

SEP 25 2003



K032030

510(k) SUMMARY

*blink*TM CL Lubricant Eye Drops

This summary uses the format provided in 21 CFR 807.92:

- (a)(1) **Submitter:** Paul J. Nowacki
Manager
Regulatory Affairs
Advanced Medical Optics
1700 E. St. Andrew Place
Santa Ana, CA 92799-5162

Phone: (714) 247-8601
Fax: (714) 247-8677
EMail: paul.nowacki@amo-inc.com
- Summary Prepared:** June 30, 2003
- (a)(2) **Device Trade Name:** *blink*TM CL Lubricant Eye Drops
Device Common Name: Soft (Hydrophilic) and Rigid Gas Permeable Contact Lens Lubricating and Rewetting Solution
Device Classification/Panel: Class II (Special Controls)/Ophthalmic Device
Device Classification Names: Accessories to Contact Lenses – Cleaning and Wetting Agents
- (a)(3) **Identification of Predicate Device:** *blink*TM CL Lubricant Eye Drops is substantially equivalent to other lubricating and rewetting solutions currently marketed or cleared for commercial distribution in the U.S. These include REFRESH[®] CONTACTSTM Lubricating and Rewetting Drops (Allergan), AQUIFY Lens Comfort Drops (CIBA Vision) and HYLASHIELD[®] CL Lubricating Eye Drop (Biomatrix).
- (a)(4) **Device Description:** *blink*TM CL Lubricant Eye Drops is a sterile, isotonic, buffered solution containing a lubricant, a preservative, buffers, tonicity agents, and purified water.

The product is a clear, colorless solution packaged in plastic bottles with controlled dropper tips.

510(k) SUMMARY
***blink*[™] CL Lubricant Eye Drops**
June 30, 2003
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- (a)(5) **Intended Use (Indications for Use):** Use *blink*[™] CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses, to help relieve dryness, irritation and discomfort that maybe associated with lens wear, and to cushion lenses by placing a drop on the lens prior to application on the eye. The intended use is comparable to that of the predicate devices.
- (a)(6) **Comparison of Technological Characteristics:** *blink*[™] CL Lubricant Eye Drops has the same intended use and the same technological characteristics as the predicate lubricants/rewetters. The lubricant and preservative are materials which are used in the predicate lubricants/rewetters but not in combination in any one product. The ophthalmic demulcent, while not listed in 21 CFR 349.12, is used in one of the three predicate lubricants/rewetters in which we are requesting a determination of substantial equivalence. Additionally, a chemically similar lubricant is used in another one of the predicate lubricants/rewetters. Both of these lubricants have been cleared for commercial distribution in the U.S. All excipients are commonly recognized and used in ophthalmic and contact lens care products, including the predicate lubricants/rewetters.

Description of Safety and Substantial Equivalence

Nonclinical and clinical studies were performed to demonstrate the substantial equivalence of *blink*[™] CL Lubricant Eye Drops to the predicate device(s). Testing was conducted in accordance with and in conformance to applicable device regulations. The following is a discussion of the study results.

(b)(1) **Discussion of Nonclinical:**

Lens Compatibility: *In vitro* lens compatibility testing was conducted to establish product compatibility with both soft (hydrophilic) and RGP contact lenses. The results show that the product is compatible with soft (hydrophilic) and RGP contact lenses and substantially equivalent to the control.

Solution Compatibility: A study was conducted to evaluate the compatibility of *blink*[™] CL Lubricant Eye Drops when used with leading contact lens care products on the market. The results indicate that the product is compatible with these leading contact lens care products.

Preservative Uptake and Release: A study was conducted with soft (hydrophilic) and RGP contact lenses to determine the uptake and release of the preservative in *blink*[™] CL Lubricant Eye Drops. The results show that there is very little, if any, uptake of the preservative in or onto soft or RGP lenses. Any amounts taken up are quickly released. The results indicate that the product is compatible and acceptable for use with soft (hydrophilic) and RGP contact lenses.

510(k) SUMMARY
***blink*[™] CL Lubricant Eye Drops**
June 30, 2003
Page 3 of 3

(b)(1) Discussion of Nonclinical (Continued):

Contact Lens Wetting Angle: A wetting angle study was conducted to assess the effectiveness of *blink*[™] CL Lubricant Eye Drops in enhancing the wettability of RGP lenses compared with predicate lubricating and rewetting products. The results indicate that *blink*[™] CL Lubricant Eye Drops is substantially equivalent in wetting properties to the predicate devices.

Microbiological Studies: The product was evaluated for preservative efficacy and sterility:

- The product meets the acceptance criteria for Preservative Effectiveness Testing as outlined in ISO 14730:2000(E), "Ophthalmic optics – Contact lens care products – Antimicrobial preservative efficacy testing and guidance on determining discard date."
- The product meets USP Sterility test requirements.

Stability: Accelerated testing predicts that the product will remain stable for the labeled shelf-life.

Toxicology: The safety of *blink*[™] CL Lubricant Eye Drops was evaluated using cytotoxicity and acute ocular toxicity tests. The results of the testing demonstrate that *blink*[™] CL Lubricant Eye Drops is non-cytotoxic, non-irritating and well-tolerated.

(b)(2) Discussion of Clinical Data:

AMO conducted a multi-center, double-masked, randomized, parallel-group, one-month evaluation to assess the safety and acceptability of *blink*[™] CL Lubricant Eye Drops. The results of this study indicate that the investigational formulation is safe, acceptable, and substantially equivalent to the control.

(b)(3) Conclusions Drawn from Data Supporting Equivalence Determination: It is concluded that the safety, efficacy and performance of *blink*[™] CL Lubricant Eye Drops is substantially equivalent to the predicate products currently on the market or cleared for commercial distribution in the U.S.



SEP 25 2003

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Advanced Medical Optics, Inc
c/o Paul J. Nowacki
1700 E. St. Andrew Place
P.O. Box 25162
Santa Ana, CA 92799

Re: K032030
Trade/Device Name: *blink*TM CL Lubricant Eye Drops
Regulation Number: 21 CFR 886.5928; 21 CFR 886.5918
Regulation Name: Soft (hydrophilic) contact lens care products;
Rigid gas permeable contact lens care products
Regulatory Class: Class II
Product Code: LPN; MRC
Dated: June 30, 2003
Received: July 1, 2003

Dear Mr. Nowacki:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Page 2 - Paul J. Nowacki

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4613. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address <http://www.fda.gov/cdrh/dsma/dsmamain.html>

Sincerely yours,



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

Enclosure

Page 1 of 1

510(k) NUMBER:
(IF KNOWN): K032030

DEVICE NAME: blink™ CL Lubricant Eye Drops

INDICATIONS FOR USE:

- Use *blink*™ CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses; to help relieve dryness, irritation and discomfort that may be associated with lens wear; and to cushion lenses by placing a drop on the lens prior to application on the eye.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____
(Per 21 CFR 801.109)

OR

Over-The-Counter-Use X _____
(Optional Format 1-2-96)

(Division Sign-Off)
Division of Ophthalmic Ear,
Nose and Throat Devices

510(k) Number K032030

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration

Memorandum

Date: 3/5/09

From: DMC (HFZ-401)

Subject: Premarket Notification Number(s): K032030 / A3

To: Division Director: JP/DUMED

The attached information has been received by the 510(k) DMC on the above referenced 510(k) submission(s). Since a final decision has been rendered, this record is officially closed.

Please review the attached document and return it to the DMC, with one of the statements checked below.

Information does not change the status of the 510(k); no other action required by the DMC; please add to image file. (Prepare K-25) THIS DOES NOT APPLY TO TRANSFER OF OWNERSHIP. PLEASE BRING ANY TRANSFER OF OWNERSHIP TO POS.

Additional information requires a new 510(k); however, the information submitted is incomplete; (Notify company to submit a new 510(k); [Prepare the K30 Letter on the LAN]

No response necessary (e.g., hard copy of fax for the truthful and accuracy statement, 510(k) statement, change of address, phone number, or fax number).

CLIA CATEGORIZATION refers to laboratory test system devices reviewed by the Division of Clinical Laboratory Devices (HFZ-440)

Information requires a CLIA CATEGORIZATION; the complexity may remain the same as the original 510(k) or may change as a result of the additional information (Prepare a CAT letter)

Additional information requires a CLIA CATEGORIZATION; however, the information submitted is incomplete; (call or fax firm)

No response necessary

This information should be returned to the DMC within 10 working days from the date of this Memorandum.

Reviewed by: _____

Date: _____

POS

16032030/A3



March 3, 2009

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

RE: Transfer of Rights to Premarket Notifications (510(k)s) from Advanced Medical Optics, Inc. to Abbott Medical Optics Inc.

This is to inform you that Abbott Laboratories (Abbott) has completed its acquisition of Advanced Medical Optics, Inc. Effective February 26, 2009, our name has changed to Abbott Medical Optics Inc.

Advanced Medical Optics, Inc. hereby releases rights to the attached list of 510(k)s (Attachment 1) to Abbott Medical Optics Inc.

Please contact me at 714/247-8866, or Jeanne Isaacs, Regulatory Affairs Manager, with any questions.

Sincerely,

Richard J. DeRiso
Corporate Vice President
Global Public Policy and Regulatory Affairs

FDA CDRH DMC

MAR - 5 2009

Received

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PREMARKET NOTIFICATIONS (510(k)s)

510(K)	Device Name
K760684	Vitreous Aspirating and Cutting Instrument (TAC)
K792096	2 FR Kelman Chamber Maintainer
K813500	Gould I/A Handpiece and accessories
K820223	OMS Quartz Infusion Contact Lens
K820680	Disposable Tubing Sets OPO-1, -2, -3, -4
K821051	LIQUIFILM® Wetting Solution
K821052	SOAKARE® Contact Lens Soaking Solution
K821054	TOTAL® Hard Contact lens Solution
K821055	BLINK-N-CLEAN® Contact Lens Solution
K821496	Disposable Irrigation/Aspiration System OPO-5
K822706	PRE-SERT® Contact Lens Cushioning Solution
K822707	CLEAN-N-SOAK® Contact Lens Cleaning and Soaking Solution
K823222	Intraocular Lens Glide
K832235A	OPO-16 Disposable Vitrectomy Handpiece
K833405	Medical Optics Irrigation/Aspiration Kit
K840695	AISP Phaco Kits OPOSL19, OPOSL21
K841072	Irrigation/Aspiration Tubing Sets OPO-13, -14, -15
K843041	Heslin Disposable Tubing Set OPO-9
K843342	LENSKEEPER® Lens Carrying Case
K844373	OMS Ultra Phaco Products
K844374	Vitreous Aspiration & Cutting Instrument
K844448	OMS/Gonvers Retinal Perforator
K851262	Mono and Binocular Indirect Ophthalmoscope
K851263	
K851264	
K854225	4Plus Surgical System, Sensory V, Sensory V160
K864003	Phaco Folder IOL Forceps
K861642	LENSKEEPER® Contact Lens Carrying Case
K861643	STYLEKEEPER® Contact Lens Carrying Case
K863569	BKS 1000™
K864003	AMO® Phaco-Folder™ Intraocular Lens Forceps
K864065	BKS-2 Disposable Vacuum Tubing Pack
K870807	BKS-1000™ Refractive Set
K872312	Ophthalmic Surgical System Model 3000
K874543	OPO32 Irrigation Sleeve
K881987	DURACLEAN® Daily Cleaner
K884251	ALLERGAN® Lens Case
K893199	AMO® Phaco-Injector™ Intraocular Lens Implant Instrument (Prodigy)
K893880	AMO® Collagen Shields
K904909	Vitrectomy System Vitrophage YPR 2001
K905129	Baerveldt Glaucoma Implant

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

ATTACHMENT 1**PREMARKET NOTIFICATIONS (510(k)s)**

510(K)	Device Name
K911998	Multitome Model 1000 Vitrectomy Driving System
K924235	AMO® Elite™ Phacoemulsification System Products
K924235A	AMO® Prestige™ Phacoemulsification System Products
K925254	AMO® Flex-Tip™ Disposable Handpiece OPO38
K930320	AMO® PhacoFlex Insertion Instrument PIC-I, PIH-I
K935003	AMO® IV Pole OM770101P2
K935223	AMO® Opsys Phaco System
K935226	OMS Programmable IV Pole or PIVP2
K941603	AMO® PhacoFlex Inserter Disposable Cartridge PIC-II
K946054	AMO® OMS Diplomax™ Phaco System
K950218	Slimline Phaco Handpiece
K951462	AMO® Profinesse III® Ultrasonic Handpiece System
K955455	Baerveldt Pars Plana Glaucoma Implant
K961242	AMO® PhacoFlex II Insertion System
K962402	AMO® Prestige® Day Pack
K971186	Modified AMO® Diplomax™ and AMO® Opsys® consoles
K980775	COMPLETE® Solution (Upgrade A Protein Removal)
K981116	AMO® Sovereign Cataract Extraction System
K981168	COMPLETE® Solution (Upgrade B)
K983150	COMPLETE® (Upgrade B Lubricating & Rewetting Drops)
K984383	ULTRACARE® Neutralizing Tablets (Coating Change)
K992028	REFRESH CONTACTS L&R Solution
K993153	ILS 600C Laser Keratome
K000164	COMPLETE® Solution (Conditioning Claim)
K001211	Modified 600C Keratome
K002890	600C Laser Keratome
K003109	Blink-N-Clean Lens Drops
K003252	COMPLETE® Solution (No Rub-Frequent Replacement)
K003638	Mojave Cataract Extraction System
K010223	TOTALCARE Conditioning & Soaking Solution
K013479	COMPLETE® Solution (No Rub-Conventional)
K013941	Pulsion FS Laser Keratome
K014202	COMPLETE® Solution (Upgrade B Without HPMC)
K024166	COMPLETE C MPS (9451X)
K030092	COMPLETE BC MPS (8941X)
K031126	IntraLase Laser
K031960	FS Laser
K032030	Blink CL Lubricant Eye Drops (9464X)
K040839	COMPLETE A Blink-N-Clean Lens Drops (8772X)
K041893	FS Laser
K042562	LensPlus Rewetting Drops (7317X)
K050494	COMPLETE Moisture Plus MP Disinfecting Solution

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ATTACHMENT 1**PREMARKET NOTIFICATIONS (510(k)s)**

510(K)	Device Name
K050648	Sovereign High Vacuum Pack
K053396	COMPLETE D MPS (9560X)
K060366	AMO Ophthalmic Surgical System (Sterling Signature System)
K060372	FS Laser
K063682	FS Laser (smaller version)
K061399	ULTRACARE Cleaning & Disinfecting Solution-Neutralizing system
K073404	iFS Laser
K081545	1VIPR30
K081681	Vitrectomy Cutter and Sleeve

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAR 11 2009

Richard J. DeRisio
Advanced Medical Optics
1700 E. St. Andrew Place
Santa Ana, CA 92705

Re: See Enclosed List

Dear Mr. DeRisio:

We have reviewed your letter dated March 3, 2009, stating that the rights to the above referenced premarket notifications (510(k)s) has been transferred. Transfer of 510(k) rights alone does not require submission of a new 510(k) under 21 CFR 807.81(a)(3). Consequently, we cannot change the name of the original 510(k) submitter in our database. Please note, as per 21 CFR 807.85(b), a firm may not **both** manufacture and distribute a device under their own name without having their own 510(k).

We suggest that information showing the transfer of the 510(k)s and their current ownership should be maintained in the company's files for review by an FDA investigator. You may contact the Center for Devices and Radiological Health's Office of Compliance at (240) 276-0100 if you have any questions on what information we expect to be maintained in your files.

If you have any other questions regarding this letter, please contact the 510(k) Staff at (240) 276-4040.

Sincerely yours,

Julie "Brandi" Stuart
Consumer Safety Officer
Premarket Notification Section
Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

K032030/A1

*blink*TM CL Lubricant Eye Drops

510(k): K032030
Additional Information Requested
by FDA (fax dated 9 Sept 2003)

September 11, 2003

2003 SEP 12 A 9:29

FDA/CDRH/OCE/PIH

Copy 1 of 2

5/1
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September 11, 2003

510k Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

FDA/CDRH/OCE/PHD
2003 SEP 12 A 9:29

**RE: K032030 – *blink*™ CL Lubricant Eye Drops
9 September 2003 FDA Request for Additional Information**

TO WHOM IT MAY CONCERN:

Advanced Medical Optics (AMO) hereby provides duplicate copies of a submission to the above-referenced 510(k). This is being sent in response to a request for additional information from Daniel W.C. Brown, Ph.D., of FDA (fax dated 9 Sept 2003).

In that fax, the following information was requested:

The *blink* CL Lubricant Eye Drops contains sodium hyaluronate as a lubricant, the following information about sodium hyaluronate is needed:

1. The origin of sodium hyaluronate
2. The average molecular weight of sodium hyaluronate
3. Protein concentration
4. Bioburden
5. Residual solvent

In response to item #1, the sodium hyaluronate used in *blink* CL Lubricant Eye Drops is derived by (b)(4) Confidential and Proprietary Information

In response to items #2 through #5, as stated in our 510(k) notification, the sodium hyaluronate used in *blink* CL Lubricant Eye Drops complies with the monograph in the European Pharmacopoeia (EP). Enclosed in Appendix 1 is a table showing the EP specifications and AMO's test results for (b) lots of the vendor's material. This table includes information regarding the protein concentration and the bioburden. For information on the average molecular weight and residual solvent, the raw material manufacturer's certificates of analysis for the three tested lots are also enclosed. The results show that the sodium hyaluronate used in *blink* CL Lubricant Eye Drops meets the EP specifications.

In Dr. Brown's fax, we were also requested to provide information on the ethylene oxide (EtO) sterilization of the bottle components. The sterilization validation meets the requirements of ISO 11135:1994, Medical Devices – Validation and routine control of ethylene oxide sterilization. Enclosed in Appendix 2 is the method used to validate the sterilization cycle, which includes the acceptance limit for EtO residues. The sterility assurance level is 10⁻⁶.

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K032030 – *blink*™ CL Lubricant Eye Drops
Response to 9 Sept 2003 FDA Request
September 11, 2003
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Additionally, we confirm that the sterility test data will be available to support the product's expiration date prior to marketing. Enclosed in Appendix 3 is a sterility test report showing results after 7 months storage at 37°C. Sterility testing will continue to be carried out in accordance with the test schedule included in the stability report submitted in the 510(k) notification.

Labeling for the predicate device, Refresh Contacts Contact Lens Comfort Drops, is included in Appendix 4. Labeling for the other two predicate devices, Hylashield and AQUify, is not available as these products have not yet been marketed in the United States.

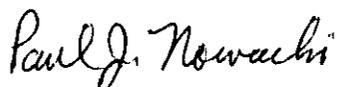
Lastly, AMO does not agree that "ANY" should be deleted in the labeling in the phrase "For Use With Any Contact Lenses". For several years, members in the contact lens care industry have been allowed to use this statement and, without any information to the contrary, we feel we should also be allowed to use this phrase.

To the best of my knowledge, all data and information submitted in this premarket notification are truthful and accurate; no material fact has been omitted. An FDA Truthful and Accurate Statement form follows this cover letter. We therefore request a determination of substantial equivalence.

We ask that the existence of this 510(k) be kept confidential since:

- The intent to market the product covered by this 510(k) has been kept confidential. No disclosures have been made to persons other than those bound by secrecy agreements
- Precautions have been taken to preserve confidentiality
- FDA will be immediately notified of any disclosure of intent to market

Sincerely,



Paul J. Nowacki
Manager
Regulatory Affairs

Phone: 714-247-8601
Fax: 714-247-8677
Email: paul.nowacki@amo-inc.com

PREMARKET NOTIFICATION TRUTHFUL AND ACCURATE STATEMENT

[As Required by 21 CFR 807.87(j)]

I certify that, in my capacity as Manager, Regulatory Affairs, of
Advanced Medical Optics, I believe to the best of my knowledge, that all
data and information submitted in this premarket notification are truthful
and accurate and that no material fact has been omitted.

Paul J. Nowacki
(Signature)

Paul J. Nowacki
(Typed Name)

11 Sep 2003
(Date)

K032030
*(Premarket Notification [510(k)] Number)

*For a new submission, leave the 510(k) number blank.

