facility. Such testing would be applicable to all other RGP lenses when manufactured and packaged in the same facility, under the same conditions, using the same packaging materials, as long as a routine bioburden monitoring program, as outlined below, is currently performed.

2. Implementation of written quality assurance measures designed to insure consistently low bioburden levels during routine manufacture and storage.

Quality Control measures to maintain cleanliness in the lens cleaning and packaging environment are essential for maintaining low bioburden levels on the packaged lens.

3. Routine Bioburden Monitoring of Packaged Lenses.

Manufacturers may satisfy this requirement by testing lenses representative of routine manufacture and packaging in the same facility. Appropriate bioburden action and alert levels should be set and corrective measures implemented. Manufacturers should determine the necessary frequency for monitoring based on the significance of such factors as manufacturing process changes, personnel changes, and seasonal fluctuations in bioburden. Maintaining consistently low bioburden levels would result in less frequent monitoring; whereas, high or fluctuating bioburden levels would trigger increased bioburden monitoring.

4. Cautionary labeling statement.

The following labeling statement should be added to the lens package (e.g., flat pack): "Caution: Non-sterile. Clean and condition lenses prior to use."

IV. Manufacturer Lens Care Recommendations:

A lens manufacturer should assure that the lenses can be effectively cleaned and disinfected by consumers using the lens care system recommended in the labeling. When lens care disinfection systems recommended by the lens manufacturer are approved for the lens group under review in the 510(k), manufacturers will not be required to submit data from disinfection efficacy testing (i.e., Multi-Item Microbial Challenge Test) because reasonable assurance of disinfection efficacy will be considered to have been established by the lens care product manufacturer. However, if preservative uptake studies are conducted and demonstrate higher uptake than measured for the predicate device, the manufacturer of a new lens group should submit Multi-item Microbial Challenge test data to support the efficacy of the lens care regimen.

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I. Introduction:

This section of the guidance is designed to assist manufacturers in developing clinical performance data in order to collect the safety and effectiveness data necessary to demonstrate substantial equivalence to a class II daily wear contact lens.

Class II contact lenses generally include daily wear soft (hydrophilic) and hydrophobic (nonhydrophilic, such as rigid gas permeable) contact lenses which have the following intended uses: (1) non-therapeutic contact lenses (e.g., refractive ametropia [myopia, hyperopia and astigmatism], aphakia, and presbyopia [bifocal and multifocal]), (2) specialized use contact lenses (e.g., keratoconus), and (3) therapeutic daily wear contact lenses. Contact lenses remaining in class III would include those intended for extended wear.

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 patient records. Monitoring of the study, accountability of all patients, and details of complications or discontinuations are all essential elements.

It is important to note that CDRH recommends the appropriate use of controlled studies such as randomized controlled trials as a means of minimizing study biases. The study should follow the protocol suggestions in Clin--Appendix A. It is recommended that this randomized controlled study involve evaluable (completed) subjects divided evenly between independent investigators. The control lens should be the same predicate lens as cited and tested preclinically.

Clinical study designs should include either interpatient controls, utilizing a 2:1 test to control subject ratio, or intrapatient controls which require slightly more subjects. Alternatives to the recommended protocols, such as historical controls, may be utilized by a sponsor when adequate justification is provided. Intrapatient randomized controls would require increasing the number of evaluable subjects to achieve comparable overall numbers of eyes as recommended in the protocol. For example, interpatient controls involves 20 test subjects (40 eyes) and 10 control subjects, therefore, intrapatient controls would require a minimum of 40 subjects to achieve the same number of test eyes (40). If historical controls are used instead of interpatient or intrapatient controls, the historical control group should be defined and adequately characterized for comparison to the test group.

Any contact lens 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 protocol study design should, 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.

The Trend Analysis Profile (TAP) form should be completed for all clinical studies and included in the clinical report section of the 510(k) application. The TAP helps identify trends in contact lens clinical data. The identification of trends assists 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 the TAP does not replace the clinical report. A sample TAP form is available in Clin--Appendix D. Sponsors with questions concerning the TAP should contact DOD staff for clarification.

II. Necessity for Clinical Performance Data and Study Size and Duration Recommendations:

A. Claim of Substantial Equivalence to a Lens with an Existing USAN:

1. same manufacturing process (e.g., lathe-cut or cast-molded compared to the same)

Claims of substantial equivalence to a lens with an existing USAN and the same manufacturing processes generally will not require submission of clinical performance data providing that the pre-clinical testing (i.e., physical/chemical/optical and toxicological data) supports the claim.