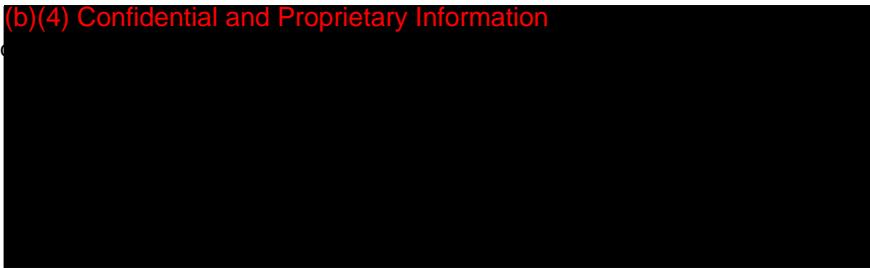
Must be signed by a responsible person of the firm required to
submit the premarket notification [e.g., not a consultant for the
510(k) submitter].

Raw Materials (cont.)

Test	EP Specification	Results		
		(b)(4) Confidential and Proprietary Information		
Visual Appearance	White or almost white powder or fibrous aggregate	Pass	Pass	Pass
Infrared Spectrum	Matches Reference	Pass	Pass	Pass
Appearance of 0.33% solution	Clear	Clear	Clear	Clear
A600, 1cm of 0.33% solution	< 0.01	0.0017	0.0016	0.0011
pH of 0.5% solution	5.0 – 8.5	6.15	6.02	6.10
Nucleic Acid (A260, 0.33%, 1cm)	< 0.5	0.0129	0.0137	0.0090
Protein Content	≤ 0.3%	0.01	0.00	0.00
Chlorides	≤ 0.5%	≤ 0.5%	≤ 0.5%	≤ 0.5%
Iron	≤ 80 PPM	17 PPM	10 PPM	11 PPM
Loss on Drying	≤ 20%	6.1%	4.5%	8.5%
Total Microbial Count	≤ 100 CFU/g	< 100 CFU/g	< 100 CFU/g	< 100 CFU/g
Bacterial Endotoxins	≤ 0.5 I.U./mg	0.018 I.U./mg	< 0.005 I.U./mg	< 0.005 I.U./mg
Sodium Hyaluronate (dry basis)	95.0 – 105.0%	102.3%	103.0%	96.7%
Intrinsic Viscosity	90% to 120% of label value	107%	94%	99%

Copies of the vendor C of A's for PURITE® and sodium hyaluronate follow.

Re

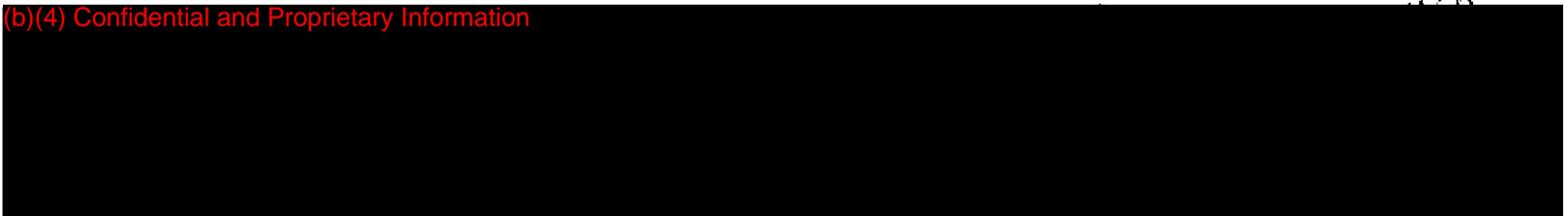


Certificate of Analysis
SPEC 80080

Product Information

Part Number	80080
Product	Medical Grade Sodium Hyaluronate Powder
Lot Number	P9911-1
Expiration Date	12/01/2003

<u>Characteristic</u>	<u>Specification</u>	<u>Actual</u>
Safety:		
Bioburden, cfu/g	≤ 100	SAB: 0 cfu/g TSA: 1 cfu/g
Microbial Identification / Differentiation	None of the following observed: <i>E. coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Salmonella sp.</i>	Complies
Endotoxin (1% solution)	0.07 EU/mg maximum	0.06 EU/mg
Chemical / Physical Characteristics:		
Visual Appearance	White to off white fluffy to small grain powder	White, fluffy to small grain powder
Odor	None	None
Viscosity (3% in water)	$2.20 \times 10^4 - 2.25 \times 10^5$ cps	8.02×10^4 cps
IR Spectrum (4000 - 800 cm^{-1}) (1% solution)	Matches Standard	Matches Standard
UV-Vis Spectrum (820 -190 nm) (1% solution)	Matches Standard	Matches Standard
pH (1% solution)	6.2 - 7.8	6.6





Certificate of Analysis
SPEC 80080

Lot #: P9911-1

Acetate Concentration (1% solution)	1.0% maximum	<u>0.2%</u>
Osmolality (1% solution)	75 mOsmo/kg maximum	<u><50 mOsmo/kg</u>
Protein Concentration, (1% solution)	0.1% maximum	<u><0.1%</u>
Hyaluronidase Sensitivity (1% solution)	Positive	<u>Positive</u>
Water	10.0% maximum	<u>5.1%</u>
Arsenic	2 ppm maximum	<u><1 ppm</u>
Cadmium	5 ppm maximum	<u><1 ppm</u>
Chromium	5 ppm maximum	<u>3 ppm</u>
Cobalt	10 ppm maximum	<u><1 ppm</u>
Copper	10 ppm maximum	<u>1 ppm</u>
Iron	51 ppm maximum	<u><10 ppm</u>
Lead	10 ppm maximum	<u><1 ppm</u>
Mercury	10 ppm maximum	<u><1 ppm</u>
Nickel	5 ppm maximum	<u><1 ppm</u>
Ethanol	1.0% maximum	<u><0.1%</u>
Isopropanol	0.5% maximum	<u><0.1%</u>
Molecular Weight, viscosity average	$5.0 \times 10^5 - 1.2 \times 10^6$ dalton	<u>8.1×10^5 dalton</u>
Intrinsic viscosity	10-20 dl/g	<u>15 dl/g</u>



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Certificate of Analysis
PH 1.5 Powder
SPEC 80080

Product Information

Part Number	<u>80080</u>
Product	<u>Medical Grade Sodium Hyaluronate Powder</u>
Lot Number	<u>P0203-9</u>
Expiration Date	<u>4/18/07</u>

<u>Characteristic</u>	<u>Specification</u>	<u>Actual</u>
Safety:		
Bioburden	≤ 100 cfu/g	<u><10 cfu/g</u>
Microbial Identification / Differentiation	None of the following observed: <i>E. coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Salmonella sp.</i>	<u>N/A</u>
Endotoxin	0.07 EU/mg maximum	<u><0.01 EU/mg</u>
Chemical / Physical Characteristics:		
Visual Appearance	White to off white fluffy to small grain powder	<u>Complies</u>
Odor	None	<u>None</u>
Viscosity (3% in water)	$2.20 \times 10^4 - 2.25 \times 10^5$ cps	<u>9.78×10^4 Daltons</u>
IR Spectrum (4000 - 800 cm^{-1}) (1% solution)	Matches Standard	<u>Matches Standard</u>
UV-Vis Spectrum (820 -190 nm) (1% solution)	Matches Standard	<u>Matches Standard</u>
pH (1% solution)	6.2 - 7.8	<u>6.9</u>

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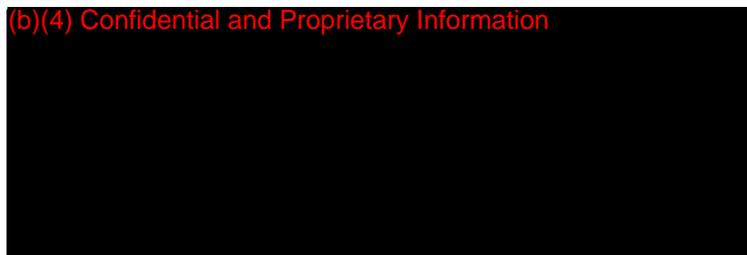
Certificate of Analysis
 PH 1.5 Powder
 SPEC 80080

Lot #: P0203-9

Acetate Concentration (1% solution)	1.0% maximum	<0.1%
Osmolality (1% solution)	75 mOsmo/kg maximum	<50 mOsmo/kg
Protein Concentration, (1% solution)	0.1% maximum	<0.1%
Hyaluronidase Sensitivity (1% solution)	Positive	Positive
Water	10.0% maximum	4.5%
Arsenic	2 ppm maximum	<1 ppm
Cadmium	5 ppm maximum	<1 ppm
Chromium	5 ppm maximum	<2 ppm
Cobalt	10 ppm maximum	<1 ppm
Copper	10 ppm maximum	<1 ppm
Iron	51 ppm maximum	12 ppm
Lead	10 ppm maximum	<1 ppm
Mercury	10 ppm maximum	<1 ppm
Nickel	5 ppm maximum	<1 ppm
Total Volatile Organic Compounds (VOC)	73 ppm alert level 94 ppm action level	8 ppm
Ethanol	1.0% maximum	<0.1%
Isopropanol	0.5% maximum	0.1%
Methanol	0.25% maximum	<0.01%
Molecular Weight, viscosity average	$5.0 \times 10^5 - 1.2 \times 10^6$ dalton	8.8×10^5 dalton
Intrinsic viscosity	10-20 dl/g	16 dl/g



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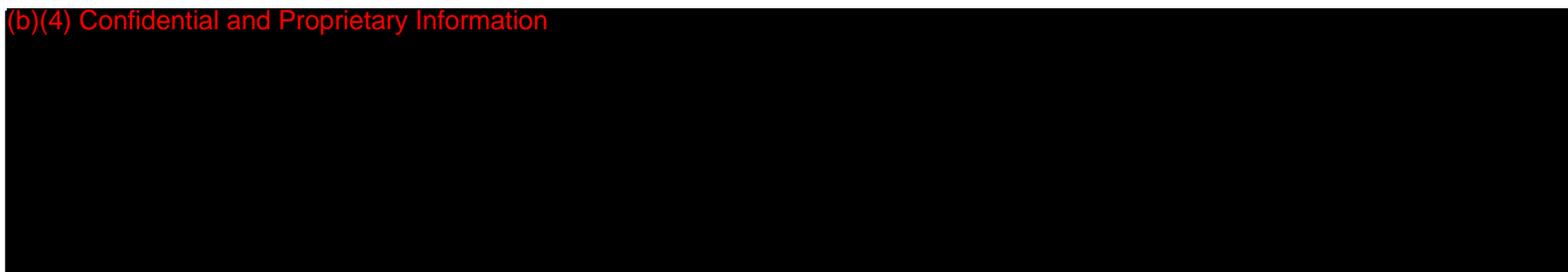
Certificate of Analysis
PH 1.5 Powder
SPEC 80080

Product Information

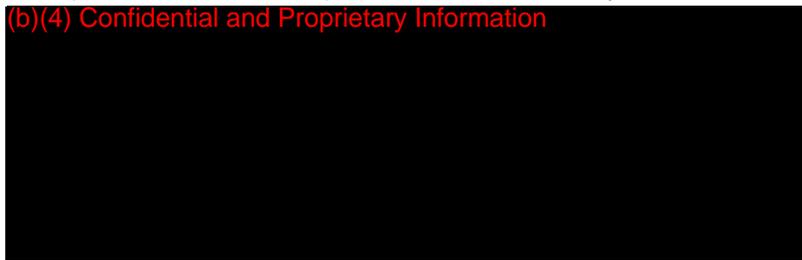
Part Number	80080
Product	Medical Grade Sodium Hyaluronate Powder
Lot Number	P9902-12B
Expiration Date	9/11/04

<u>Characteristic</u>	<u>Specification</u>	<u>Actual</u>
Safety:		
Bioburden	≤ 100 cfu/g	<10 cfu/g
Microbial Identification / Differentiation	None of the following observed: <i>E. coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Salmonella sp.</i>	Complies
Endotoxin (1% solution)	0.07 EU/mg maximum	<0.01 EU/mg
Chemical / Physical Characteristics:		
Visual Appearance	White to off white fluffy to small grain powder	Complies
Odor	None	None
Viscosity (3% in water)	$2.20 \times 10^4 - 2.25 \times 10^5$ cps	5.05×10^4 cps
IR Spectrum (4000 - 800 cm^{-1}) (1% solution)	Matches Standard	Matches Standard
UV-Vis Spectrum (820 -190 nm) (1% solution)	Matches Standard	Matches Standard
pH (1% solution)	6.2 - 7.8	6.8

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Certificate of Analysis
PH 1.5 Powder
SPEC 80080

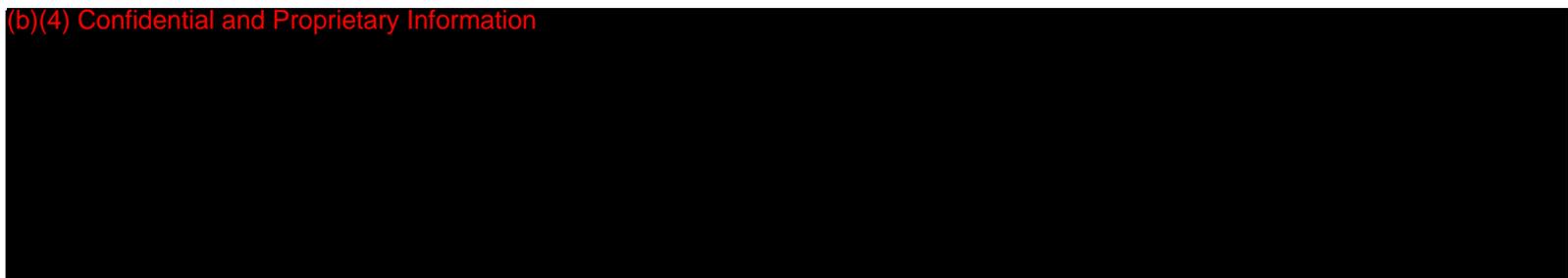
Lot #: P9902-12B

Acetate Concentration (1% solution)	1.0% maximum	<u>0.2%</u>
Osmolality (1% solution)	75 mOsm/kg maximum	<u><50 mOsm/kg</u>
Protein Concentration, (1% solution)	0.1% maximum	<u><0.1%</u>
Hyaluronidase Sensitivity (1% solution)	Positive	<u>Positive</u>
Water	10.0% maximum	<u>6.1%</u>
Arsenic	2 ppm maximum	<u><1 ppm</u>
Cadmium	5 ppm maximum	<u><1 ppm</u>
Chromium	5 ppm maximum	<u><1 ppm</u>
Cobalt	10 ppm maximum	<u><1 ppm</u>
Copper	10 ppm maximum	<u><1 ppm</u>
Iron	51 ppm maximum	<u><8 ppm</u>
Lead	10 ppm maximum	<u><1 ppm</u>
Mercury	10 ppm maximum	<u><1 ppm</u>
Nickel	5 ppm maximum	<u><1 ppm</u>
Total Volatile Organic Compounds (VOC)	73 ppm alert level 94 ppm action level	<u>12 ppm</u>
Ethanol	1.0% maximum	<u><0.1%</u>
Isopropanol	0.5% maximum	<u><0.1%</u>
Methanol	0.25% maximum	<u><0.10%</u>
Molecular Weight, viscosity average	$5.0 \times 10^5 - 1.2 \times 10^6$ dalton	<u>7.0×10^5 dalton</u>
Intrinsic viscosity	10-20 dl/g	<u>13 dl/g</u>

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STANDARD OPERATING PROCEDURE

DEPARTMENT: (b)(4) Confidential

WRITTEN BY: (b)(4) Confidential and Proprietary Information

PAGE 1 OF 4 PAGES

ISSUE DATE: (b)(4) Confidential and Proprietary Information

EFFECTIVE DATE:
ISSUE DATE + 1 DAY

SOP NO.: WGP-106

REVISION NO.: 9.0

SUPERSEDES: (b)(4) Confidential and Proprietary

MATERIALS APPROVAL

(b)(4) Confidential and Proprietary Information

DATE: 1/29/02

PRODUCTION APPROVAL

DATE: 1/29/2002

QUALITY ASSURANCE

DATE: 1/25/02

DISTRIBUTION: Refer to Waco SOP Distribution Listing

DESCRIPTION: Preparation and ETO Sterilization of Allergan Containers and Closures at IBA

1.0 PURPOSE

The purpose of this procedure is to define the guidelines for the preparation and ETO sterilization of Allergan packaging components at IBA.

2.0 RESPONSIBILITY

It shall be the responsibility of the Director of QA/QC, the Director of Materials Management, (b)(4) Manager and/or a designated competent and responsible individual(s) to adhere to and update as necessary the contents of this procedure.

It shall be the responsibility of the (b)(4) Confidential and Proprietary Director of Operations and/or a designated competent and responsible individual(s) to adhere to the contents of this procedure.

3.0 PROCEDURE

3.1 Allergan, Inc. will provide (b) the biological indicators (Bacillus subtilis) to use for the preparation of the test packs for the ETO sterilization cycles.

3.2 Materials - Purchasing will place the order for components with Allergan Medical Plastic and (b) (4) according to the SOPs applicable to the area. They will also coordinate the arrival of components to IBA.

3.3 Components will arrive to (b) from Allergan Medical Plastics & Montebello Tubes identified with part #, description, lot # and quantity of components per box.

3.4 (b) (4) will label each pallet as "Non-Sterile Components". Refer to Attachment I.

3.5 (b)(4) will place the pallets of components in the awaiting for processing area until there are enough components for a sterilization cycle.

Date:

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DESCRIPTION: Preparation and ETO Sterilization of Allergan Containers and Closures (b) (4)

- 3.6 Materials – Purchasing will identify the components that will comprise a load based on this procedure. Purchasing will inform IBA the part #, the description, lot # and number of cases per pallet in a load. Purchasing will coordinate the sterilization of components with IBA.
- 3.7 (b) (4) prepare a sterilization load with the information provided by Purchasing.
- 3.8 The sterilization load will consist of thirteen (13) pallets. Refer to Attachment II for pallet order for possible configurations. If there are not enough components to configure a load of thirteen pallets, dummy pallets will be used to complete the thirteen pallets load. These dummy pallets shall be clearly identified as "Dummy Pallets". Refer to Attachment V. Each case of the "Dummy" pallets shall be clearly identified as a Dummy case. Dummy cases can be used to complete a pallet of components for sterilization; i.e. 8 cases of bottles & 8 cases of "dummy" bottles can make a full pallet of bottles.
- 3.9 Each case that will be sterilized shall have a piece of ETO sterilization tape on it before going into the ETO sterilization chamber.
- 3.10 The maximum load configuration will consist of the following number of pallets of components:
- Two (2) pallets of caps (13mm and 15mm)
 - Two (2) pallets of tips (13mm and 15mm)
 - Nine (9) pallets of Blue Flip top caps

Changes to the above load configuration could take place only if the final density of the load is not exceeded. For example:

- Only a maximum of four (4) pallets of tips/ caps maybe used for each run with any combination of Blue Flip top caps, bottles and/ or tubes completing the remaining nine (9) pallets.

OR

- Any combination of components or zero (0) pallets of tips / caps any combination of Blue Flip top caps, bottles, and or tubes completing a total of thirteen (13) pallets.

NOTES:

1. ***Five different component densities have been identified in the validated load described in Attachment II: 13 mm tip/cap (~0.35 g/mL), 15 mm tip/cap (~0.22 g/mL), Blue Flip top caps (~0.16 g/ml), bottles, (~0.10 g/mL) & tubes (~0.05 g/mL). The 13 mm caps & tips are the items with the highest densities. The tubes have the lowest densities. Other load configurations can be made using this as reference, without exceeding the maximum quantity of pallets of 13-mm tips and/or caps which is two- (2).***

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DESCRIPTION: Preparation and ETO Sterilization of Allergan Containers and Closures at IBA

2. **Components can be substituted in a load with components of the same or lower density without exceeding the total density of the load, i.e., a load can have: two (2) pallets of 13 mm caps, two (2) pallets of 15 mm caps, nine (9) blueflip caps OR four (4) pallets of 15 mm caps or tips, nine (9) pallets of bottles, flip top caps or tubes.**
 3. **ALL loads will include not more than two pallets of 13-mm tips and/or caps.**
 4. **IBA personnel will verify the quantity of boxes per pallet according to Attachment II.**
- 3.11 (b) (4) wrap the pallets of components, if they are not wrapped already, and affix a Sterilization Status Tag (GMS-1176 current revision) to each pallet to be sterilized.
 - 3.12 (b) (4) personnel will request thirty-one (31) test packs from (b) (4) personnel. Prepare thirty-one (31) test packs for each sterilization load as outlined in the following instructions. Each test pack will contain one spore strip of the biological indicator *Bacillus subtilis*. Each test pack shall be sequentially numbered. The last test pack will be identified as positive control.
 - 3.12.1 With the open end of the pouch facing towards you and the clear plastic side facing up, fold over at the perforated line and unfold.
 - 3.12.2 Insert one spore strip of the biological indicator *Bacillus subtilis* in a DualPeel® Self Seal Pouch.
 - 3.12.3 Peel off paper strip from tape.
 - 3.12.4 To completely seal, fold forward onto clear side plastic and press down at the center with your thumbs.
 - 3.12.5 Pressing firmly, draw one thumb from the center of the flap to the outside edge, sealing that side of the package.
 - 3.12.6 Repeat for the other side. Run your thumb twice along to insure full adhesive contact.
 - 3.12.7 Number the test pack in sequential order from #1 through #30.
 - 3.12.8 The last test pack will be identified as "Positive Control".
 - 3.13 (b) (4) production personnel will request (b) (4) from (b) (4) and distribute the test packs externally throughout the load as described in Attachment III. The test pack with the positive control will always be placed on pallet #1.
 - 3.14 (b) (4) personnel will follow all applicable SOPs to assign a unique vacugas sterilization number, VGL#, to the load to be sterilized.
 - 3.15 (b) (4) personnel will follow all applicable SOPs to process the load of components into the pre-conditioning, sterilization & degassing chambers. The pallets will be loaded in ascending order into the sterilizer.
 - 3.16 The load will be processed as outlined in Attachment IV.

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DESCRIPTION: Preparation and ETO Sterilization of Allergan Containers and Closures at IBA

- 3.17 (b) personnel will schedule the sterilization load so test packs can be tested within twenty-four (24) hours after retrieval.
- 3.18 (b) personnel will remove the positive control after the pre-conditioning phase and prior to the sterilization phase.
- 3.19 (b) personnel will retrieve the thirty (30) test packs from the load after eight (8) hours of heated aeration. The load will be placed back in the aeration chamber to complete the degassing phase.
- 3.20 (b) personnel will send the thirty (30) BIs and the positive control to (b) (4) for testing. The biological indicators shall be dropped in media and placed in the incubators within twenty-four (24) hours of retrieval from the load.
- 3.21 After the aeration phase has been completed, IBA personnel will remove the "Allergan, Inc. Non – Sterile Components" sign from the pallets and will place the load in the "Quarantine Area" of IBA Warehouse Facility until all the BIs have come out from incubation.
- 3.22 After the heated aeration phase, Blue Flip top caps and tubes shall sit at ambient temperature for 7 days additional de-gassing. Bottles, 15mm tips and caps and 13mm tips and caps shall sit at ambient temperature for a total of 14 days of additional de-gassing
- 3.23 (b) (4) will issue a BI Sterility Test Report for each sterilization cycle once the incubation period has been completed. All exposed BIs must exhibit no growth in order to release the components and send them to Allergan Inc. Waco. The Positive Control BI shall exhibit growth.
- 3.24 (b) (4) send the following document to Allergan Inc. Waco – Incoming Department:
 - 3.24.1 Summary of Process Sterilization
 - 3.24.2 Work Order: with part #, lot # and quantity of cases sterilized
 - 3.24.3 Placement of BIs
 - 3.24.4 Sterilization Cycle Printout
 - 3.24.5 Biological Indicator Sterility Test Report
- 3.25 Allergan Inc. Waco Micro Lab will evaluate the sterilization cycle documentation to determine if all validated parameters were met. A sterilized load will be able to be released if all validated sterilization parameters have been met and if seven or fourteen days (as applicable) after heated aeration's have elapsed.
- 3.26 Allergan Inc. Waco Micro Lab will assign a year expiration date from the sterilization date of the load.
- 3.27 A load could be re-sterilized if the first sterilization fails or the first sterilization of the components is due, new test packs will be placed throughout the load as specified in Attachment III and re-processed as previously described.
- 3.28 Sterilized components with the usable date expired can be re-sterilized only once.

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ATTACHMENT I

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ALLERGAN INC. NON-STERILE COMPONENTS

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STERILIZATION LOAD CONFIGURATION:

Pallet #	Description of Component
1	Flip top caps, Bottles or Tubes
2	Flip top caps, Bottles or Tubes
3	Flip top caps, Bottles or Tubes
4	Flip top caps, Bottles or Tubes
5	Flip top caps, Bottles or Tubes
6	Flip top caps, Bottles or Tubes
7	Flip top caps, Bottles or Tubes
8	Flip top caps, Bottles or Tubes
9	Flip top caps, Bottles or Tubes
10	Flip top caps, Bottles, Tubes, Tips (15mm) or Caps (15mm)
11	Flip top caps, Bottles, Tubes, Tips (15mm) or Caps (15mm)
12	Flip top caps, Bottles, Tubes, Tips (15mm or 13mm) or Caps (15mm or 13mm)
13	Flip top caps, Bottles, Tubes, Tips (15mm or 13mm) or Caps (15mm or 13mm)

***- The 13 mm caps & tips are the items with the highest densities. The tubes have the lowest densities. Load configurations can be made using this as reference, without exceeding the maximum quantity of pallets of 13 mm tips and/or caps, which is two (2).**

QUANTITY OF BOXES PER PALLET OF COMPONENTS:

Components	Boxes per Pallet
Bottles	16
Tubes	18
Blue Flip Tops Caps	16
Tips – 15mm	18
Tips – 13mm	18
Caps – 15mm	16
Caps – 13mm	24

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TEST PACK PLACEMENT THIRTEEN PALLETS LOAD

Sterilization Cycle: _____

Date: _____

POSITIVE BI Test Pack: Pallet #1

PALLET #	LOCATION	TEST PACK #
1	Back side: top, middle, bottom	1 - 3
2	Back side: top, bottom	4 - 5
3	Back side: top, bottom	6 - 7
4	Back side: top, bottom	8 - 9
5	Back side: top, bottom / Front side middle	10, 11 / 12
6	Back side: top, bottom	13 - 14
7	Back side: top, bottom	15 - 16
8	Back side: top, bottom	17 - 18
9	Back side: top, bottom	19 - 20
10	Front side: top, bottom / Back side middle	21, 22 / 23
11	Back side: top, bottom	24 - 25
12	Back side: top, bottom	26 - 27
13	Back side: top, middle, bottom	28 - 30

Performed by: _____

Date: _____

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FULL CYCLE PARAMETERS

	Process Stage	Sterilization Parameters
A. Pre-humidication		(b)(4) Confidential and Proprietary Information
	Pre-conditioning Time	
	Pre-conditioning Temp	
	Pre-conditioning Humidity	
B. Initial Vacuum		
	Evacuate to	
	Evacuation Rate	
C. Humidity Dwell		
	Moisture Injection	
	Humidity Level	
	Humidity Time	
	Humidity Temperature	
D. Gas Dwell		
	Gas Injection to	
	Injection Rate	
	Chamber Exposure Pressure	
	Chamber Exposure Temperature	
	Dwell Time	
E. After Vacuum		
	Evacuate to	
	Evacuation Rate	
F. Air Wash		
	Air Injection to	
	Injection Rate	
	Evacuation Termination	
	Evacuation Rate	
	Total # of air washes	
G. Release		
	Release to	
	Evacuation Rate	
H. Aeration - Degassing		
	Post-Conditioning Time	
	Post Conditioning Temp.	

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DUMMY PALLET

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STANDARD OPERATING PROCEDURE

DEPARTMENT: (b) (4)

WRITTEN BY: (b)(4) Confidential and Proprietary Information

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ISSUE DATE: [Redacted]

SOP NO: WVAL-016 REVISION NO.: (b)

SUPERSEDES:

PRODUCTION APPROVAL: (b)(4) Confidential and Proprietary Information

DATE: 1/17/2002 1/19/02

QUALITY ASSURANCE APPR [Redacted]

DATE: 1/18/02

DISTRIBUTION: Refer to Waco SOP Distribution Listing

DESCRIPTION: Validation of Ethylene Oxide Sterilization Cycle

1.0 PURPOSE

The purpose of this procedure is to define the guidelines for the validation of the ethylene oxide sterilization cycle for plastic packaging components.

2.0 RESPONSIBILITY

It shall be the responsibility of the Validations Manager and/or a designated competent and responsible individual(s) to adhere to and update as necessary the contents of this procedure.

3.0 GENERAL

- 3.1 Validation shall be performed according to Worldwide Quality assurance Policy 09-02.
- 3.2 A validation protocol shall be written for each performance qualification following the format described in WVAL-005.
- 3.3 Ethylene Oxide is a colorless, toxic and hazardous gas. Follow MSDS indications when working in the sterilizing area.

4.0 PROCEDURE

- 4.1 Initial validation of an ethylene oxide sterilization cycle shall comprise of three half cycles for biological kill and one full cycle for EO, EC and EG residuals.
- 4.2 All validations shall be performed using calibrated temperature and humidity data tracers or equivalent equipment. A data tracer shall be placed beside a sterilization pouch with a biological indicator.
- 4.3 The biological indicators (*Bacillus subtilis* var. *niger*) shall be distributed throughout the load to ensure monitoring of all planes of each pallet. The number of biological indicators will depend on the size of the sterilizer (i.e. cubic feet) and should be specified in the validation protocol. As general guideline, use one spore strip per 10 cubic feet of vessel volume or not less than 10 BIs, whichever is greater.

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DESCRIPTION: Validation of Ethylene Oxide Sterilization Cycle

- 4.4 The biological indicators shall be removed from the load according to the instructions stated in the protocol and sent to a designated Microbiology Lab for incubation.
- 4.5 For the annual requalification, one half cycle run for microbial kill shall be performed using BIs and one full cycle for EO, EC and EG residuals.
- 4.6 The acceptance criteria for any EO sterilization cycle validation shall meet the following parameters:
 - 4.6.1 Exposed BIs shall be negative for growth for the indicator organism. Positive control BI must exhibit growth for the indicator organism.
 - 4.6.2 Successful half and full sterilization cycles must be performed.
 - 4.6.3 EO residuals for final post aeration must be ≤ 1 ppm for EO, ≤ 20 ppm for EC and ≤ 60 ppm for EG.

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FINAL REPORT

PRODUCT STERILITY TEST

PROCEDURE NO. (b)(4) Confidential and Proprietary Information

LABORATORY NO. 240637

PREPARED FOR:

LAUREN CRAWFORD
ADVANCED MEDICAL OPTICS, INC.
1700 EAST ST. ANDREWS PLACE
SANTA ANA, CA 92705

SUBMITTED BY:

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PRODUCT STERILITY TEST

LABORATORY NUMBER: 240637
PROCEDURE NUMBER: SOP/STR/002O.1
SAMPLE SOURCE: Advanced Medical Optics, Inc.
SAMPLE IDENTIFICATION: (b)(4) Confidential and Proprietary Information

3) 02RD45A, 4) 02RD45B, 5) 02RD51A,
6) 02RD51B

DEVIATIONS: None
DATA ARCHIVE LOCATION: Sequentially by lab number
TEST REQUESTED: Product sterility
TYPE OF TEST: Direct transfer
INCUBATION TIME: 15 days
INCUBATION TEMPERATURES: Soybean casein digest broth: 20-25°C
Fluid thioglycollate medium: 30-35°C

POSITIVE CONTROL(S): Passed growth promotion
NEGATIVE CONTROL(S): Negative
MEDIA: SCDB lot #14032
THIO lot #2178

MEDIA VOLUME: 340 mL
NUMBER OF UNITS: 120 (60 SCDB / 60 THIO)
QUANTITY TESTED PER UNIT: Entire volume of bottle
SAMPLE RECEIVED DATE: 09 Jul 2003
LAB PHASE START DATE: 10 Jul 2003
LAB PHASE COMPLETION DATE: 25 Jul 2003
REPORT ISSUE DATE: 28 Jul 2003
TOTAL NUMBER OF PAGES: 7

ACCEPTANCE CRITERIA:

As stated in the current USP, no growth in any samples submitted. In addition, a current, acceptable bacteriostasis/fungistasis (B/F) test.

RESULTS:

The results are summarized in Tables 1-2. The sterility test results are only valid with an acceptable B/F on this product (a separate study).

Advanced Medical Optics, Inc.

Product Sterility Test

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Page 3

STATEMENT OF UNCERTAINTY:

The uncertainty of the product sterility test is based on (1) growth promotion properties of the media and (2) the aseptic transfer rate for the analysts performing the test. The aseptic transfer rate includes all environmental factors. (b)(4) performs growth promotion tests on each batch of media to demonstrate growth of minimal numbers of organisms. The rate of non-product related contamination for the laboratory is 1 per 9625 or 0.010%. Using the value as a combined standard uncertainty, the expanded uncertainty at a 95% confidence interval, is 0.008%, assuming that the product has a sterility assurance level (SAL) of 10^{-6} .

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Advanced Medical Optics, Inc.
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Product Sterility Test
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TABLE 1. Results
 Soybean Casein Digest Results

UNIT NUMBER	RESULTS	UNIT NUMBER	RESULTS	UNIT NUMBER	RESULTS
1 45A	No Growth	41 51A	No Growth	81 24A	No Growth
2 45A	No Growth	42 51A	No Growth	82 24A	No Growth
3 45A	No Growth	43 51A	No Growth	83 24A	No Growth
4 45A	No Growth	44 51A	No Growth	84 24A	No Growth
5 45A	No Growth	45 51A	No Growth	85 24A	No Growth
6 45A	No Growth	46 51A	No Growth	86 24A	No Growth
7 45A	No Growth	47 51A	No Growth	87 24A	No Growth
8 45A	No Growth	48 51A	No Growth	88 24A	No Growth
9 45A	No Growth	49 51A	No Growth	89 24A	No Growth
10 45A	No Growth	50 51A	No Growth	90 24A	No Growth
21 45B	No Growth	61 51B	No Growth	101 24B	No Growth
22 45B	No Growth	62 51B	No Growth	102 24B	No Growth
23 45B	No Growth	63 51B	No Growth	103 24B	No Growth
24 45B	No Growth	64 51B	No Growth	104 24B	No Growth
25 45B	No Growth	65 51B	No Growth	105 24B	No Growth
26 45B	No Growth	66 51B	No Growth	106 24B	No Growth
27 45B	No Growth	67 51B	No Growth	107 24B	No Growth
28 45B	No Growth	68 51B	No Growth	108 24B	No Growth
29 45B	No Growth	69 51B	No Growth	109 24B	No Growth
30 45B	No Growth	70 51B	No Growth	110 24B	No Growth

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Product Sterility Test
 Page 5

TABLE 2. Results
 Thioglycollate Results

UNIT NUMBER	RESULTS	UNIT NUMBER	RESULTS	UNIT NUMBER	RESULTS
11 45A	No Growth	51 51A	No Growth	91 24A	No Growth
12 45A	No Growth	52 51A	No Growth	92 24A	No Growth
13 45A	No Growth	53 51A	No Growth	93 24A	No Growth
14 45A	No Growth	54 51A	No Growth	94 24A	No Growth
15 45A	No Growth	55 51A	No Growth	95 24A	No Growth
16 45A	No Growth	56 51A	No Growth	96 24A	No Growth
17 45A	No Growth	57 51A	No Growth	97 24A	No Growth
18 45A	No Growth	58 51A	No Growth	98 24A	No Growth
19 45A	No Growth	59 51A	No Growth	99 24A	No Growth
20 45A	No Growth	60 51A	No Growth	100 24A	No Growth
31 45B	No Growth	71 51B	No Growth	111 24B	No Growth
32 45B	No Growth	72 51B	No Growth	112 24B	No Growth
33 45B	No Growth	73 51B	No Growth	113 24B	No Growth
34 45B	No Growth	74 51B	No Growth	114 24B	No Growth
35 45B	No Growth	75 51B	No Growth	115 24B	No Growth
36 45B	No Growth	76 51B	No Growth	116 24B	No Growth
37 45B	No Growth	77 51B	No Growth	117 24B	No Growth
38 45B	No Growth	78 51B	No Growth	118 24B	No Growth
39 45B	No Growth	79 51B	No Growth	119 24B	No Growth
40 45B	No Growth	80 51B	No Growth	120 24 B	No Growth

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Product Sterility Test

Page 6

REFERENCES:

United States Pharmacopeia & National Formulary. Current revision. (and supplements) <71> Sterility Test. United States Pharmacopeial Convention, Inc., Rockville, MD.

PIC/SPI012-1. Current revision. Recommendation on Sterility Testing. Pharmaceutical Inspection Convention. Pharmaceutical Inspection Co-Operation Scheme. Geneva, Switzerland.

Convention on the Elaboration of a European Pharmacopoeia. Current revision. <2.6.1> Sterility. European Department for Quality of Medicines, Strasbourg, France (as supplemented).

The Society of Japanese Pharmacopoeia. Current revision. <JP XIV. 54.> Sterility Test. The Research and Development Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare. Tokyo, Japan.

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Information

Product Sterility Test

Page 7

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FINAL REPORT
BACTERIOSTASIS AND FUNGISTASIS
PROCEDURE NO. SOP/STR/006I.2
LABORATORY NO. 231313

PREPARED FOR:

LAUREN CRAWFORD
ADVANCED MEDICAL OPTICS, INC.
1700 EAST ST. ANDREWS PLACE
SANTA ANA, CA 92705

SUBMITTED BY:

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BACTERIOSTASIS AND FUNGISTASIS

LABORATORY NUMBER: 231313
 PROCEDURE NUMBER: SOP/STR/006I.2
 SAMPLE SOURCE: Advanced Medical Optics, Inc.
 SAMPLE IDENTIFICATION: 9464X (Formulation Number) Project Gemini

(b) (4)

DEVIATIONS: P.O. #Lauren Crawford
 DATA ARCHIVE LOCATION: None
 TYPE OF TEST: Sequentially by lab number
 TEST MEDIA CONTAINER VOLUME: Method II: Direct Transfer
 SAMPLE RECEIVED DATE: 180 mL, 340 mL
 LAB PHASE START DATE: 18 Mar 2003
 LAB PHASE COMPLETION DATE: 23 Mar 2003
 REPORT ISSUE DATE: 06 May 2003
 TOTAL NUMBER OF PAGES: 07 May 2003
 6

REFERENCES:

United States Pharmacopeia & National Formulary. Current revision. United States Pharmacopeial Convention, Inc., Rockville, MD.

Convention on the Elaboration of a European Pharmacopoeia. Current revision. European Department for Quality of Medicines, Strasbourg, France.

The Society of Japanese Pharmacopoeia, Current revision. The Research and Development Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare. Tokyo, Japan.

British Pharmacopoeia (BP), Current revision. The Stationary Office Limited, London, England.

ACCEPTANCE CRITERIA:

As stated in USP, the method is valid for conducting the sterility test if the growth of each test organism in the test containers is visually comparable to the growth in the positive control.

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Advanced Medical Optics, Inc.

Bacteriostasis and Fungistasis

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Page 3

STATEMENT OF UNCERTAINTY:

The ability to detect growth of organisms if present. This is demonstrated by inoculating each lot of media with less than 100 organisms and showing growth.

PROCEDURE:

Bottles of soybean casein digest broth (SCDB) and fluid thioglycollate broth (THIO) containing the test product were inoculated with less than 100 organisms. The SCDB bottles were inoculated with *Bacillus subtilis*, *Aspergillus niger*, and *Candida albicans* then incubated at 20-25°C for a maximum of 7 days. The THIO bottles were inoculated with *Bacillus subtilis*, *Micrococcus luteus*, and *Clostridium sporogenes* then incubated at 30-35°C for a maximum of 7 days. Bottles were checked for growth after 3 days (approximately 72 hours), and at the end of incubation. Positive controls (containers of media without test product) were also inoculated and incubated as described above.

A re-analysis of *Aspergillus niger* was performed by increasing the media volume to 340 mL, using the same procedure as above.

RESULTS:

Growth in the bottles containing test product was compared to the positive controls. The initial results are summarized in Table 1. The re-analysis results are summarized in Table 2.