2. different or unknown manufacturing process (e.g., lathe-cut compared to cast-molded)

Claims of substantial equivalence to a lens with an existing USAN but a different manufacturing process may require clinical performance data to be submitted, in addition to physical/ chemical/optical and toxicological data, to support the claim. If any of these characteristics differ (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 (see "MANUFACTURING/CHEMISTRY" section of the guidance).

If clinical performance data are necessary, it is recommended that this randomized controlled study involve at least thirty (30) evaluable subjects divided evenly between three independent investigators and followed for at least thirty (30) days. For an interpatient control design, these thirty (30) subjects should be divided into two groups with one group prescribed the test lens and the other group a control lens (predicate lens cited and tested preclinically). The ratio of evaluable test subjects to control subjects should be 2 to 1.

B. Claim of Substantial Equivalence to a Lens with the Same Parent USAN but a Different Suffix (Modified USAN):

Claims of substantial equivalence to a lens with the same parent USAN but different suffix will generally require clinical performance data to be submitted, 30 subjects for 30 days as above, in addition to physical/chemical/optical and toxicological data to support the claim.

C. Claim of Substantial Equivalence for a Lens with Different Repeating Monomer Units (New Parent USAN):

Claims of substantial equivalence for a lens with different repeating monomer units (new parent USAN) will require submission of clinical performance data, in addition to physical/chemical/optical and toxicological data, to support the claims. It is recommended that this randomized controlled study involve at least fifty (50) evaluable subjects divided evenly between five independent investigators and followed for at least three (3) months. For interpatient control study design, these fifty (50) subjects should be divided into two groups with one group prescribed the test lens and the other group a control lens (predicate lens cited and tested preclinically). The ratio of evaluable test subjects to control subjects should be 2 to 1.

D. Specialized Use Indications and Additional Labeling Claims of Enhanced Indications:

Specialized use lenses include limited-use applications (e.g., keratoconus) and daily wear therapeutic indications.

The sponsor should design the study to collect data demonstrating the substantial equivalence of the lens to a legally marketed device in terms of the safety and effectiveness of the device for its intended use. Because of the specialized nature and considerations of many of these lenses, sponsors should contact DOD prior to initiating studies.

E. Lens Modification Recommendations:

1. Modifications in a Contact Lens Material:

A manufacturer holding an SE 510(k) for a class II daily wear contact lens may, for a variety of reasons, want to modify the chemical, physical, or optical characteristics of the lens material. CDRH has characterized certain changes to plastic lens materials that could significantly affect safety and effectiveness of the lens (refer to the "MANUFACTURING/ CHEMISTRY" section of this guidance for a listing of changes).

Claims of substantial equivalence after a modification of the lens material has been made, may require clinical performance data (30 subjects followed for 30 days as above) if the results of the pre-clinical testing (physical/chemical/optical and toxicological data) are not sufficient to support the claim and performance data are needed to assess effects of the new characteristics.

2. Expansion of Daily Wear Contact Lens Refractive Powers and Dimensions:

In 1986, under premarket approval, CDRH concluded that the refractive powers and dimensions of <u>daily wear</u> contact lens should not be limited to those powers and dimensions tested in the clinical trials that provide data for a lens' approval.

This conclusion was based upon the determination that higher powers and different dimensions do not change the biocompatibility or optical characteristics of an approved daily wear lens material or the manufacturing quality

control procedures. Even though a material's permeability may not be affected by powers or dimensions, the total oxygen available to the eye may be affected by these factors. However, the lenses are prescribed by licensed eyecare practitioners who are able to assess the patient's need for refractive correction and monitor the potential impact of a specific lens design on the patient's ocular health.

Alterations of lens power or dimensional parameters related to an SE 510(k), including, but not necessarily limited to; base curve, chord and optic zone diameters, bevels, edges and peripheral curves, are considered to be nonsignificant changes that will not affect the safety and effectiveness of the lens.

Sponsors having an SE 510(k) for a daily wear contact lenses should:

a. document all the modifications of lens power or dimensional parameters to the lens in the GMP DMF to be made available to FDA upon request.

b. include in all labeling intended for the eyecare practitioner the following Precautions:

"Due to the small number of patients enrolled in clinical investigation of lenses, all refractive powers, design configurations, or lens parameters available in the lens material are not evaluated in significant numbers. Consequently, when selecting an appropriate lens design and parameters, the eyecare practitioner should consider all characteristics of the lens that can affect lens performance and ocular health, including oxygen permeability, wettability, central and peripheral thickness, and optic zone diameter.