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Bacteriostasis and Fungistasis

Page 4

TABLE 1. Initial Results

ORGANISM	AVERAGE NUMBER OF ORGANISMS INOCULATED	GROWTH			
		THIOGLYCOLLATE		SOYBEAN BROTH	
		TEST	CONTROL	TEST	CONTROL
<i>B. subtilis</i>	43	N/A	N/A	[+]	[+]
<i>A. niger</i>	33	N/A	N/A	[0]	[+]
<i>C. albicans</i>	81	N/A	N/A	[+]	[+]
<i>B. subtilis</i>	43	[+]	[+]	N/A	N/A
<i>M. luteus</i>	40	[+]	[+]	N/A	N/A
<i>C. sporogenes</i>	61	[+]	[+]	N/A	N/A

"+" = Substantial Growth

"0" = Insufficient Growth

CONCLUSION: Is test article bacteriostatic/fungistatic?

YES NO

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Bacteriostasis and Fungistasis

Page 5

TABLE 2. Re-analysis Results

ORGANISM	AVERAGE NUMBER OF ORGANISMS INOCULATED	GROWTH	
		SOYBEAN BROTH	
		TEST	CONTROL
<i>A. niger</i>	53	[+]	[+]

"+" = Substantial Growth

"0" = Insufficient Growth

CONCLUSION: Is test article bacteriostatic/fungistatic?

[] YES [X] NO

Note: The re-analysis was performed by increasing the media volume to 340 mL. Sterility testing must be performed with a minimum of 340 mL.

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Bacteriostasis and Fungistasis
Page 6

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Refresh Contacts™

Contact Lens Comfort Drops

For use with soft and rigid gas permeable* (RGP) contact lenses.

For lasting comfort.

REFRESH CONTACTS™ Contact Lens Comfort Drops provides moisturizing relief from dryness and irritation associated with lens wear. The unique formula contains a long-lasting lubricant that actually helps your eyes retain moisture, creating a cushion of comfort and protection. **REFRESH CONTACTS™** may be used with soft and RGP (silicone acrylate and fluorosilicone acrylate) contact lenses. Safe to use as often as needed. For added comfort, place a drop in lenses prior to insertion.



DIRECTIONS: TO LUBRICATE AND REWET LENSES DURING THE DAY:

- With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT:

- Place 1 or 2 drops of **REFRESH CONTACTS™** Contact Lens Comfort Drops on each contact lens before application.

CONTENTS: Sterile, isotonic, buffered, preserved solution containing carboxymethylcellulose sodium, sodium chloride, boric acid, sodium borate decahydrate, potassium chloride, calcium chloride, magnesium chloride, purified water, and is preserved with PURITE® (stabilized oxchloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients.

If you are allergic to any ingredient in this product. **DO NOT USE.**

PRECAUTIONS: Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

WARNING: SEE PACKAGE INSERT FOR DIRECTIONS AND IMPORTANT SAFETY INFORMATION.

LENSES: REFRESH CONTACTS™ Contact Lens Comfort Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP)* contact lenses.

*Silicone acrylate and fluorosilicone acrylate rigid gas permeable lenses are recommended for use with **REFRESH CONTACTS™**. Consult your eye care practitioner to identify the lens you wear.

REFRESH CONTACTS™ Contact Lens Comfort Drops is used to lubricate and rewet soft and rigid gas permeable (RGP)* contact lenses as well as to cushion lenses prior to application.

US Pat. 5,424,078; 5,735,165; 5,858,346; 6,024,954.

Questions or Comments
 ☎ 1-800-377-7790
 8 A.M. - 5 P.M. Pacific Time
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7	1	7	1	7
8	2	8	2	8
9	3	9	3	9
10	4	10	4	10
11	5	11	5	11
12	6	12	6	12

011681

LOT/EXP.:

40364



USE ONLY IF IMPRINTED OVERWRAP ON BOTTLE IS INTACT.
CONTENTS: Sterile, isotonic, buffered, preserved solution containing carboxymethylcellulose sodium, sodium chloride, boric acid, sodium borate decahydrate, potassium chloride, calcium chloride, magnesium chloride, purified water, and is preserved with PURITE® (stabilized oxchloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients. If you are allergic to any ingredient in this product, **DO NOT USE.**
PRECAUTIONS: Store at room temperature. For in-eye use only. Do not use in the lens case. Use before the expiration date marked on the bottle and carton.
*** SEE PACKAGE INSERT FOR DIRECTIONS AND IMPORTANT SAFETY INFORMATION.**
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Lot No: 20609
Exp. Date: APR 04

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ALLERGAN



**REFRESH CONTACTS™
Contact Lens Comfort Drops**

For use with soft (hydrophilic) contact lenses and for use with rigid gas permeable (RGP) contact lenses*.



DESCRIPTION:

REFRESH CONTACTS™ Contact Lens Comfort Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes carboxymethylcellulose sodium, sodium chloride, boric acid, sodium borate decahydrate, potassium chloride, calcium chloride, magnesium chloride, purified water and is preserved with PURITE® (stabilized oxychloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients.

ACTIONS:

REFRESH CONTACTS™ has been formulated for use with both soft and rigid gas permeable (RGP)* contact lenses to rewet lenses before insertion and lubricate lenses during wear to moisten and reduce lens friction against the cornea. It also relieves minor irritation, discomfort, dryness, blurring and itchiness, which may occur while wearing your lenses.

INDICATIONS:

Use REFRESH CONTACTS™ Contact Lens Comfort Drops to lubricate and rewet soft and rigid gas permeable (RGP)* contact lenses, to help relieve dryness, discomfort and irritation that may be associated with lens wear and to cushion lenses by placing a drop on the lens prior to application on the eye.

CONTRAINDICATIONS:

If you are allergic to any ingredient in REFRESH CONTACTS™, do not use this product.

WARNINGS:

PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN SERIOUS INJURY TO THE EYE. It is essential that you 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 that the risk of serious adverse reactions is increased when these lenses are worn overnight.

Extended wear lenses should be regularly removed for cleaning and disinfecting 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 disinfecting or for disposal and replacement.

Studies have also shown that smokers had a higher incidence of adverse reactions.

It is recommended that contact lens wearers see their eye care practitioner twice each year or if directed, more frequently.

To avoid contamination, do not touch the dropper tip of the bottle to any surface. Replace cap after using.

PRECAUTIONS:

Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

ADVERSE REACTIONS (POSSIBLE PROBLEMS) AND WHAT TO DO:

The following may occur:

- Eyes stinging, burning or itching
- Excessive watering (tearing) of the eyes
- Unusual eye secretions
- Redness of the eyes
- Reduced sharpness of vision (visual acuity)
- Blurred vision
- Sensitivity to light (photophobia)
- Dry eyes

If you notice any of the above, IMMEDIATELY remove and examine your lenses. If a lens appears to be damaged, do not reapply; consult your eye care practitioner. If the problem stops and the lenses appear to be undamaged, follow the "Directions" below, before reapplying the lens.

If the problem continues IMMEDIATELY remove your lenses; discontinue use of all lens care products that contact the eye, and consult your eye care practitioner.

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

DIRECTIONS:

TO LUBRICATE AND REWET LENSES DURING THE DAY:

With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT: Place 1 or 2 drops of REFRESH CONTACTS™ Contact Lens Comfort Drops on each side of each lens before application.

HOW SUPPLIED:

REFRESH CONTACTS™ is supplied in sterile 0.1 fl. oz. (3mL) and 0.4 fl. oz. (12mL) plastic bottles. The bottles are marked with the lot number and expiration date.

LENSES:

REFRESH CONTACTS™ Contact Lens Comfort Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP)* contact lenses.

* Silicone acrylate and fluorosilicone acrylate rigid gas permeable lenses are recommended for use with REFRESH CONTACTS™. Consult your eye care practitioner to identify the lens you wear.

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Revised: August 2001

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 9/25/03

From: DMC (HFZ-401)

Subject: Premarket Notification Number(s): ~~K0302~~ K032030/A2

To: Division Director: OP/DOED

The attached information has been received by the 510(k) DMC on the above referenced 510(k) submission(s). Since a final decision has been rendered, this record is officially closed.

Please review the attached document and return it to the DMC, with one of the statements checked below.

Information does not change the status of the 510(k); no other action required by the DMC; please add to image file. (Prepare K-25) THIS DOES NOT APPLY TO TRANSFER OF OWNERSHIP. PLEASE BRING ANY TRANSFER OF OWNERSHIP TO POS.

Additional information requires a new 510(k); however, the information submitted is incomplete; (Notify company to submit a new 510(k); [Prepare the K30 Letter on the LAN])

Additional information requires a new 510(k); please process [This information will be made into a new 510(k)]

No response necessary (e.g., hard copy of fax for the truthful and accuracy statement, 510(k) statement, change of address, phone number, or fax number).

CLIA CATEGORIZATION refers to laboratory test system devices reviewed by the Division of Clinical Laboratory Devices (HFZ-440)

Information requires a CLIA CATEGORIZATION; the complexity may remain the same as the original 510(k) or may change as a result of the additional information (Prepare a CAT letter)

Additional information requires a CLIA CATEGORIZATION; however, the information submitted is incomplete; (call or fax firm)

No response necessary

This information should be returned to the DMC within 10 working days from the date of this memorandum.

Reviewed by: J Savola
Date: 2/28/05

Draft #2 : 9/8/99

Draft #3: 1/3/00

DMC
2/28

K032030/A2



September 24, 2003

510k Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

2003 SEP 25 A 9:24
FDA/CDRH/ODT/PHO

**RE: K032030 – blink™ CL Lubricant Eye Drops
15 September 2003 FDA Request for Labeling Changes**

TO WHOM IT MAY CONCERN,

Advanced Medical Optics (AMO) hereby provides duplicate copies of a submission to the above-referenced 510k. This is being sent in response to a request for three (3) labeling changes from Daniel W.C. Brown, Ph.D. of FDA (facsimile dated 15 September 2003) and a teleconference with James F. Saviola, O.D. and Gene N. Hilmantel, O.D.

Number 1

We recommend that the following should be added to the Warnings section of the labeling: "To avoid contaminating your solution, DO NOT transfer to other bottles or containers."

AMO has revised the Warnings section of the labeling by combining the above statement with an already existing statement regarding contamination. The new Warning reads as follows:

"To avoid contamination do not touch dropper tip to any surface and DO NOT transfer contents to any other bottle or container."

Number 2

The bottle label does not contain any directions. Please modify the label to include Directions.

AMO has added the following to the bottle label:

"DIRECTIONS: Apply 1 to 2 drops to each eye as needed. Blink several times."

Number 3

At several places in the Package Insert, Bottle label and Carton label, the statement is made that the product is, "For use with any contact lens." Please either remove the "any" statement from all labeling, or provide data showing the clinical compatibility with every currently marketed contact lens brand.

AMO has replaced this statement throughout all the labeling with the following:

SK 41

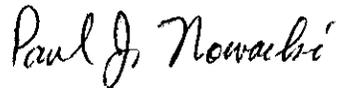
“For use with soft and RGP contact lenses.”

A copy of the labeling incorporating the changes discussed above is enclosed.

We ask that the existence of this 510k be kept confidential since:

- The intent to market the product covered by this 510k has been kept confidential. No disclosures have been made to persons other than those bound by secrecy agreements.
- Precautions have been taken to preserve confidentiality.
- FDA will be immediately notified of any disclosure of intent to market.

Sincerely,



Paul J. Nowacki
Manager
Worldwide Regulatory Affairs
And Medical Compliance

Phone: 714-247-8601
Facsimile: 714-247-8677
E-mail: paul.nowacki@amo-inc.com

blink™
CL Lubricant Eye Drops

PACKAGE INSERT

blink™ CL Lubricant Eye Drops

For Soft and RGP Contact Lenses

DESCRIPTION:

blink™ CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients.

ACTIONS:

blink™ CL Lubricant Eye Drops has been formulated for use with both soft and rigid gas permeable (RGP) contact lenses; to rewet lenses before insertion and lubricate lenses during wear and to moisturize and refresh tired, dry eyes. It also relieves minor irritation, discomfort, dryness, blurring and itchiness, which may occur while wearing your lenses.

INDICATIONS:

Use **blink™** CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses, to help relieve dryness, discomfort and irritation that may be associated with lens wear and to cushion lenses by placing a drop on the lens prior to application on the eye.

CONTRAINDICATIONS:

If you are allergic to any ingredient in **blink™** CL Lubricant Eye Drops, do not use this product.

WARNINGS:

PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS

COULD RESULT IN SERIOUS INJURY TO THE EYE. It is essential that you 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 that the risk of serious adverse reactions is increased when these lenses are worn overnight.

Extended wear lenses should be regularly removed for cleaning and disinfecting 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 disinfecting or for disposal and replacement.

Studies have also shown that smokers had a higher incidence of adverse reactions.

It is recommended that contact lens wearers see their eye care practitioner twice each year or if directed, more frequently.

To avoid contamination, do not touch the dropper tip of the bottle to any surface and DO NOT transfer contents to any other bottle or container. Replace cap after using.

PRECAUTIONS:

Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

ADVERSE REACTIONS (POSSIBLE PROBLEMS) AND WHAT TO DO:

The following may occur:

- Eyes stinging, burning or itching
- Excessive watering (tearing) of the eyes
- Unusual eye secretions
- Redness of the eyes
- Reduced sharpness of vision (visual acuity)
- Blurred vision
- Sensitivity to light (photophobia)
- Dry eyes

If you notice any of the above, **IMMEDIATELY** remove and examine your lenses.

If a lens appears to be damaged, do not reapply; consult your eye care practitioner. If the problem stops and the lenses appear to be undamaged, follow the “Directions” below, before reapplying the lens.

If the problem continues **IMMEDIATELY** remove your lenses, discontinue use of all lens care products that contact the eye, and consult your eye care practitioner.

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

DIRECTIONS:

TO LUBRICATE AND REWET LENSES DURING THE DAY:

With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT: Place 1 or 2 drops of **blink™** CL Lubricant Eye Drops on each side of each lens before application.

HOW SUPPLIED:

blink™ CL Lubricant Eye Drops is supplied in sterile 0.08 fl oz (2.5mL) and .03 fl oz (10mL) plastic bottles. The bottles are marked with the lot number and expiration date.

LENSES:

blink™ CL Lubricant Eye Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP) contact lenses.

September 2003

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SINGLE LABEL

Front:

(logo) AMO

blink™ CL Lubricant Eye Drops
For Soft and RGP Lenses

USE ONLY IF BREAKSEAL ON BOTTLE CAP IS INTACT

10 mL (0.3 fl oz) STERILE

Back:

CONTENTS: **blink™** CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. If you are allergic to any ingredient in this product, **DO NOT USE.** **DIRECTIONS:** Apply 1 to 2 drops to each eye as needed. Blink several times. **PRECAUTIONS:** Store at room temperature. Use before the expiration date marked on the bottle and carton.

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Lot No.:

Exp. Date:

UNIT CARTON

Front Panel

(logo) AMO

blink™ CL Lubricant Eye Drops

For Soft and RGP Lenses

10mL (0.3 fl oz)

STERILE

Back Panel

blink™ CL Lubricant Eye Drops

For Soft and RGP Lenses.

DIRECTIONS:

TO LUBRICATE AND REWET LENSES DURING THE DAY:

With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT: Place 1 or 2 drops of **blink™** CL Lubricant Eye Drops on each side of each lens before application.

Top Flap

blink™ CL Lubricant Eye Drops

10mL (0.3 fl oz) STERILE

USE ONLY IF BREAKSEAL ON BOTTLE CAP IS INTACT.

Side Panel

blink™ CL Lubricant Eye Drops is used to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses as well as to cushion lenses prior to application. Questions or Comments? 1-800-347-5005

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Side Panel

CONTENTS: **blink™** CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%.

If you are allergic to any ingredient in this product, DO NOT USE.

PRECAUTIONS: Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

WARNING: SEE PACKAGE INSERT FOR ADDITIONAL AND IMPORTANT SAFETY INFORMATION.

LENSES:

blink™ CL Lubricant Eye Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP) contact lenses.

Lot#

Part #

Expiration Date

XXXXX



SEP 25 2003

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Advanced Medical Optics, Inc
c/o Paul J. Nowacki
1700 E. St. Andrew Place
P.O. Box 25162
Santa Ana, CA 92799

Re: K032030
Trade/Device Name: *blink*TM CL Lubricant Eye Drops
Regulation Number: 21 CFR 886.5928; 21 CFR 886.5918
Regulation Name: Soft (hydrophilic) contact lens care products;
Rigid gas permeable contact lens care products
Regulatory Class: Class II
Product Code: LPN; MRC
Dated: June 30, 2003
Received: July 1, 2003

Dear Mr. Nowacki:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Page 2 - Paul J. Nowacki

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (301) 594-4613. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address <http://www.fda.gov/cdrh/dsma/dsmamain.html>

Sincerely yours,



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

Enclosure

Page 1 of 1

510(k) NUMBER:
(IF KNOWN): K032030

DEVICE NAME: blink™ CL Lubricant Eye Drops

INDICATIONS FOR USE:

- Use *blink*™ CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses; to help relieve dryness, irritation and discomfort that may be associated with lens wear; and to cushion lenses by placing a drop on the lens prior to application on the eye.

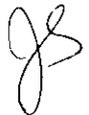
(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____
(Per 21 CFR 801.109)

OR

Over-The-Counter-Use X
(Optional Format 1-2-96)



Donald W. C. Brown

(Division Sign-Off)
Division of Ophthalmic Ear,
Nose and Throat Devices

510(k) Number K032030

1 007 3

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

July 02, 2003

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

ADVANCED MEDICAL OPTICS, INC.
1700 E. ST. ANDREW PLACE
P.O. BOX 25162
SANTA ANA, CA 92799
ATTN: PAUL J. NOWACKI

510(k) Number: K032030
Received: 01-JUL-2003
Product: BLINK CL LUBRICANT
EYE DROPS

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

The Act, as amended by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA)(Public Law 107-250), authorizes FDA to collect user fees for premarket notification submissions. (For more information on MDUFMA, you may refer to our website at <http://www.fda.gov/oc/mdufma>).

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC)(HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review". Please refer to this guidance for information on current fax and e-mail practices at www.fda.gov/cdrh/ode/a02-01.html.

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMICA. If you have other procedural or policy questions, or want information on how to check on the status of your submission, please contact DSMICA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address <http://www.fda.gov/cdrh/dsmamain.html> or me at (301)594-1190.

Sincerely yours,

Marjorie Shulman
Supervisory Consumer Safety Officer
Office of Device Evaluation
Center for Devices and Radiological Health

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

July 01, 2003

ADVANCED MEDICAL OPTICS, INC.
1700 E. ST. ANDREW PLACE
P.O. BOX 25162
SANTA ANA, CA 92799
ATTN: PAUL J. NOWACKI

510(k) Number: K032030
Received: 01-JUL-2003
Product: BLINK CL LUBRICANT
User Fee ID Number: 7109

The Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

The Act, as amended by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (Public Law 107-250), specifies that a submission shall be considered incomplete and shall not be accepted for filing until fees have been paid (Section 738(f)). Our records indicate that you have not submitted the user fee payment information and therefore your 510(k) cannot be filed and has been placed on hold. The payment information we need in order to begin the review of your 510(k) includes, the user fees cover sheet with the payment ID faxed to the Office of Financial Management at (301) 827-9213 and a check mailed to:

By Regular Mail

By Private Courier (e.g., Fed Ex, UPS, etc.)

Food and Drug Administration
P.O. Box 956733
St. Louis, MO 63195-6733.

U.S. Bank
956733
1005 Convention Plaza
St. Louis, MO 63101
(314) 418-4983

The check should be made out to the Food and Drug Administration referencing the payment identification number, and a copy of the User Fee Cover sheet should be included with the check. A copy of the Medical Device User Fee Cover Sheet should also be faxed to CDRH at (301) 594-2977 referencing the 510(k) number if you have not already sent it in with your 510(k) submission. After the FDA has been notified of the receipt of your user fee payment, your 510(k) will be filed and the review will begin. If payment has not been received within 30 days, your 510(k) will be deleted from the system. Additional information on user fees and how to submit your user fee payment may be found at <http://www.fda.gov/oc/mdufma>.