The potential impact of these factors on the patient's ocular health should be carefully weighed against the patient's need for refractive correction; therefore, the continuing ocular health of the patient and lens performance on the eye should be carefully monitored by the prescribing eyecare practitioner."

3. Alternate Lens Design Configurations:

CDRH had previously issued a Federal Register notice on April 12, 1988, pertaining to alternate designs of approved daily wear contact lenses regulated under premarket approval. It is the intention of CDRH to expand this policy to allow manufacturers of daily wear contact lenses to

receive premarket notification clearance for the correction of refractive ametropia (myopia, hyperopia and astigmatism, e.g., toric, bitoric and low eccentricity aspheric) as well as the specialized use indication of aphakia as part of the SE 510(k) determination. This determination is based upon the expansion of daily wear contact lens refractive powers and dimensions noted above.

The indication for the correction of refractive ametropia is not applicable wherein changes to the lens design characteristics alter the intended use to include correction of presbyopic patients by a multifocal lens. Alternate designs for multifocal lenses (e.g., concentric, segmented and high eccentricity aspheric) will require a 510(k) submission containing the information as described below. Further clinical performance data will not be necessary if the applicant can provide valid scientific evidence to demonstrate the substantial equivalence of the proposed alternate design consideration to a legally marketed lens in terms of safety and effectiveness using the criteria set forth in the policy. In addition, this is not applicable for the approval of other specialized indications for use, such as keratoconus or daily wear therapeutic indications.

The following data should be included in 510(k) documents submitted for alternate lens design configurations:

a. i. A sponsor applying for alternate lens design characteristics at the time of original 510(k) submission for a spherical lens should submit a statement that all preclinical data regarding biocompatibility and clinical performance data respecting safety and effectiveness are equally applicable to the additional alternate lens design, or

ii. A sponsor applying for alternate lens design configurations as a separate 510(k) should provide reference to the SE 510(k) for the lens material which will be used to manufacture the alternate lens designs for biocompatibility and clinical performance data respecting safety and effectiveness.

b. Engineering drawing and complete narrative description of the new lens. The description should include such items as: physical shape; manufacturing description (e.g., lathe or molded) and any modifications to overall shape such as truncation or prism ballasting.

c. Optical explanation and theory of how the lens works. Supporting material, if any, from journal references, text books, etc., may be included. A justification of the design in terms of the requested labeling indications (e.g., a multifocal design for the correction of presbyopia) should be included.

d. Complete description of the manufacturing techniques for the alternate design. A minimum of 10 lenses manufactured to a variety of prescribed specifications within the distribution of available parameters for the alternate design will be manufactured and the verification submitted for review. This is done to verify the manufacturing process in terms of such parameters as: diameter, power, and base curve. The finished lenses should be verified and evaluated to determine if the lenses meet specification tolerances.

e. Sponsors should include in all labeling intended for the eyecare practitioner the Precautions that are listed under the heading entitled, "Expansion of Daily Wear Contact Lens Refractive Powers and Dimensions," (item 2 (b)). In addition, sponsors should review the labeling section for "Monovision" wear and modify the information as appropriate for a presbyopic lens. This modification should be included in the Professional Fitting Guide and Patient Instructions so that practitioners and patients may receive necessary information on patient selection and use of a presbyopic lens.

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 control lens(es) utilized
2. Study design and procedures; to include randomization procedures
3. Data analysis

C. Subjects

1. Demographic data
2. Completed and discontinued for both control and trial groups
3. Lens care regimen

D. Data to support substantial equivalence - sample tables included in Clin--Appendix C (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. Keratometric Changes/Refractive Changes
5. Visual Acuity
6. Average Wear Time
7. Discontinued Eyes
8. Lens Replacements

E. Trend Analysis Profile - Clin--Appendix D

F. Conclusion

CLIN--APPENDIX A

CLINICAL PROTOCOL SUGGESTIONS

OUTLINE

I. ALL STUDY DESIGNS

II. NON-SPECIALIZED USE DAILY WEAR LENS STUDIES

A. PROTOCOL CONSIDERATIONS

1. Statement of Specific Study Objective(s)
2. Sample Size and Study Duration
3. Sample Selection Criteria (a-f)
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. Keratometry Readings
5. Refractive Changes
6. Visual Acuity
7. Average Wear Time
8. Discontinued Eyes
9. 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. NON-SPECIALIZED USE DAILY WEAR LENS STUDIES:

Such studies may include hydrophilic and hydrophobic lenses which are investigated for daily wear for the following indications (e.g., the visual correction of myopia, hyperopia, presbyopia, astigmatism, aphakia, and some special use indications such as keratoconus).