Please note that since your 510(k) has not been reviewed, additional information may be required during the review process and the file may be placed on hold once again. If you are unsure as to whether or not you need to file an application with FDA or what type of application to file, you should first telephone the Division of Small Manufacturers, International and Consumer Assistance (DSMICA), for guidance at (301)443-6597 or its toll-free number (800)638-2041, or contact them at their Internet address <http://www.fda.gov/cdrh/dsmamain.html>, or you may submit a 513(g) request to the Document Mail Center at the address above. If you have any questions concerning the contents of this letter, you may contact me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Office of Device Evaluation
Center for Devices and
Radiological Health

K032030

TRADE SECRET AND CONFIDENTIAL

2016-09-14 11:00
FOIA STATUS

With the exception of the 510(k) Summary (Section 1), the contents of this application are trade secret and confidential. We ask that the existence of this 510(k) be kept confidential for at least 90 days since:

- **The intent to market the product covered by this 510(k) has been kept confidential. No disclosures have been made to persons other than those bound by secrecy agreements**
- **Precautions have been taken to preserve confidentiality**
- **FDA will be immediately notified of any disclosure of intent to market**

SK 15

OP
H
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MEDICAL DEVICE USER FEE COVER SHEET

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION MEDICAL DEVICE USER FEE COVER SHEET	PAYMENT IDENTIFICATION NUMBER: (b)(4) Confidential and Proprietary Information Write the Payment Identification Number on your check.
---	--

See Instructions Before Completing This Cover Sheet

A completed cover sheet must accompany each original premarket application or supplement listed in Box 3 of this cover sheet. Other premarket application types do not require the use of this cover sheet; see list in the instructions. Payment instructions and fee rates can be found at the following website: <http://www.fda.gov/oc/mdufma>. The following three actions must be taken to properly submit your premarket application and fee payment:

1. FAX a copy of this completed cover sheet to the Food and Drug Administration at (301) 827-9213 before payment is sent.
2. Include a copy of this completed cover sheet with the check made payable to the Food and Drug Administration and mail them to the Food and Drug Administration, P.O. Box 956733, St. Louis, MO 63195-6733. *(Note: In no case should payment be submitted with the premarket application.)* Also remember that the Payment Identification Number must be written on the check. If you prefer to send a check by a courier, the courier may deliver the check and cover sheet to: US Bank, 956733, 1005 Convention Plaza, St. Louis, MO 63101. *(Note: This address is for courier delivery only. Contact the US Bank at 314-418-4821 if you have any questions concerning courier delivery.)*
3. Include a copy of this completed cover sheet in volume one of the premarket application when submitting to the Food and Drug Administration at either the CBER or CDRH Document Mail Center.

1. COMPANY NAME AND ADDRESS (Include name, street address, city, state, country, and post office code) ADVANCED MEDICAL OPTICS, INC. 1700 E. ST. ANDREW PLACE P.O. BOX 25162 SANTA ANA, CA 92799-5162 US	2. CONTACT NAME PAUL J. NOWACKI 2.1 E-MAIL ADDRESS paul.nowacki@amo-inc.com 2.2 TELEPHONE NUMBER (Include area code) 714-247-8601 2.3 FACSIMILE (FAX) NUMBER (Include area code) 714-247-8677
1.1 EMPLOYER IDENTIFICATION NUMBER (EIN) 330986820	

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: <http://www.fda.gov/oc/mdufma>)

Select an application type: <input checked="" type="checkbox"/> Premarket notification (510(k)); except for third party reviews <input type="checkbox"/> Biologic License Application (BLA) <input type="checkbox"/> Premarket Approval Application (PMA) <input type="checkbox"/> Modular PMA <input type="checkbox"/> Product Development Protocol (PDP) <input type="checkbox"/> Premarket Report (PMR)	3.1 Select one of the types below: <input checked="" type="checkbox"/> Original Application Supplement Types: <input type="checkbox"/> Efficacy (BLA) <input type="checkbox"/> Panel Track (PMA, PMR, PDP) <input type="checkbox"/> Real-Time (PMA, PMR, PDP) <input type="checkbox"/> 180-day (PMA, PMR, PDP)
--	--

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status.)

YES, I meet the small business criteria and have submitted the required qualifying documents to FDA
 NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number:

5. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.

<input type="checkbox"/> This application is the first PMA submitted by a qualified small business, including any affiliates, parents, and partner firms <input type="checkbox"/> This biologic application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only	<input type="checkbox"/> The sole purpose of the application is to support conditions of use for a pediatric population <input type="checkbox"/> The application is submitted by a state or federal government entity for a device that is not to be distributed commercially
--	--

6. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).)

YES NO

7. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

(b)(4) Confidential and Proprietary

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CDRH SUBMISSION COVER SHEET

***blink*[™] CL Lubricant Eye Drops**

CDRH SUBMISSION COVER SHEET				
Date of submission: June 30, 2003			FDA Document Number:	
Section A Type of Submission				
PMA <input type="checkbox"/> Original submission <input type="checkbox"/> Modular submission <input type="checkbox"/> Amendment <input type="checkbox"/> Report <input type="checkbox"/> Report Amendment	PMA Supplement <input type="checkbox"/> Regular <input type="checkbox"/> Special <input type="checkbox"/> Panel Track <input type="checkbox"/> 30-day Supplement <input type="checkbox"/> 30-day Notice <input type="checkbox"/> 135-day Supplement <input type="checkbox"/> Real-time Review <input type="checkbox"/> Amendment to PMA Supplement	PDP <input type="checkbox"/> Presubmission summary <input type="checkbox"/> Original PDP <input type="checkbox"/> Notice of intent to start clinical trials <input type="checkbox"/> Intention to submit Notice of Completion <input type="checkbox"/> Amendment to PDP <input type="checkbox"/> Report	510(k) <input checked="" type="checkbox"/> Original submission <input checked="" type="checkbox"/> Traditional <input type="checkbox"/> Special <input type="checkbox"/> Abbreviated <input type="checkbox"/> Additional information <input type="checkbox"/> Traditional <input type="checkbox"/> Special <input type="checkbox"/> Abbreviated	Meeting <input type="checkbox"/> Pre-IDE meeting <input type="checkbox"/> Pre-PMA meeting <input type="checkbox"/> Pre-PDP meeting <input type="checkbox"/> 180-day meeting <input type="checkbox"/> Other (specify):
IDE <input type="checkbox"/> Original submission <input type="checkbox"/> Amendment <input type="checkbox"/> Supplement	Humanitarian Device Exemption <input type="checkbox"/> Original submission <input type="checkbox"/> Amendment <input type="checkbox"/> Supplement <input type="checkbox"/> Report	Class II Exemption <input type="checkbox"/> Original submission <input type="checkbox"/> Additional information	Evaluation of Automatic Class III Designation <input type="checkbox"/> Original submission <input type="checkbox"/> Additional information	Other Submission Describe submission:
Section B Applicant or Sponsor				
Company/Institution name: Advanced Medical Optics, Inc.			Establishment registration number: 2020664	
Division name (if applicable): N/A			Phone number (include area code): (714) 247-8601	
Street address: 1700 E. St. Andrew Place, P.O. Box 25162			FAX number (include area code): (714) 247-8677	
City: Santa Ana	State/Province: California 92799-5162	Country: USA		
Contact name: Paul J. Nowacki				
Contact title: Manager, Regulatory Affairs			Contact e-mail address: paul.nowacki@amo-inc.com	
Section C Submission correspondent (if different from above)				
Company/Institution name:			Establishment registration number:	
Division name (if applicable):			Phone number (include area code):	
Street address:			FAX number (include area code):	
City:	State/Province:	Country:		
Contact name:				
Contact title:			Contact e-mail address:	

Section D1 Reason for Submission - PMA, PDP, or IDE		
<input type="checkbox"/> New device <input type="checkbox"/> Withdrawal <input type="checkbox"/> Additional or expanded indications <input type="checkbox"/> Licensing agreement	<input type="checkbox"/> Change in design, component, or specification: <input type="checkbox"/> Software <input type="checkbox"/> Color Additive <input type="checkbox"/> Material <input type="checkbox"/> Specifications <input type="checkbox"/> Other (specify below)	<input type="checkbox"/> Location change: <input type="checkbox"/> Manufacturer <input type="checkbox"/> Sterilizer <input type="checkbox"/> Packager <input type="checkbox"/> Distributor
<input type="checkbox"/> Process change: <input type="checkbox"/> Manufacturing <input type="checkbox"/> Sterilization <input type="checkbox"/> Packaging <input type="checkbox"/> Other (specify below)	<input type="checkbox"/> Labeling change: <input type="checkbox"/> Indications <input type="checkbox"/> Instructions <input type="checkbox"/> Performance characteristics <input type="checkbox"/> Shelf life <input type="checkbox"/> Trade name <input type="checkbox"/> Other (specify below)	<input type="checkbox"/> Report submissions: <input type="checkbox"/> Annual or periodic <input type="checkbox"/> Post-approval study <input type="checkbox"/> Adverse reaction <input type="checkbox"/> Device defect <input type="checkbox"/> Amendment
<input type="checkbox"/> Response to FDA correspondence: <input type="checkbox"/> Request for applicant hold <input type="checkbox"/> Request for removal of applicant hold <input type="checkbox"/> Request for extension <input type="checkbox"/> Request to remove or add manufacturing site		<input type="checkbox"/> Change in ownership <input type="checkbox"/> Change in correspondent
<input type="checkbox"/> Other reason (specify):		
Section D2 Reason for Submission - IDE		
<input type="checkbox"/> New device <input type="checkbox"/> Addition of institution <input type="checkbox"/> Expansion/extension of study <input type="checkbox"/> IRB certification <input type="checkbox"/> Request hearing <input type="checkbox"/> Request waiver <input type="checkbox"/> Termination of study <input type="checkbox"/> Withdrawal of application <input type="checkbox"/> Unanticipated adverse effect <input type="checkbox"/> Notification of emergency use <input type="checkbox"/> Compassionate use request <input type="checkbox"/> Treatment IDE <input type="checkbox"/> Continuing availability request	<input type="checkbox"/> Change in: <input type="checkbox"/> Correspondent <input type="checkbox"/> Design <input type="checkbox"/> Informed consent <input type="checkbox"/> Manufacturer <input type="checkbox"/> Manufacturing process <input type="checkbox"/> Protocol - feasibility <input type="checkbox"/> Protocol - other <input type="checkbox"/> Sponsor	<input type="checkbox"/> Response to FDA letter concerning: <input type="checkbox"/> Conditional approval <input type="checkbox"/> Deemed approved <input type="checkbox"/> Deficient final report <input type="checkbox"/> Deficient progress report <input type="checkbox"/> Deficient investigator report <input type="checkbox"/> Disapproval <input type="checkbox"/> Request extension of time to respond to FDA <input type="checkbox"/> Request meeting
	<input type="checkbox"/> Report Submission: <input type="checkbox"/> Current investigator <input type="checkbox"/> Annual progress <input type="checkbox"/> Site waiver limit reached <input type="checkbox"/> Final	
<input type="checkbox"/> Other reason (specify):		
Section D3 Reason for Submission - 510(k)		
<input checked="" type="checkbox"/> New device <input type="checkbox"/> Addition or expanded indications <input type="checkbox"/> Other reason (specify):	<input type="checkbox"/> Change in technology <input type="checkbox"/> Change in design	<input type="checkbox"/> Change in materials <input type="checkbox"/> Change in manufacturing process

Section E: Additional Information on 510(k) Submissions							
Product codes of devices to which substantial Equivalence is claimed:				Summary of, or statement concerning, safety and effectiveness data:			
1 86LPN	2 86MRC	3	4	<input checked="" type="checkbox"/> 510(k) summary attached <input type="checkbox"/> 510(k) statement			
5	6	7	8				
Information on devices to which substantial equivalence is claimed:							
510(k) Number		Trade or proprietary or model name		Manufacturer			
1 510(k) K992028		1 REFRESH® CONTACTS™ Lubricating & Rewetting Drops		1 Allergan, Inc.			
2 510(k) K013204		2 AQuify Lens Comfort Drops		2 CIBA Vision Corporation			
3 510(k) K994170		3 Hylashield® CL Lubricating Eye Drops		3 Biomatrix, Inc.			
4		4		4			
Section F: Product Information - Applicable to All Applications							
Common or usual or classification name: Accessories to Contact Lenses – Cleaning and Wetting Agents							
Trade or proprietary or model name				Model number			
1 <i>blink</i> ™ CL Lubricant Eye Drops				N/A			
2							
3							
4							
FDA document numbers of all prior related submissions (regardless of outcome):							
1	2	3	4	5	6	7	8
9	10	11	12	13	14	15	16
Data included in submission: <input checked="" type="checkbox"/> Laboratory testing <input checked="" type="checkbox"/> Animal trials <input checked="" type="checkbox"/> Human trials							
Section G: Product Classification - Applicable to All Applications							
Product code: 86LPN 86MRC		C.F.R. section 21 CFR §886.5928 21 CFR §886.5918 (Reclassified July 7, 1997)			Device class: <input type="checkbox"/> Class I <input checked="" type="checkbox"/> Class II <input type="checkbox"/> Class III <input type="checkbox"/> Unclassified		
Classification panel: Ophthalmic Device Panel							
Indications (from labeling): Use <i>blink</i> ™ CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable contact lenses; to help relieve dryness, discomfort and irritation that may be associated with lens wear; and to cushion lenses by placing a drop on the lens prior to application on the eye.							

	FDA Document Number:
--	----------------------

Section II Manufacturing/Packaging/Sterilization Sites Relating to Submission

<input checked="" type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA establishment registration number:	<input type="checkbox"/> Manufacturer <input checked="" type="checkbox"/> Contract manufacturer <input type="checkbox"/> Contract sterilizer <input type="checkbox"/> Repackager/relabeler
Company/Institution name: Patheon UK Limited		Establishment registration number:

(b)(4) Confidential and Proprietary Information



<input type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA establishment registration number:	<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract manufacturer <input type="checkbox"/> Contract sterilizer <input type="checkbox"/> Repackager/relabeler	
Company/Institution name:		Establishment registration number:	
Division name (if applicable):		Phone number (include area code):	
Street address:		Fax number (include area code):	
City:	State/Province:	Country:	ZIP/Postal Code:
Contact name:			
Contact title:		Contact e-mail address:	
<input type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA establishment registration number:	<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract manufacturer <input type="checkbox"/> Contract sterilizer <input type="checkbox"/> Repackager/relabeler	
Company/Institution name:		Establishment registration number:	
Division name (if applicable):		Phone number (include area code):	
Street address:		Fax number (include area code):	
City:	State/Province:	Country:	ZIP/Postal Code:
Contact name:			
Contact title:		Contact e-mail address:	

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PREMARKET NOTIFICATION 510(K)

CHECKLIST FOR ACCEPTANCE

**blink™ CL Lubricant Eye Drops
510(k) Premarket Notification**

Premarket Notification [510(k)] Checklist for Acceptance Decision

K _____ Date DMC Received _____

Device Trade Name: blink™ CL Lubricant Eye Drops

Reason for 510(k): New device

Division/Branch: Ophthalmic/VEDB

Administrative Reviewer Signature: _____ Date: _____

Supervisory Signature: _____ Date: _____

510(k) Element	Yes/ Present/ Omission Justified	No/ Inadequate/ Omitted	Page in 510(k) Submission Where Item is Located
I. Critical Elements:			
A. Is the product a device?	X		Section 1 510(k) Summary
B. Is the device exempt from 510(k) by regulation or policy?		X	Not Applicable
C. Is device subject to review by CDRH?	X		Not Applicable
D. (i) Are you aware that this device has been the subject of a previous NSE decision? (ii) If yes, does this new 510(k) address the NSE issue(s) (e.g., performance data)?		X	Not Applicable
E. (i) Are you aware of the submitter being the subject of an integrity investigation? If yes, consult the ODE Integrity Officer.		X	Not Applicable
(ii) Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N-0332, September 10, 1991.)		X	Not Applicable
F. Does the submission contain the information required under Sections 510(k), 513(f), and 513(i) of the Federal Food, Drug, and Cosmetic Act (Act) and Subpart E of Part 807 in Title 21 of the Code of Federal Regulations?:			
1. Device trade or proprietary name	X		Section 1 510(k) Summary
2. Device common or usual name or classification name	X		Section 1 510(k) Summary
3. Establishment registration number	X		CDRH Cover Sheet

**blink™ CL Lubricant Eye Drops
510(k) Premarket Notification**

510(k) Element	Yes/ Present/ Omission Justified	No/ Inadequate/ Omitted	Page in 510(k) Submission Where Item is Located
4. Class into which the device is classified under (21 CFR Parts 862 to 892)	X		Section 1 510(k) Summary
5. Classification Panel	X		Section 1 510(k) Summary
6. Action taken to comply with Section 514 of the Act		X	Not Applicable
7. Proposed labels, labeling, and advertisements (if applicable) that describe the device, its intended use, and directions for use (Blue Book Memo #G91-1)	X		Section 3 Draft Labeling
8. A 510(k) summary of safety and effectiveness or a 510(k) statement that safety and effectiveness information will be made available to any person upon request	X		Section 1 510(k) Summary
9. For class III devices only, a class III certification and a class III summary		X	Not Applicable
10. Photographs of the device		X	Not Applicable
11. Engineering drawings for the device with dimensions and tolerances		X	Not Applicable
12. The marketed device(s) to which equivalence is claimed including labeling and description of the device	X		Section 1 510(k) Summary
13. Statement of similarities and/or differences with marketed device(s)	X		Section 1 510(k) Summary
14. Data to show consequences and effects of a modified device(s)	X		Section 4 Nonclinical Section 5 Clinical
II. Additional Information that is necessary under 21 CFR 807.87(h):			
A. Submitter's name and address	X		Cover Letter
B. Contact person, telephone number and fax number	X		Cover Letter
C. Representative/Consultant if applicable		X	Not Applicable
D. Table of Contents with pagination	X		Tab: T of C
E. Address of manufacturing facility/facilities and, if appropriate, sterilization site(s)	X		CDRH Cover Sheet
III. Additional Information that may be necessary under 21 CFR 807.87			

ADVANCED MEDICAL OPTICS, INC. – CONFIDENTIAL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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**blink™ CL Lubricant Eye Drops
510(k) Premarket Notification**

510(k) Element	Yes/ Present/ Omission Justified	No/ Inadequate/ Omitted	Page in 510(k) Submission Where Item is Located
A. Comparison table of the new device to the marketed Device(s)	X		Section 2 General Manufacturing
B. Action taken to comply with voluntary standards		X	Not Applicable
C. Performance Data			
Marketed Device			
bench testing	X		Section 4 Chemistry
animal testing	X		Section 4 Toxicology
clinical data	X		Section 5 Clinical
New Device			
bench testing	X		Section 4 Chemistry/ Stability
animal testing	X		Section 4 Toxicology
clinical testing	X		Section 5 Clinical
D. Sterilization information	X		Section 2 Manufacturing
E. Software information		X	Not Applicable
F. Hardware information		X	Not Applicable
G. If this 510(k) is for a kit, has the kit certification statement been provided?		X	Not Applicable
H. Is this device subject to issues that have been addressed in specific guidance documents?	X		[510(k)] Guidance Doc. for Contact Lens Care Products, of May 1, 1997
I. Truthful and Accurate Statement	X		Follows Cover Letter
If yes, continue review with checklist from any appropriate guidance documents.			
If no, is 510(k) sufficiently complete to allow substantive review?			
I. Other (specify)			

**PREMARKET
NOTIFICATION
510(K)**

***blink*TM CL
Lubricant Eye Drops**



June 30, 2003

510k Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

RE: 510(k) Notification: *blink*™ CL Lubricant Eye Drops

TO WHOM IT MAY CONCERN:

Advanced Medical Optics (AMO) hereby provides duplicate copies of a 510(k), Premarket Notification, requesting a determination of substantial equivalence for the contact lens lubricating and rewetting drop, *blink*™ CL Lubricant Eye Drops. The product formulation contains active ingredients in the same or similar concentrations to other lubricating and rewetting drops currently on the market or cleared for commercial distribution in the U.S. No new ingredients for ophthalmic use have been used.

Testing for in-eye contact lens products has been conducted in accordance with US FDA's "Premarket Notification [510(k)] Guidance Document for Contact Lens Care Products". The test results are included in this 510(k) Notification.

Also included in this 510(k) Notification is the labeling for *blink*™ CL Lubricant Eye Drops. The labeling provides the intended use, which is comparable to the intended use indicated in predicate device labeling.