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.

   a. 50 evaluable subjects (one evaluable subject assumes two eyes) for a minimum of 3 months for a claim of substantial equivalence based upon the same intended use, but a new USAN, or

   b. at least 30 evaluable subjects for a minimum of 30 days for claims of substantial equivalence based upon the same USAN.

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 patient from contact lens wear as described in the lens indication for use. 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 patient from consideration as an acceptable lens candidate with respect to the requested indication for use. For example, a finding of severe dry eye or corneal hypoesthesia may preclude a patient from consideration for cosmetic lens use.

a. Patients may have worn contact lenses previously, provided their eyes are shown to be normal at the start of the investigation.

b. Patient selection for entry into the study should be randomized and therefore not preselect for previously successful wearers.

c. The eyes of the patients should be randomly assigned to either the control or the test group and the sponsor should detail the randomization procedure.

d. There should be a need of an optical correction and a reasonable expectation of improved visual acuity with the use of contact lenses.

e. Patients 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.

f. Patients 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 patient 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 patient'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. As an example, the agency would expect sponsors to target the minimum number of investigators in a 50 subject study at approximately 5 investigators and in a 30 subject study at 3 investigators. This ratio demonstrates that varied practitioners can work with the lens material and configuration, while also assigning enough patients to

each investigator to allow for an evaluation of trends between investigators. The training, experience, and objectivity of investigators should also be considered when attempting to reduce study biases. 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 strongly suggests protocols which incorporate the appropriate use of controlled studies such as randomized controlled clinical trials (RCT) as a means of minimizing biases in clinical data.

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

The care regimens used in the study should be specified. If the manufacturer of an existing material wishes to recommend a specific care regimen in the labeling, the compatibility with the lens should be confirmed preclinically and/or during the clinical trial. The manufacturer of a new material should confirm the compatibility of the proposed recommended care regimen with the lens both preclinically and during the clinical trial. 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. 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 patients 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 patient 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 the lenses)

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.

Daily Wear Study:

2 hour (optional visit), 1 week, 2 weeks, 4 weeks, then monthly through study (if indicated)

Any patient reporting for an unscheduled visit shall 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 patient is considered enrolled when he or she signs the informed consent form. This form should be signed prior to any trial lens fitting. All patients enrolled should be accounted for even if they are not dispensed lenses. Once enrolled, a patient 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 C) may be used by sponsors as a basis for developing clinical reporting forms.

1. Adverse Reaction Data

CDRH considers an "adverse reaction" to 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. Culturing of infections is necessary. Appropriate culturing procedures are discussed in Clin--Appendix E.

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 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 SLIT LAMP FINDINGS CLASSIFICATION SCALE is included in Clin--Appendix B. The results should be tabulated, and all findings over grade 2 should be explained in the 510(k).

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.

4. Keratometry (K) Readings

a. Hydrophobic and hydrophilic plastic lenses: readings should be taken at the patient's initial and final visit. In the case of patient discontinuation, a reading should be taken at the patient's final visit.

b. K data should be analyzed for trends such as:

The tendency towards corneal sphericity or toricity.

The correlations of K changes to fitting relationship (initial K reading to lens base curve selected).

The amount of refractive change from initial to final visit.

5. Refractive Changes (Absolute Value)

Refractive changes (absolute value) from baseline to the final visit should be provided. Analysis for trends based on previous wear experience or associated with keratometric changes aids in the evaluation of corneal physiological effects from lens wear.

6. Visual Acuity (VA) Data

Distance Snellen acuity should be taken at each visit (near acuity should be included for presbyopic indications). 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 Snellen lines should be reported. 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 acuity during the course of the study should be reported and explained.

When near VA is measured, a sponsor may select any clinically acceptable scale such as reduced Snellen scale, Jaeger, or "M" scales.

7. Average Wear Time (AWT)

The lens AWT should be recorded at each visit. Data should be collected and analyzed to determine the mean, median, and mode wear times as well as ranges. A tabulated report of daily average wear time in hours by visit should be provided to assess trends during the study.