We ask that the existence of this 510(k) be kept confidential for at least 90 days since:

- The intent to market the product covered by this 510(k) has been kept confidential. No disclosures have been made to persons other than those bound by secrecy agreements
- Precautions have been taken to preserve confidentiality
- FDA will be immediately notified of any disclosure of intent to market

To the best of my knowledge, all data and information submitted in this premarket notification are truthful and accurate; no material fact has been omitted. An FDA Truthful and Accurate Statement form follows this cover letter. We therefore request a determination of substantial equivalence.

Sincerely,

Paul J. Nowacki
Manager
Regulatory Affairs

Phone: 714-247-8601
Fax: 714-247-8677
E-Mail: paul.nowacki@amo-inc.com

2003 JUL -1 A

PREMARKET NOTIFICATION TRUTHFUL AND ACCURATE STATEMENT

[As Required by 21 CFR 807.87(j)]

I certify that, in my capacity as Manager, Regulatory Affairs, of
Advanced Medical Optics, I believe to the best of my knowledge, that all
data and information submitted in this premarket notification are truthful
and accurate and that no material fact has been omitted.

Paul J. Nowacki
(Signature)

Paul J. Nowacki
(Typed Name)

30 June 03
(Date)

*(Premarket Notification [510(k)] Number)

*For a new submission, leave the 510(k) number blank.

Must be signed by a responsible person of the firm required to
submit the premarket notification [e.g., not a consultant for the
510(k) submitter].

Note: Throughout this 510(k) Notification and the study reports contained herein, *blink*[™] CL Lubricant Eye Drops may also be referred to as Purite® HA Rewetter, Purite/HA Rewetter, or *blink*[™] brand Contact Lens Rewetter Solution.

510(K) NOTIFICATION TABLE OF CONTENTS

VOLUME 1 OF 1

*blink*TM CL Lubricant Eye Drops

Section	Volume	Content	Page
1	1	510(k) Summary	N/A
2	1	General Manufacturing	1 001
3	1	Indications for Use Draft Labeling	1 006
4	1	Nonclinical Reports <ul style="list-style-type: none">• Chemistry• Stability• Toxicology	1 015 1 016 1 093 1 170
5	1	Clinical FDA Form 3454 Clinical Report	1 249 1 252 1 254



510(k) SUMMARY

*blink*TM CL Lubricant Eye Drops

This summary uses the format provided in 21 CFR 807.92:

- (a)(1) **Submitter:** Paul J. Nowacki
Manager
Regulatory Affairs
Advanced Medical Optics
1700 E. St. Andrew Place
Santa Ana, CA 92799-5162

Phone: (714) 247-8601
Fax: (714) 247-8677
EMail: paul.nowacki@amo-inc.com
- Summary Prepared:** June 30, 2003
- (a)(2) **Device Trade Name:** *blink*TM CL Lubricant Eye Drops
- Device Common Name:** Soft (Hydrophilic) and Rigid Gas Permeable Contact Lens Lubricating and Rewetting Solution
- Device Classification/Panel:** Class II (Special Controls)/Ophthalmic Device
- Device Classification Names:** Accessories to Contact Lenses – Cleaning and Wetting Agents
- (a)(3) **Identification of Predicate Device:** *blink*TM CL Lubricant Eye Drops is substantially equivalent to other lubricating and rewetting solutions currently marketed or cleared for commercial distribution in the U.S. These include REFRESH[®] CONTACTSTM Lubricating and Rewetting Drops (Allergan), AQUify Lens Comfort Drops (CIBA Vision) and Hylashield[®] CL Lubricating Eye Drop (Biomatrix).
- (a)(4) **Device Description:** *blink*TM CL Lubricant Eye Drops is a sterile, isotonic, buffered solution containing a lubricant, a preservative, buffers, tonicity agents, and purified water.

The product is a clear, colorless solution packaged in plastic bottles with controlled dropper tips.

510(k) SUMMARY

blink[™] CL Lubricant Eye Drops

June 30, 2003

Page 2 of 3

- (a)(5) **Intended Use (Indications for Use):** Use *blink*[™] CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses, to help relieve dryness, irritation and discomfort that maybe associated with lens wear, and to cushion lenses by placing a drop on the lens prior to application on the eye. The intended use is comparable to that of the predicate devices.
- (a)(6) **Comparison of Technological Characteristics:** *blink*[™] CL Lubricant Eye Drops has the same intended use and the same technological characteristics as the predicate lubricants/rewetters. The lubricant and preservative are materials which are used in the predicate lubricants/rewetters but not in combination in any one product. The ophthalmic demulcent, while not listed in 21 CFR 349.12, is used in one of the three predicate lubricants/rewetters in which we are requesting a determination of substantial equivalence. Additionally, a chemically similar lubricant is used in another one of the predicate lubricants/rewetters. Both of these lubricants have been cleared for commercial distribution in the U.S. All excipients are commonly recognized and used in ophthalmic and contact lens care products, including the predicate lubricants/rewetters.

Description of Safety and Substantial Equivalence

Nonclinical and clinical studies were performed to demonstrate the substantial equivalence of *blink*[™] CL Lubricant Eye Drops to the predicate device(s). Testing was conducted in accordance with and in conformance to applicable device regulations. The following is a discussion of the study results.

(b)(1) **Discussion of Nonclinical:**

Lens Compatibility: *In vitro* lens compatibility testing was conducted to establish product compatibility with both soft (hydrophilic) and RGP contact lenses. The results show that the product is compatible with soft (hydrophilic) and RGP contact lenses and substantially equivalent to the control.

Solution Compatibility: A study was conducted to evaluate the compatibility of *blink*[™] CL Lubricant Eye Drops when used with leading contact lens care products on the market. The results indicate that the product is compatible with these leading contact lens care products.

Preservative Uptake and Release: A study was conducted with soft (hydrophilic) and RGP contact lenses to determine the uptake and release of the preservative in *blink*[™] CL Lubricant Eye Drops. The results show that there is very little, if any, uptake of the preservative in or onto soft or RGP lenses. Any amounts taken up are quickly released. The results indicate that the product is compatible and acceptable for use with soft (hydrophilic) and RGP contact lenses.

510(k) SUMMARY
***blink*[™] CL Lubricant Eye Drops**
June 30, 2003
Page 3 of 3

(b)(1) Discussion of Nonclinical (Continued):

Contact Lens Wetting Angle: A wetting angle study was conducted to assess the effectiveness of *blink*[™] CL Lubricant Eye Drops in enhancing the wettability of RGP lenses compared with predicate lubricating and rewetting products. The results indicate that *blink*[™] CL Lubricant Eye Drops is substantially equivalent in wetting properties to the predicate devices.

Microbiological Studies: The product was evaluated for preservative efficacy and sterility:

- The product meets the acceptance criteria for Preservative Effectiveness Testing as outlined in ISO 14730:2000(E), "Ophthalmic optics – Contact lens care products – Antimicrobial preservative efficacy testing and guidance on determining discard date."
- The product meets USP Sterility test requirements.

Stability: Accelerated testing predicts that the product will remain stable for the labeled shelf-life.

Toxicology: The safety of *blink*[™] CL Lubricant Eye Drops was evaluated using cytotoxicity and acute ocular toxicity tests. The results of the testing demonstrate that *blink*[™] CL Lubricant Eye Drops is non-cytotoxic, non-irritating and well-tolerated.

(b)(2) Discussion of Clinical Data:

AMO conducted a multi-center, double-masked, randomized, parallel-group, one-month evaluation to assess the safety and acceptability of *blink*[™] CL Lubricant Eye Drops. The results of this study indicate that the investigational formulation is safe, acceptable, and substantially equivalent to the control.

(b)(3) Conclusions Drawn from Data Supporting Equivalence Determination: It is concluded that the safety, efficacy and performance of *blink*[™] CL Lubricant Eye Drops is substantially equivalent to the predicate products currently on the market or cleared for commercial distribution in the U.S.

GENERAL MANUFACTURING

1. Chemical Composition (Formulation)

Initially during the feasibility stage of product development, AMO screened (b) formulation candidates for acceptability and preference in a one-day clinical study. These six formulations contained varying concentrations of sodium hyaluronate (HA) or a combination of HA and hydroxypropyl methylcellulose (HPMC).

All six formulations showed good acceptability as determined by comfort scores. The study indicated a higher preference for the formulas with higher viscosity. Based on this information, the formulation choices were narrowed down to three for further evaluation in the one-month clinical study.

The three formulations of *blink*TM CL Lubricant Eye Drops evaluated in the one-month clinical study are presented below. Results from the study showed a preference for Formula Number 9464X (outlined in bold). Formula Number 9464X also demonstrated good thermal stability and thus was selected as the formulation for marketed product.

INGREDIENT	9463X % (w/v)	9464X % (w/v)	9467X % (w/v)	FUNCTION
Sodium Hyaluronate, EP	0.1	0.15	0.075	Lubricant/Demulcent
Hydroxypropyl Methylcellulose (HPMC), F4M, USP	N/A	N/A	0.075	Lubricant/Demulcent
Sodium Chloride, USP	0.39	0.39	0.39	Tonicity Agent
Boric Acid, NF	0.6	0.6	0.6	Buffer
Sodium Borate Decahydrate, NF	0.035	0.035	0.035	Buffer
Potassium Chloride, USP	0.14	0.14	0.14	Tonicity Agent
Calcium Chloride, Dihydrate, USP	0.006	0.006	0.006	Tonicity Agent
Magnesium Chloride.6H ₂ O, USP	0.006	0.006	0.006	Tonicity Agent
Purite [®] (stabilized oxychloro complex)	0.005	0.005	0.005	Preservative
Sodium Hydroxide, NF	*	*	*	pH Adjust
Purified water, USP	q.s. ad	q.s. ad	q.s. ad	Vehicle

N/A – These formulations do not contain any HPMC.

* Sufficient quantity to adjust pH to 7.2 ± 0.1

All ingredients, except Purite (stabilized oxychloro complex), are compendial. Purite (stabilized oxychloro complex) is the same preservative used in REFRESH CONTACTS Lubricating and Rewetting Drops (510(k) Number: K992028, Oct. 7, 1999).

Chemical Composition (Formulation), *continued*

The following table shows that the qualitative chemical composition of *blink*™ CL Lubricant Eye Drops is substantially equivalent to the predicate devices.

Comparison of the Qualitative Chemical Composition with Predicate Devices

FUNCTION	<i>blink</i>™ CL Lubricant Eye Drops (subject device)	Refresh Contacts Lubricating and Rewetting Drops (K992028)	<i>Alba Vis</i> AQuify Lens Comfort Drops (K013204)	Hylashield CL Lubricating Eye Drop* (K994170)
Lubricant	Sodium hyaluronate	Carboxymethyl cellulose	Sodium hyaluronate	Hylan A (crosslinked sodium hyaluronate)
Tonicity Agent(s)	Sodium chloride Potassium chloride Calcium chloride Magnesium chloride	Sodium chloride Potassium chloride Calcium chloride Magnesium chloride	Sodium chloride	Sodium chloride
Buffer(s)	Sodium borate Boric acid	Sodium borate Boric acid	Sodium phosphate	Sodium phosphate
Preservative	Purite	Purite	Sodium perborate (stabilized with phosphonic acid)	None
Vehicle	Purified water	Purified water	Purified water	Sterile water for injection

* Unit-dose, preservative-free formula.

Chemical Composition (Specifications)

FINAL PRODUCT SPECIFICATIONS	
Ingredient	9464X
Physical Appearance	(b)(4) Confidential and Proprietary Information
pH	
Potential Chlorine Dioxide (Purite)	
Sodium Hyaluronate	
Osmolality	
Viscosity	
Sterility, Current USP	
Preservative Effectiveness, ISO 14730:2000	

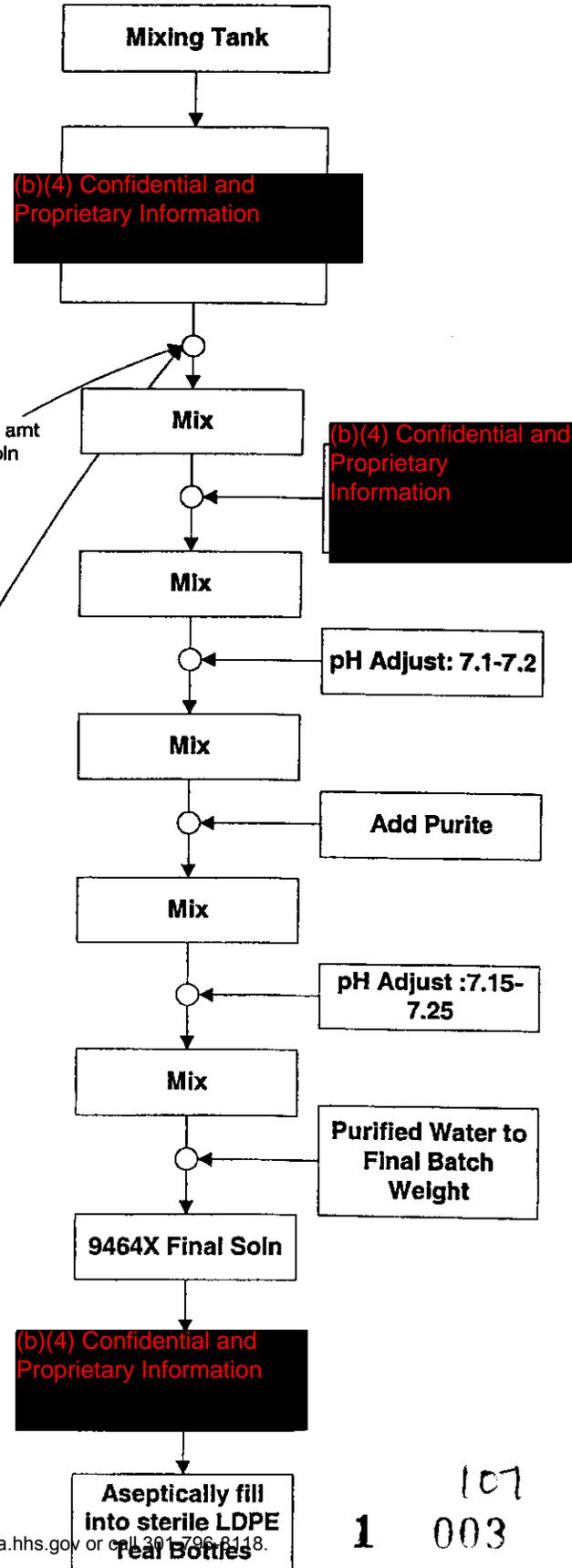
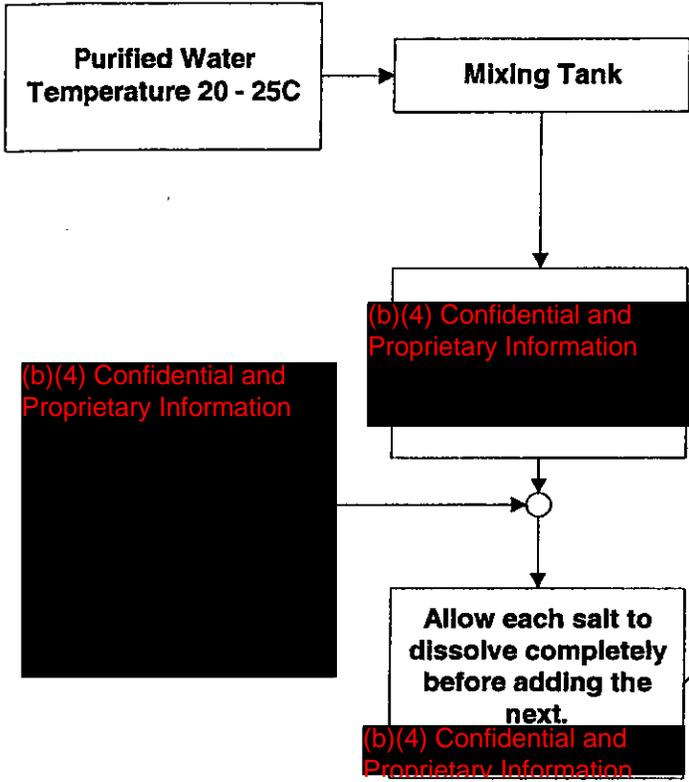
2. Manufacturing Process:

The manufacturing process for *blink* CL Lubricant Eye Drops uses conventional (b)(4) Confidential and Proprietary Information Compounding is conducted in bulk tanks with overhead mixers. Sterile filtration is conducted by pressurized linear flow of bulk solution through a 0.2 micron sterilization filter into a Class 100 aseptic filling room. The product is filled aseptically into sterile, low-density polyethylene (LDPE) bottles. A flow chart of the manufacturing process and sterile filtration system is included on the following page.

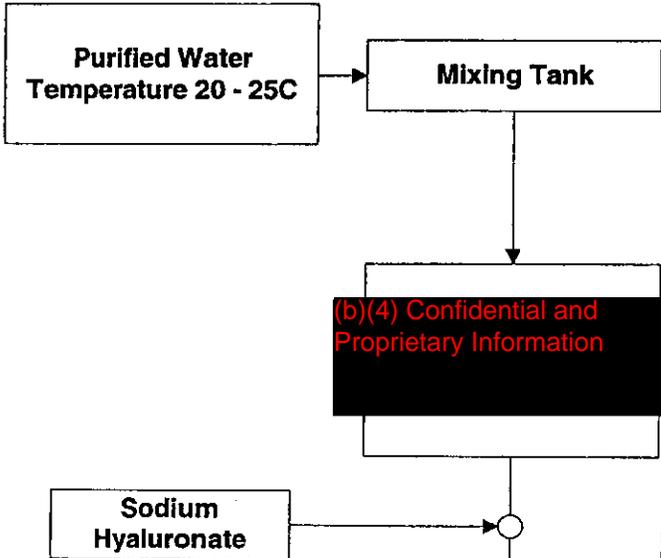
PURITE HA REWETTER (9464X) REGISTRATION STABILITY SUPPLIES PROCESS FLOW DIAGRAM

9464X Salt Solution

Purite HA Rewetter (9464X)



(b)(4) Confidential and Proprietary Information



Required amt Sodium Hyaluronate Soln

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3. Sterility:

Each lot is sterility tested by membrane filtration in accordance with the current United States Pharmacopoeia. Sterility assurance will meet current USP requirements. Results of USP sterility tests on research lots (all pass) are included in the stability report appended in Section 4, Nonclinical. The results show that manufacturing process and packaging maintain product sterility.

The container/closure system for *blink*TM CL Lubricant Eye Drops is designed to protect the sterility of the product. The system utilizes a cap with a 'break' seal, which ensures sterility until the seal is broken. All components (bottle, tip, cap) will be sterilized prior to filling using ethylene oxide (EtO) in accordance with and in conformance to applicable device regulations. The EtO residues will not exceed allowable limits.

As noted in the table above, sterility must meet USP specifications.

4. Microbial Limits Test:

This section is not applicable.

5. Multi-Dose Containers:

*blink*TM CL Lubricant Eye Drops is packaged in multi-dose containers and is therefore formulated with an appropriate preservative to prevent contamination after opening.

6. Preservative Effectiveness:

Results of Preservative Effectiveness testing, conducted in accordance with ISO 14730:2000, on research lots are included in the stability report appended in Section 4, Nonclinical. The results of accelerated testing show that the preservative remains effective through the three-month test interval. Since the preservative, Purite (stabilized oxychloro complex), in *blink*TM CL Lubricant Eye Drops is a proven preservative in other contact lens care products (Refresh Contacts Lubricating and Rewetting Drops, K992028, Oct. 7, 1999; Allergan Preserved Saline Solution, N18-020/S28, Oct. 16, 1989), there is strong reason to believe it will be an equally effective preservative for this product.

7. Shelf-Life (Stability):

The stability report in Section 4 details specifications and test results justifying an expiration dating of nine (9) months at this time. The protocol used for and the resultant data generated from the ongoing R&D stability study will be used to extend expiration dating when these data are sufficient to support it.

8. Tamper Resistant Packaging:

*blink*TM CL Lubricant Eye Drops is packaged in tamper-resistant multi-dose containers in accordance with 21 CFR 800.12.

9. Lens Compatibility:

Lens compatibility, tested in accordance with FDA's Premarket Notification [510(k)] Guidance Document for Contact Lens Care Products, issued May 1, 1997 is included in Section 4. The results show that this product is compatible with soft and RGP contact lenses.