8. Discontinuations

Complete data should be provided on all discontinued patients including the reason for discontinuation and visual status at the final visit. If problems persist, the patient 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 patient's last visit. Copies of patient report forms for all discontinued patients should be provided in the submission.

9. 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 B

SLIT LAMP FINDINGS CLASSIFICATION SCALE

A. EDEMA

It may be appropriate to include a separate category for microcystic findings. Sponsors may elect to collect microcyst data separately from edema.

0 - NONE: No edema

1 - TRACE: Slight localized or generalized edema

a. Dull glass appearance (slightly hazy appearance) of the corneal epithelium, OR

b. Just detectable central corneal clouding (CCC) without distinct borders.

2 - MILD: Mild localized or generalized edema

a. Less than 15 vacuoles (microcystic), OR

b. Light density CCC. Borders distinct but visible only against pupil, OR

c. Corneal striae (1 or more).

3 - MODERATE: Significant localized or generalized edema

a. 15 - 50 vacuoles (microcysts), OR

b. Very distinct borders on CCC, OR

c. Multiple striae including folds in Descemet's membrane (black lines).

4 - SEVERE: Advanced localized or generalized edema

a. More that 50 vacuoles (microcysts)

b. Epithelial bullae

c. Epithelial sloughing

B. CORNEAL NEOVASCULARIZATION

0 - NONE: No vascular changes

1 - TRACE: Congestion and dilation of the limbal vessels

Single vessel extension <1.5 mm from the prefitting position.

2 - MILD: Extension of vessels <1.5 mm from the prefitting position.

3 - MODERATE: Extension of limbal vessels 1.5 mm - 2.5 mm from prefitting position.

4 - SEVERE: Segmented or circumscribed extensions of limbal vessels more than 2.5 mm inside the limbus, OR extension to within 3.0 mm of corneal apex.

Location (optional):

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.

0 - NONE: No staining

1 - TRACE: Minimal superficial staining or stippling

a. Central or generalized

b. Peripheral including 3-9 o'clock staining, OR

c. Dimpling associated with bubbles under lens, OR

d. 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: Significant dense coalesced staining, corneal abrasion or foreign body tracks

4 - SEVERE: Severe abrasions greater than 2 mm diameter, ulcerations, epithelial loss, or full thickness abrasion. Diagram and explain.

Location:

N	Nasal	T	Temporal
I	Inferior	S	Superior
C	Central	O	3-9 o'clock

D. INJECTION

0 - NONE: No injection present

1 - TRACE: Slight limbal (mild segmented), bulbar (mild regional), and/or palpebral injection

2 - MILD: Mild limbal (mild circumcorneal), bulbar (mild diffuse), and/or palpebral injection

3 - MODERATE: Significant limbal (marked segmented), bulbar (marked regional or diffuse), or palpebral injection

4 - SEVERE: Severe limbal (marked circumcorneal), bulbar (diffuse episcleral or scleral), or palpebral injection

E. TARSAL ABNORMALITIES

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: Significant papillae/follicles less than 1 mm in diameter, and/or marked conjunctival injection

4 - SEVERE: Localized or generalized papillae/follicles 1 mm or more in diameter with or without marked injection

F. OTHER COMPLICATIONS (List all reports by specific finding and grade by severity)

Examples include but are not limited to:

0 - NONE: No other significant biomicroscopic findings

1 - TRACE: Minimal findings such as a tear film abnormality (debris or low tear break up time)

2 - MILD: Mild findings such as:

a. Few faint infiltrates

b. Lens adhesion

3 - MODERATE: Significant findings such as:

a. Infiltrates (multiple or dense)

b. Iritis with minimal cells or flare

c. Conjunctivitis or EKC

4 - SEVERE: Severe finding such as:

a. Marked infiltrates with overlying staining

b. Iritis with marked cells and/or flare

c. Corneal or conjunctival infection

d. Corneal ulcer

e. Recurrent erosion

CLIN--APPENDIX C

SUMMARY REPORTING TABLES

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 patients who signed an informed consent form prior to trial lens fitting and had lenses dispensed to them.

Completed Eyes: Eyes which had worn the lens for the prescribed investigational period and for which a final visit form was completed and submitted.

Active Eyes: Eyes which were wearing the lens but had not completed the prescribed investigational period.