10. Preservative Uptake/Release:

*blink*TM CL Lubricant Eye Drops is preserved with the same preservative, Purite (stabilized oxychloro complex), in the same concentration (0.005% w/v) as Refresh Contacts Lubricating and Rewetting Drops. Since the formulations differ only in the lubricant that is used (sodium hyaluronate replaces carboxymethyl cellulose), a study was undertaken to determine if the lubricant could have an influence on the uptake of the preservative in or onto soft and RGP lenses. The results show that there is little or no uptake of the preservative and, therefore, *blink*TM CL Lubricant Eye Drops is considered substantially equivalent to Refresh Contacts Lubricating and Rewetting Drops regarding preservative uptake and release.

Refer to Section 4 for a summary of this study.

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Indications for Use and Draft Labeling

***blink*[™] CL Lubricant Eye Drops**

510(k) NUMBER:
(IF KNOWN): K032030

DEVICE NAME: blink™ CL Lubricant Eye Drops

INDICATIONS FOR USE:

- Use *blink*™ CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses; to help relieve dryness, irritation and discomfort that may be associated with lens wear; and to cushion lenses by placing a drop on the lens prior to application on the eye.

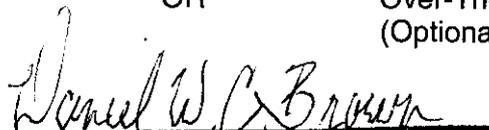
(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED.)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____
(Per 21 CFR 801.109)

OR

Over-The-Counter-Use X
(Optional Format 1-2-96)



(Division Sign-Off)
Division of Ophthalmic Ear,
Nose and Throat Devices

510(k) Number K032030

blink™
CL Lubricant Eye Drops

PACKAGE INSERT

blink™ CL Lubricant Eye Drops

For use with any contact lens.

DESCRIPTION:

blink™ CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients.

ACTIONS:

blink™ CL Lubricant Eye Drops has been formulated for use with both soft and rigid gas permeable (RGP) contact lenses; to rewet lenses before insertion and lubricate lenses during wear and to moisturize and refresh tired, dry eyes. It also relieves minor irritation, discomfort, dryness, blurring and itchiness, which may occur while wearing your lenses.

INDICATIONS:

Use **blink™** CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses, to help relieve dryness, discomfort and irritation that may be associated with lens wear and to cushion lenses by placing a drop on the lens prior to application on the eye.

CONTRAINDICATIONS:

If you are allergic to any ingredient in **blink™** CL Lubricant Eye Drops, do not use this product.

WARNINGS:

PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS

COULD RESULT IN SERIOUS INJURY TO THE EYE. It is essential that you 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 that the risk of serious adverse reactions is increased when these lenses are worn overnight.

Extended wear lenses should be regularly removed for cleaning and disinfecting 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 disinfecting or for disposal and replacement.

Studies have also shown that smokers had a higher incidence of adverse reactions.

It is recommended that contact lens wearers see their eye care practitioner twice each year or if directed, more frequently.

To avoid contamination, do not touch the dropper tip of the bottle to any surface.

Replace cap after using.

PRECAUTIONS:

Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

ADVERSE REACTIONS (POSSIBLE PROBLEMS) AND WHAT TO DO:

The following may occur:

- Eyes stinging, burning or itching
- Excessive watering (tearing) of the eyes
- Unusual eye secretions
- Redness of the eyes
- Reduced sharpness of vision (visual acuity)
- Blurred vision
- Sensitivity to light (photophobia)
- Dry eyes

If you notice any of the above, **IMMEDIATELY** remove and examine your lenses.

If a lens appears to be damaged, do not reapply; consult your eye care practitioner. If the problem stops and the lenses appear to be undamaged, follow the “Directions” below, before reapplying the lens.

If the problem continues **IMMEDIATELY** remove your lenses, discontinue use of all lens care products that contact the eye, and consult your eye care practitioner.

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

DIRECTIONS:

TO LUBRICATE AND REWET LENSES DURING THE DAY:

With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT: Place 1 or 2 drops of **blink™** CL Lubricant Eye Drops on each side of each lens before application.

HOW SUPPLIED:

blink™ CL Lubricant Eye Drops is supplied in sterile 0.08 fl oz (2.5mL) and .03 fl oz (10mL) plastic bottles. The bottles are marked with the lot number and expiration date.

LENSES:

blink™ CL Lubricant Eye Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP) contact lenses.

June 2003

Distributed by:
Advanced Medical Optics, Inc.
Santa Ana, CA 92705 U.S.A.
©2003 AMO, Inc.

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(b) (4)

SINGLE LABEL

B. 2.0!

Front:

(logo) AMO

blink™ CL Lubricant Eye Drops

For any contact lens.

USE ONLY IF BREAKSEAL ON BOTTLE CAP IS INTACT

10 mL (0.3 fl oz) STERILE

Back:

CONTENTS: **blink™** CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients. If you are allergic to any ingredient in this product, **DO NOT USE.**

PRECAUTIONS: Store at room temperature. For in-eye use only. Do not use in the lens case. Use before the expiration date marked on the bottle and carton. **SEE PACKAGE INSERT FOR DIRECTIONS AND IMPORTANT SAFETY INFORMATION.**

Distributed by:
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Santa Ana, CA 92705 U.S.A.
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W. rec. file

XXXXXX
(b) (4)

Lot No.:

Exp. Date:

1 012
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UNIT CARTON

Front Panel

(logo) AMO

blink™ CL Lubricant Eye Drops

For any contact lens

10mL (0.3 fl oz)

STERILE

Back Panel

blink™ CL Lubricant Eye Drops

For use any contact lens.

DIRECTIONS:

TO LUBRICATE AND REWET LENSES DURING THE DAY:

With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT: Place 1 or 2 drops of **blink™** CL Lubricant Eye Drops on each side of each lens before application.

Top Flap

blink™ CL Lubricant Eye Drops

10mL (0.3 fl oz) STERILE

USE ONLY IF BREAKSEAL ON BOTTLE CAP IS INTACT.

Side Panel

blink™ CL Lubricant Eye Drops is used to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses as well as to cushion lenses prior to application. Questions or Comments? 1-800-347-5005

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Santa Ana, CA 92705 U.S.A.

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1 013

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Side Panel

CONTENTS: **blink™** CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients.

If you are allergic to any ingredient in this product, DO NOT USE.

PRECAUTIONS: Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

WARNING: SEE PACKAGE INSERT FOR DIRECTIONS AND IMPORTANT SAFETY INFORMATION.

LENSES:

blink™ CL Lubricant Eye Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP) contact lenses.

Lot#

Part #

Expiration Date

XXXXX

NONCLINICAL REPORTS

	Study Type	Study Number	Study Date
Chemistry	Lens Compatibility (hydrophilic)	TR No. 2260	June 10, 2003
	Lens Compatibility (RGP)	TR No. 2261	June 10, 2003
	Solution Compatibility	TR. No. QD 1409	June 5, 2003
	Preservative Uptake and Release	TR No. QD 1406	June 13, 2003
	Contact Lens Wetting Angle (RGP)	TR No. QD 1410	June 19, 2003
Stability	Six Month Interim Stability Report for <i>blink</i> TM CL Lubricant Eye Drops, Formulation 9464X	TR No. 2209	June 18, 2003
Toxicology	Cytotoxicity	(b)(4) Confidential and Proprietary Information	Feb. 13, 2003
	Acute Ocular Toxicity		Dec. 20, 2002

CHEMISTRY

Study Type	Page
Summaries	1 017
Lens Compatibility (hydrophilic lenses)	1 022
Lens Compatibility (RGP lenses)	1 050
Solution Compatibility	1 064
Preservative Uptake and Release	1 070
Contact Lens Wetting Angle (RGP lenses)	1 085

NONCLINICAL REPORT SUMMARIES

Department: Brand Support Technologies
Study Type: Lens Compatibility (hydrophilic lenses)
Title: Compatibility Study of Purite/HA Rewetter, Formula's 9464X and 9467X with Hydrophilic Contact Lenses for Regulatory Registration
Study Date: June 10, 2003
Study Number: (b)(4) Confidential and Proprietary
Study Summary:

AMO conducted a lens compatibility study with *blink*TM CL Lubricant Eye Drops to support product registration. Two formulations were studied as the formulation we intend to market (9464X) had not yet been decided at this stage of product development (refer to Section 2, General Manufacturing, Chemical Composition). The formulation intended for market, 9464X, is a sodium hyaluronate (HA) only formula with the highest concentration of HA (0.15%). The other formulation studied, 9467X, is a combination HA and HPMC formula with a concentration of 0.075% for each lubricant.

A regimen using Refresh Contacts Lubricating and Rewetting Drops (L992028) was run concurrently as a control. The multipurpose solution used in the regimen is a currently marketed multipurpose solution. Group 1 and 4 contact lenses represented all hydrophilic contact lenses. Lens parameters (diameter, power and basecurve) were measured initially and at the end of thirty (30) cycles. Also, total reflection and visual appearance (lens cleanliness, discoloration and deformities) of the lenses were monitored and evaluated.

In the study, all test lenses met the acceptance criteria for lens parameters as established in the protocol for this study and compared favorably to the results of the control. Additionally, total reflection and visual appearance met the acceptance criteria by showing equivalence to the control solution.

Therefore, it can be concluded that *blink*TM CL Lubricant Eye Drops is compatible with soft (hydrophilic) contact lenses.

NONCLINICAL REPORT SUMMARIES

Department: Brand Support Technologies
Study Type: Lens Compatibility (RGP lenses)
Title: Lens Compatibility Study of Purite/HA Rewetter, Formula's 9464X and 9467X with RGP Contact Lenses for Regulatory Registration
Study Date: June 10, 2003

Study Number: (b)(4) Confidential and Proprietary

Study Summary: A second study was conducted to evaluate the compatibility of two formulations of *blink*TM CL Lubricant Eye Drops with RGP lenses. The same two formulations used in the soft lens compatibility study were evaluated. A regimen using Refresh Contacts Lubricating and Rewetting Drops was run concurrently as a control. The cleaning and soaking solutions used in the regimen are currently marketed RGP contact lens cleaning and soaking solutions.

A representative silicone acrylate (SA) lens and a representative fluorosilicone acrylate (FSA) were used. The lens parameters (diameter, power, base curve) and physical appearance were measured initially and at the end of thirty (30) cycles.

The test lenses met the acceptance criteria for lens parameters as established in the protocol for this study and compared favorably to the results of the control. The results for physical appearance showed no evidence of surface deposits, discoloration and/or deformities.

Therefore, it can be concluded that *blink*TM CL Lubricant Eye Drops is compatible with RGP contact lenses.

NONCLINICAL REPORT SUMMARIES

Department: Formulation Development
Study Type: Solution Compatibility
Title: Report for Purite® HA Rewetter (9464X and 9467X) Solution Compatibility

Study Date: June 5, 2003

Study Number: (b)(4) Confidential

Study Summary: A study was conducted to evaluate the compatibility of *blink*TM CL Lubricant Eye Drops when used with leading contact lens care products (e.g., peroxide systems and multipurpose solutions) on the market. Two formulations of *blink*TM CL Lubricant Eye Drops were tested (b)(4) Confidential and (b)(4) Confidential. Each formulation was mixed with each of the leading lens care products and the mixtures were evaluated for interactions by noting changes in physical appearance (discoloration or precipitate formation), pH and osmolality.

No visible changes in physical appearance of any of the mixtures were observed. Changes in pH and osmolality were minimal and remained within physiological acceptable ranges.

Therefore, it can be concluded that *blink*TM CL Lubricant Eye Drops is compatible and acceptable for use with currently marketed leading lens care products.

NONCLINICAL REPORT SUMMARIES

Department: Formulation Development
Study Type: Preservative Uptake/Release
Title: Report for the Preservative Uptake and Release of Purite® from Purite HA Rewetter (9464X and 9467X) with Hydrophilic and Rigid Gas Permeable Contact Lenses

Study Date: June 13, 2003

Study Number: [REDACTED]

Study Summary:

(b)
(4)
*blink*TM CL Lubricant Eye Drops is preserved with the same preservative, Purite (stabilized oxychloro complex), in the same concentration (0.005% w/v) as Refresh Contacts Lubricating and Rewetting Drops. Since *blink*TM CL Lubricant Eye Drops (9464X) and Refresh Contacts Lubricating and Rewetting Drops differ only in the lubricant that is used (sodium hyaluronate replaces carboxymethyl cellulose), a study was undertaken to determine if the lubricant could have an influence on the uptake of the preservative in or onto soft and RGP lenses.

Two formulations of *blink*TM CL Lubricant Eye Drops (9464X and 9467X) were evaluated in this study. Representative soft lenses from FDA Groups 1 and 4 and representative RGP lenses from silicone acrylate (SA) and fluorosilicone acrylate (FSA) materials were used. The lenses were soaked in the test solutions up to 48 hours. At specified time points, the test solutions were assayed for Purite content. The procedure was continued until the uptake reached a plateau. Once uptake reached a plateau, the lenses were removed from the solution and placed in saline solution. At designated time intervals, the solutions were assayed for Purite content until release reached a plateau.

The results of the study indicate that there is very little, if any, uptake of Purite in or onto soft and RGP contact lenses.

Therefore, it can be concluded that *blink*TM CL Lubricant Eye Drops, preserved with Purite (stabilized oxychloro complex), is compatible and acceptable for use with soft (hydrophilic) and RGP contact lenses.

NONCLINICAL REPORT SUMMARIES

Department: Formulation Development
Study Type: Contact Lens Wetting Angle (RGP lenses)
Title: Report for the Measurement of Wetting Angles of RGP Lenses in Association with Purite® HA Rewetter (9464X)
Study Date: June 19, 2003
Study Number: (b)(4) Confidential
Study Summary: A study comparing *blink*™ CL Lubricant Eye Drops with predicate lubricant/rewetters was conducted to evaluate the wetting angle on RGP contact lenses. Silicone acrylate (SA) and fluorosilicone acrylate (FSA) buttons were used. The wetting angles were measured using the Sessile Drop Method. Additionally, surface tension by the method of pendant drop shape assessment was measured for comparison.

The results of the study show very similar wetting angle and surface tension properties among all solutions tested. The sodium hyaluronate (HA) containing solutions appeared to have slightly better wetting properties on the SA lens material than did the non-HA containing product.

It can be concluded that the wetting properties of *blink*™ CL Lubricant Eye Drops are acceptable and substantially equivalent to the predicate lubricants/rewetters for RGP contact lenses.

Lens Compatibility (hydrophilic lenses)

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June 10, 2003

ADVANCED MEDICAL OPTICS

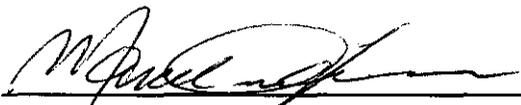
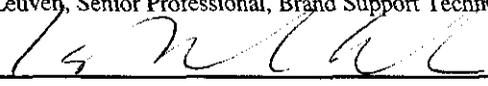
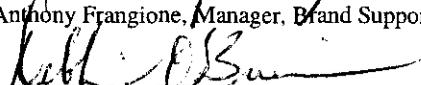
BRAND SUPPORT TECHNOLOGIES

Compatibility Study of Purite/HA Rewetter, Formula's
Hydrophilic Contact Lenses for Regulatory Registration

(b)(4) Confidential and Proprietary Information

(b)(4) Confidential and Proprietary Information

ISSUED: Date of Last Signatory

Author:		6/10/03
	Marcel Van Leuven, Senior Professional, Brand Support Technologies	Date
Reviewed by:		6/10/03
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	Debbie O'Brien, Senior Regulatory Professional, Regulatory Affairs	Date

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1.0 SUMMARY

A study was conducted to determine the compatibility of hydrophilic contact lenses with two proposed formulations for Purite/HA (Hyaluronic Acid) Rewetter, 9464X and 9467X. The study was required in support of the regulatory submission of the final product. Group 1 and Group 4 lenses were selected to represent all groups of hydrophilic lenses and were exposed to the regimen of COMPLETE® C with frequent application of the test-product (s) to the lenses during the cycling in the Artificial Tear solution. A control regimen, identical to the test regimen except that Refresh Contacts™ was substituted for the test product(s), was run concurrently. Standard test criteria (i.e. lens-parameters and visual appearance) were monitored during the 30-cycle study. The results of the study showed that the lens-parameters of all lenses with both test formulations, stayed within the limits of the standards for clinically significant parameter changes for hydrophilic contact lenses and compared favorably to the results of the control, Refresh Contacts™. In addition, visual appearance (cleanliness, discoloration and deformities) met the acceptance criteria by showing equivalence to the control solution. In conclusion, the candidate formulations 9464X and 9467X for the Purite/HA Rewetter product, in conjunction with the COMPLETE® C regimen, demonstrated compatibility and are therefore appropriate for use with hydrophilic contact lenses.

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2.0 PURPOSE

The study was conducted to determine the compatibility of two candidate formulations of the Purite/HA (Hyaluronic Acid) Rewetter (9464X and 9467X) with hydrophilic contact lenses.

3.0 INTRODUCTION

This lens compatibility study was needed in support of the regulatory submission of the Purite/HA (Hyaluronic Acid) Rewetter. Two candidate formulations were tested to determine compatibility of each formula, and the Purite/HA Rewetter product in general, with hydrophilic contact lenses.

4.0 MATERIALS AND EQUIPMENT

4.1 MATERIALS

- Purite/HA Rewetter, 9464X (0.15% sodium hyaluronate),
- Purite/HA Rewetter, 9467X (0.075% sodium hyaluronate, 0.075% HPMC), Lot#
- Refresh Contacts™, 9329X,
- COMPLETE® C, 9451X,
- COMPLETE® Lens Case
- Cooper Clear™ Contact Lenses, CooperVision, Group 1
- BioCurve Soft DW Contact Lenses, American BioCurve, Group 4
- Artificial Tear Solution

4.2 EQUIPMENT

- OPTIMEC, Contact Lens Dimension Analyzer
- NIKON, Vertexometer
- PANAMETRICS, Basecurve Measuring Instrument
- SCIENTIFIC INSTRUMENT COMPANY, Image Analysis System with Image-Pro® Plus

5.0 METHODS

Compatibility testing was performed according to SOP #PDBST-M-03. For lens cleanliness (total reflection through image analysis), SOP #PDBST-I-20 was used. The guidelines in ISO 11981 were followed to comply with ISO requirements. In accordance with the approved study (b)(4) Confidential and Proprietary Information Group 1 and Group 4 lenses were tested to represent all groups of soft contact lenses. The test lenses were cycled 30 times in a regimen of Complete® C (9451X) and Artificial Tears. The test products Purite/HA (b)(4) Confidential and Proprietary Information were applied to the lenses during the Artificial Tear soak. The control was identical but included applications of Refresh Contacts™ instead of the test product (s). All specifics of the protocol were adhered to in the execution of the study.

The procedure was as follows:

- All lenses (test and control) were conditioned and soaked in Artificial Tears for at least 2 hours at RT.
- Initial measurements of diameter, power, base curve and total reflection were made for all lenses and the lenses were visually examined for cleanliness, color and integrity.
- The test lenses (20 per lens-group, per test-product), were exposed to the following **test regimen**:
 1. Soak the lenses in 3 mL of Artificial Tears at 37° C for 8 hours.
 2. During the soak, remove the lenses from the Artificial Tear solution and apply 2-3 drops of the respective test solution to the anterior side of the lens. Return the lens to the Artificial Tear solution.
 3. Repeat the application (step 2) every 2 hours.
 4. Remove the lenses after 8 hours in Artificial Tears and rinse with COMPLETE® C, 5 seconds on each side of the lens.
 5. Place the lenses in 4 mL of COMPLETE® C in the COMPLETE® Lens Case and allow to soak for 16-18 hours (overnight).
 6. Repeat steps 1-5 (1 cycle) to a total of 30 times.
- The control lenses (10 per group) were exposed to the **control regimen**, which was identical to the test regimen, except that Refresh Contacts™ was substituted for the test product(s).
- After completion of the final cycle, diameter, power, base curve and total reflection of the lenses were measured and visual observations of the lenses were made to determine possible evidence of discoloration and deformities.