Discontinued Eyes: Eyes which had ceased wearing the lens 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 patient had signed an informed consent form, but for which lenses 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: Tabulation of Eyes by Most Recent Lens Wearing Experience and Demographics

PURPOSE: To provide data on patients' previous lens wearing experience and basic demographic data.

GENERAL: The most recent lens wearing experience of all of the eyes enrolled in the investigation must be tabulated. Successful and unsuccessful wear are to be subsets of most recent previous wear and in total must equal most recent previous wear. Grand total must equal total enrolled from Table 1.

DEFINITIONS:

Hard: Lenses made of PMMA with no significant gas permeability

Soft (hydrophilic): A soft lens that must absorb water to obtain its final form.

RGP: Rigid gas permeable lenses.

Other: Any lens not in the first three categories including soft non-hydrophilic lenses.

Demographic data should be provided as requested.

TABLE 2
TABULATION OF EYES BY MOST RECENT LENS WEARING EXPERIENCE
AND DEMOGRAPHICS

	Eyes					
	Hard	Soft (Hydrophilic)	RGP	Other	Sub Total	Total
Previous experience unknown						XX
New wearers						XX
Previous wearers most recent experience	X	X	X	X		
Successful						
daily wear	X	X	X	X	XX	
extended wear		X	X	X	XX	
Unsuccessful						
daily wear	X	X	X	X	XX	
extended wear		X	X	X	XX	
Total						XX
Grand Total						XX

DEMOGRAPHICS

Age of Patients: From _____ To _____, Average _____.

Sex: Female _____, Male _____, Ratio _____.

Lens Power Range: +_____D.
(maximums) -_____D.
Cylinder _____D.

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 scarrring, 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 patients 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 patients in proper lens care.

GENERAL: Outcome must 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 Table 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 patients 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.

Table 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
	# %	# %	# %	# %	# %	# %	# %
EDEMA							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
VASCULARIZATION							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
STAINING							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
INJECTION							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
TARSAL ABNORMALITY							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
OTHER							
grade 0	X X						
grade 1	X X						
grade 2	X X						
grade 3	X X						
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 Table 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 Table 5C and 5D, total eyes will vary by visit as a function of when patients 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 1	2	3	4	Unscheduled		Total
Total Eyes At Visit	XX	XX	XX	XX	XX	XX		XX
	# %	# %	# %	# %	# %	# %		# %
None		X	X	X	X	X	X	X
Discomfort								
Excess Tearing								
Photophobia								
Halos								
Itching/Burning								
Spectacle Blur								
Variable Vision								
Blurred Vision								
Lens Needs Cleaning								
Other (Specify)								
Total # Positive Reports	X	X	X	X	X	X	X	X

Table 6A Notes:

TITLE: Keratometry Change (Absolute Value) from Baseline to Final Visit by Meridian

PURPOSE: To provide changes in keratometry data in a concise format.

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Control Eyes (Table 6A1)
Completed Trial Eyes (Table 6A2)
Discontinued Control Eyes (Table 6A3)
Discontinued Trial Eyes (Table 6A4)

Number and percentage in the first section of Table 6A refer to the number of eyes in the diopter of change column for the corresponding row. Percentage should be calculated in accordance with the following formula:

$$\% \text{ at each diopter of change} = \frac{\text{\# of eyes at each diopter of change}}{\text{\# of total eyes}} \times 100$$

For each change that is greater than 1.00 diopter, the second section of Table 6A should be completed.

TABLE 6(A)
KERATOMETRY CHANGE (ABSOLUTE VALUE) FROM BASELINE
TO FINAL VISIT BY MERIDIAN

Diopters	Horizontal #	Horizontal %	Vertical #	Vertical %	Total Eyes #	Total Eyes %
0.00 to 1.00 D	X	X	X	X	X	X
1.12 to 1.50 D						
1.62 to 2.00 D						
(Continue as Needed)						

Mean Keratometry Change _____ D.
Minimum Keratometry Change _____ D.
Maximum Keratometry Change _____ D.

LISTING OF VERTICAL AND HORIZONTAL KERATOMETRY READINGS AND CHANGES (ABSOLUTE VALUE) FROM BASELINE TO FINAL VISIT FOR EYES THAT CHANGED MORE THAN 1 DIOPTER

Investigator	Patient	Eye	H/V	Baseline	Final Visit	Absolute Change	Reason
1.							
2.							
3.							

To Part 4 of Document