- The difference between final and initial measurements for each lens and for each test-parameter was calculated and the averaged value, as well as the visual observations, compared to the acceptance criteria as established in the protocol for the study.

Parameter-standards of acceptance:	Diameter	± 0.20 mm
	Power	± 0.25 D
	Base Curve	± 0.20 mm

6.0 RESULTS

The results of the parameter and total reflection measurements, including statistical analysis, can be found in Appendices I through XX.

Test and control lenses showed no evidence of discoloration and/or deformities during and after completion of the study.

7.0 DISCUSSION

The results for parameter measurements showed that all lens groups that were tested with both test formulations, remained within the limits of the acceptance criteria and were comparable to controls. Also, test and control lenses showed comparable results for physical appearance, obtained by visual observations.

Lens cleanliness was determined by comparison of test and control results of total reflection (ref.: Appendix V, X, XV and XX). Comparability was established when the P-value (T>=t) two tail was equal to or greater than 0.05. Comparability to the controls was obtained for Group 1 and Group 4 lenses with formula 9464X and Group 1 lenses with 9467X. Group 4 lenses showed slightly better results than controls with 9467X, as the mean values indicated cleaner test lenses than the controls (ref.: Appendix XX). Note: Negative results of the difference between final and initial measurements indicate that no surface deposits are present. The final measurement for total reflectance could yield a lower value than the initial as the sensitivity of the method allows for ± 10 units of total reflectance.

8.0 CONCLUSION

The results of this study demonstrate that two candidate formulations 9464X and 9467X for the Purite/HA Rewetter product, in conjunction with the regimen of COMPLETE® C, are compatible and appropriate for use with Hydrophilic contact lenses.

9.0 REFERENCES

1. SOP #PDBST-M-03, Method for Lens Compatibility Testing (version 2)
2. SOP #PDBST-M-04, Method to Measure the Power of Soft Hydrophilic Contact Lenses (version 2)

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3. SOP # PDBST-I-15, Calibration and Use of the Optimec Contact Lens Dimension Analyzer (version 2)
4. SOP #PDBST-I-20, Use and Maintenance of the Image Analyzer with Image-Pro® Plus (version 2)
5. ISO 11981, Assessment of Physical Compatibility of Contact Lenses with their Care Products
6. Protocol for the Compatibility study of Purite/HA Rewetter, Formula's 9464X and 9467X with Hydrophilic Contact Lenses for Regulatory Registration, No.: 2003-008
7. AMO Laboratory Note Book #656, p.p.83-99, Raw Data Binder #656, p.p. 1-19

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10.0 APPENDICES

Appendix I: Purite/HA Rewetter (b)(4) Confidential

Table 1

Diameter (mm)

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Delta
1	14.75	14.70	0.05
2	14.70	14.60	0.10
3	14.60	14.60	0.00
4	14.70	14.55	0.15
5	14.35	14.30	0.05
6	14.80	14.95	0.15
7	14.70	14.30	0.00
8	14.70	14.70	0.00
9	14.70	14.70	0.00
10	14.60	14.55	0.05
11	14.30	14.30	0.00
12	14.70	14.70	0.00
13	14.65	14.60	0.05
14	14.60	14.60	0.00
15	14.65	14.55	0.10
16	14.70	14.70	0.00
17	14.60	14.55	0.05
18	14.60	14.50	0.10
19	14.70	14.60	0.10
20	14.30	14.30	0.00
		$\bar{x} =$	0.05
		sd =	0.05

Control Lenses

#	Initial	Final	Delta
1	14.70	14.70	0.00
2	14.85	14.70	0.15
3	14.30	14.30	0.00
4	14.65	14.60	0.05
5	14.70	14.70	0.00
6	14.75	14.70	0.05
7	14.65	14.55	0.10
8	14.70	14.60	0.10
9	14.70	14.70	0.00
10	14.30	14.35	0.05
		\bar{x}	0.05
		sd =	0.05

Testing Criteria: ± 0.20 mm

Appendix II: Purite/HA Rewetter (b)(4) Confidential

Table 2

Power (D)

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Delta
1	+2.13	+2.00	0.13
2	-3.13	-3.00	0.13
3	-7.00	-7.13	0.13
4	+3.88	+3.75	0.13
5	-5.13	-5.13	0.00
6	+1.88	+1.88	0.00
7	-5.13	-5.00	0.13
8	+3.88	+4.13	0.25
9	-3.13	-3.00	0.13
10	-7.00	-6.88	0.12
11	-5.13	-5.13	0.00
12	+2.13	+1.88	0.25
13	-3.00	-3.13	0.13
14	+4.00	+4.13	0.13
15	-7.13	-7.00	0.13
16	+2.38	+2.13	0.25
17	-3.00	-3.13	0.13
18	-7.13	-7.13	0.00
19	+4.13	+4.00	0.13
20	-4.75	-5.00	0.25
		$\bar{x} =$	0.13
		sd =	0.08

Control Lenses

#	Initial	Final	Delta
1	-3.13	-3.13	0.00
2	+2.13	+2.00	0.13
3	-5.00	-5.00	0.00
4	-7.13	-7.13	0.00
5	+4.00	+3.88	0.12
6	+4.13	+4.00	0.13
7	-7.25	-7.00	0.25
8	-3.00	-3.00	0.00
9	+2.00	+2.13	0.13
10	-5.13	-4.88	0.25
		$\bar{x} =$	0.10
		sd =	0.10

Testing Criteria: ±0.25 D

Appendix III: Purite/HA Rewetter, (b)(4) Confidential

Table 3

Base Curve (mm)

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Delta
1	8.54	8.34	0.20
2	8.29	8.37	0.08
3	8.39	8.42	0.03
4	8.01	8.17	0.16
5	8.57	8.50	0.07
6	8.37	8.37	0.00
7	8.56	8.53	0.03
8	8.04	8.23	0.19
9	8.63	8.80	0.17
10	8.92	8.92	0.00
11	8.46	8.62	0.16
12	8.12	8.25	0.13
13	8.78	8.77	0.01
14	8.00	7.90	0.10
15	8.70	8.85	0.15
16	8.09	8.13	0.04
17	8.60	8.77	0.17
18	8.46	8.50	0.04
19	7.96	7.91	0.05
20	8.23	8.33	0.10
		$\bar{x} =$	0.09
		sd =	0.07

Control Lenses

#	Initial	Final	Delta
1	8.54	8.36	0.18
2	8.25	8.42	0.17
3	8.15	8.43	0.28
4	8.22	8.08	0.14
5	7.94	7.95	0.01
6	7.93	7.93	0.00
7	8.44	8.53	0.09
8	8.48	8.52	0.04
9	7.93	8.03	0.10
10	8.12	8.24	0.12
		$\bar{x} =$	0.11
		sd =	0.09

Testing Criteria: ± 0.20 mm

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Appendix IV: Purite/HA Rewetter (b)(4) Confidential

Table 4

Total Reflection

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Diff.
1	53.69	52.97	-0.72
2	61.42	52.87	-8.55
3	58.51	55.19	-3.32
4	47.43	47.14	-0.29
5	42.79	48.20	5.41
6	57.55	57.97	0.42
7	45.52	47.62	2.10
8	55.78	53.28	-2.50
9	53.71	48.29	-5.42
10	53.49	56.66	3.17
11	41.84	47.29	5.45
12	55.95	52.66	-3.29
13	57.68	52.36	-5.32
14	52.47	52.57	0.10
15	59.64	53.27	-6.37
16	54.80	51.54	-3.26
17	56.33	53.64	-2.69
18	56.37	54.61	-1.76
19	58.64	55.28	-3.36
20	46.42	47.64	1.22

Control Lenses

#	Initial	Final	Diff.
1	60.33	57.80	-2.53
2	56.02	54.13	-1.89
3	52.07	42.71	-9.36
4	57.83	48.11	-9.72
5	54.75	53.01	-1.74
6	59.21	48.06	-11.15
7	53.90	55.58	1.68
8	53.21	48.28	-4.93
9	47.76	52.42	4.66
10	52.62	40.99	-11.63

Testing Criteria: Better than or comparable to control.

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Appendix V: Statistical comparison of test and control results for Total Reflection of CooperClear™ lenses with formula (b)(4) Confidential

Test	Control
-0.72	-2.53
-8.55	-1.89
-3.32	-9.36
-0.29	-9.72
5.41	-1.74
0.42	-11.15
2.1	1.68
-2.5	-4.93
-5.42	4.66
3.17	-11.63
5.45	
-3.29	
-5.32	
0.1	
-6.37	
-3.26	
-2.69	
-1.76	
-3.36	
1.22	

t-Test: Two-Sample Assuming Unequal Variances

	Variable 1	Variable 2
Mean	-1.449	-4.661
Variance	13.96949	31.80685
Observations	20	10
Hypothesized Mean Difference	0	
df	13	
t Stat	1.630822	
P(T<=t) one-tail	0.063452	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.126905	
t Critical two-tail	2.160368	

Appendix VI: Purite/HA Rewetter (b)(4) Confidential

Table 5

Diameter (mm)

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Delta
1	14.30	14.15	0.15
2	14.40	14.20	0.20
3	14.40	14.25	0.15
4	14.90	14.70	0.20
5	14.15	14.00	0.15
6	14.15	14.15	0.00
7	14.25	14.00	0.25
8	14.25	14.20	0.05
9	14.10	13.90	0.20
10	14.20	14.00	0.20
11	14.35	14.40	0.05
12	14.60	14.65	0.05
13	14.10	14.20	0.10
14	14.30	14.10	0.20
15	14.20	14.00	0.20
16	14.05	14.00	0.05
17	14.45	14.25	0.20
18	14.15	14.00	0.15
19	14.30	14.20	0.10
20	14.40	14.25	0.15
		$\bar{x} =$	0.14
		sd =	0.07

Control Lenses

#	Initial	Final	Delta
1	14.00	13.95	0.05
2	14.20	14.10	0.10
3	14.05	13.85	0.20
4	14.10	14.05	0.05
5	14.25	14.10	0.15
6	14.45	14.25	0.20
7	14.20	14.10	0.10
8	14.40	14.20	0.20
9	14.20	14.05	0.15
10	14.70	14.55	0.15
		$\bar{x} =$	0.14
		sd =	0.06

Testing Criteria: ± 0.20 mm

Appendix VII: Purite/HA Rewetter (b)(4) Confidential

Table 6

Power (D)

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Delta
1	-7.25	-7.25	0.00
2	+4.00	+4.25	0.25
3	-2.00	-2.25	0.25
4	+2.13	+2.25	0.12
5	-7.25	-7.25	0.00
6	+4.00	+4.25	0.25
7	-2.88	-2.63	0.25
8	+4.13	+4.25	0.12
9	-2.38	-2.50	0.12
10	-7.25	-7.38	0.13
11	-2.25	-2.13	0.12
12	-2.13	-2.38	0.25
13	-3.00	-2.75	0.25
14	+3.88	+4.00	0.12
15	-6.88	-7.13	0.25
16	-2.88	-3.13	0.25
17	+4.25	+4.50	0.25
18	-3.88	-3.88	0.00
19	-7.38	-7.13	0.25
20	+4.13	+4.38	0.25
		$\bar{x} =$	0.17
		sd =	0.09

Control Lenses

#	Initial	Final	Delta
1	-3.13	-3.25	0.12
2	-3.13	-3.25	0.12
3	0.00	0.00	0.00
4	-2.50	-2.50	0.00
5	-7.25	-7.38	0.13
6	-2.63	-2.50	0.13
7	-2.88	-2.88	0.00
8	+3.75	+3.88	0.13
9	-3.13	-3.25	0.12
10	-2.88	-3.00	0.12
		$\bar{x} =$	0.09
		sd =	0.06

Testing Criteria: ± 0.25 D

Appendix VIII: Purite/HA Rewetter (b)(4) Confidential and

Table 7

Base Curve (mm)

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Delta
1	8.07	8.11	0.04
2	7.60	7.49	0.11
3	7.57	7.83	0.26
4	8.29	8.15	0.14
5	8.33	8.16	0.17
6	7.80	7.82	0.02
7	7.83	7.93	0.10
8	8.07	7.97	0.10
9	7.99	7.95	0.04
10	7.92	8.31	0.39
11	8.59	8.67	0.08
12	7.78	7.63	0.15
13	8.31	8.39	0.08
14	7.90	7.94	0.04
15	7.80	7.98	0.18
16	8.11	8.27	0.16
17	7.43	7.56	0.13
18	8.38	8.28	0.10
19	8.68	8.48	0.20
20	7.72	7.62	0.10
		$\bar{x} =$	0.13
		sd =	0.09

Control Lenses

#	Initial	Final	Delta
1	8.12	8.04	0.08
2	8.10	8.02	0.08
3	8.48	8.17	0.31
4	8.12	8.08	0.04
5	8.60	8.55	0.05
6	8.17	8.03	0.14
7	7.73	7.83	0.10
8	7.96	8.04	0.08
9	8.21	8.23	0.02
10	7.96	7.95	0.01
		$\bar{x} =$	0.09
		sd =	0.09

Testing Criteria: ± 0.20 mm

Appendix IX: Purite/HA Rewetter (b)(4) Confidential

Table 8

Total Reflection

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Diff.
1	50.70	50.88	0.18
2	51.66	63.98	12.32
3	50.84	58.89	8.05
4	58.15	62.83	4.68
5	57.76	62.56	4.80
6	60.11	56.24	-3.87
7	97.83	95.57	-2.26
8	58.43	58.50	0.07
9	95.81	57.08	*-38.73
10	57.51	60.19	2.68
11	57.42	56.72	-0.70
12	58.96	52.41	-6.55
13	56.32	59.53	3.21
14	60.10	54.84	-5.26
15	61.39	59.29	-2.10
16	58.87	54.87	-4.00
17	61.85	64.65	2.80
18	105.79	96.18	-9.61
19	59.38	59.32	-0.06
20	62.60	55.49	-7.11

Control Lenses

#	Initial	Final	Diff.
1	91.58	85.75	-5.83
2	94.36	93.62	-0.74
3	57.56	61.59	4.03
4	92.87	98.63	5.76
5	63.79	62.77	-1.02
6	57.72	62.51	4.79
7	98.18	99.00	0.82
8	63.65	58.74	-4.91
9	58.78	59.19	0.41
10	84.40	92.42	8.02

Testing Criteria: Better than or comparable to control.

* The value was rejected as outlier with the Q-test and not included in the determination of statistical comparison.

Appendix X: Statistical comparison of test and control results for Total Reflection of BioCurve lenses with formula (b)(4) Confidential

0.18	-5.83
12.32	-0.74
8.05	4.03
4.68	5.76
4.8	-1.02
-3.87	4.79
-2.26	0.82
0.07	-4.91
2.68	0.41
-0.7	8.02
-6.55	
3.21	
-5.26	
-2.1	
-4	
2.8	
-9.61	
-0.06	
-7.11	

t-Test: Two-Sample Assuming Unequal Variances

	<i>Variable 1</i>	<i>Variable 2</i>
Mean	-0.14368	1.133
Variance	30.0534	20.48573
Observations	19	10
Hypothesized Mean Difference	0	
df	22	
t Stat	-0.67005	
P(T<=t) one-tail	0.254898	
t Critical one-tail	1.717144	
P(T<=t) two-tail	0.509796	
t Critical two-tail	2.073875	

Appendix XI: Purite/HA Rewetter (b)(4)

Table 9

Diameter (mm)

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Delta
1	14.70	14.60	0.10
2	14.30	14.30	0.00
3	14.65	14.60	0.05
4	14.70	14.70	0.00
5	14.65	14.55	0.10
6	14.30	14.30	0.00
7	14.70	14.70	0.00
8	14.60	14.55	0.05
9	14.70	14.70	0.00
10	14.80	14.70	0.10
11	14.30	14.30	0.00
12	14.70	14.65	0.05
13	14.65	14.50	0.15
14	14.60	14.50	0.10
15	14.70	14.75	0.05
16	14.30	14.30	0.00
17	14.70	14.70	0.00
18	14.55	14.55	0.00
19	14.75	14.65	0.10
20	14.70	14.65	0.05
		$\bar{x} =$	0.05
		$sd =$	0.05

Control Lenses

#	Initial	Final	Delta
1	14.70	14.70	0.00
2	14.85	14.70	0.15
3	14.30	14.30	0.00
4	14.65	14.60	0.05
5	14.70	14.70	0.00
6	14.75	14.70	0.05
7	14.65	14.55	0.10
8	14.70	14.60	0.10
9	14.70	14.70	0.00
10	14.30	14.35	0.05
		$\bar{x} =$	0.05
		$sd =$	0.05

Testing Criteria: ± 0.20 mm

Appendix XII: Purite/HA Rewetter (b)(4) Confidential

Table 10

Power (D)

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Delta
1	+4.00	+4.00	0.00
2	-5.00	-4.88	0.12
3	-3.13	-3.00	0.13
4	+2.00	+1.88	0.12
5	-7.13	-7.25	0.12
6	-5.13	-5.00	0.13
7	+2.13	+2.13	0.00
8	-7.13	-7.00	0.13
9	+4.00	+3.88	0.12
10	-3.13	-3.00	0.13
11	-5.00	-5.13	0.13
12	+2.00	+2.00	0.00
13	-7.00	-7.13	0.13
14	-3.13	-3.00	0.13
15	+3.88	+4.00	0.12
16	-5.00	-5.00	0.00
17	+2.13	+2.25	0.12
18	-7.00	-7.13	0.13
19	+4.13	+3.88	0.25
20	-3.00	-3.13	0.13
		$\bar{x} =$	0.11
		sd =	0.06

Control Lenses

#	Initial	Final	Delta
1	-3.13	-3.13	0.00
2	+2.13	+2.00	0.13
3	-5.00	-5.00	0.00
4	-7.13	-7.13	0.00
5	+4.00	+3.88	0.12
6	+4.13	+4.00	0.13
7	-7.25	-7.00	0.25
8	-3.00	-3.00	0.00
9	+2.00	+2.13	0.13
10	-5.13	-4.88	0.25
		$\bar{x} =$	0.10
		sd =	0.10

Testing Criteria: ± 0.25 D

Appendix XIII: Purite/HA Rewetter, (b)(4) Confidential

Table 11

Base Curve (mm)

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Delta
1	7.97	7.92	0.05
2	8.21	8.30	0.09
3	8.38	8.28	0.10
4	8.10	8.04	0.06
5	8.64	8.77	0.13
6	8.23	8.21	0.02
7	8.12	8.25	0.13
8	8.41	8.28	0.13
9	7.94	7.89	0.15
10	8.53	8.34	0.19
11	8.36	8.40	0.04
12	8.06	8.03	0.03
13	8.30	8.25	0.05
14	8.22	8.17	0.05
15	7.92	8.16	0.24
16	8.14	8.12	0.02
17	8.00	7.78	0.22
18	8.35	8.23	0.12
19	7.93	7.87	0.06
20	8.38	8.27	0.11
		$\bar{x} =$	0.10
		sd =	0.06

Control Lenses

#	Initial	Final	Delta
1	8.54	8.36	0.18
2	8.25	8.42	0.17
3	8.15	8.43	0.28
4	8.22	8.08	0.14
5	7.94	7.95	0.01
6	7.93	7.93	0.00
7	8.44	8.53	0.09
8	8.48	8.52	0.04
9	7.93	8.03	0.10
10	8.12	8.24	0.12
		$\bar{x} =$	0.11
		sd =	0.09

Testing Criteria: ± 0.20 mm

(b)(4) Confidential and Proprietary Information

Appendix XIV: Purite/HA Rewetter (b)(4) Confidential

Table 12

Total Reflection

Group 1, CooperClear™

Test Lenses

#	Initial	Final	Diff.
1	58.12	48.23	-9.89
2	52.12	54.34	2.22
3	53.43	51.16	-2.27
4	54.45	53.44	-1.01
5	60.43	48.71	-11.72
6	44.53	55.66	11.13
7	49.95	48.22	-1.73
8	59.79	56.62	-3.17
9	56.40	52.49	-3.91
10	58.05	53.59	-4.46
11	52.19	49.02	-3.17
12	48.85	51.65	2.80
13	58.99	54.20	-4.79
14	54.37	52.02	-2.35
15	59.63	53.38	-6.25
16	49.29	47.90	-1.39
17	54.09	50.85	-3.24
18	58.52	55.74	-2.78
19	57.99	52.67	-5.32
20	57.36	53.34	-4.02

Control Lenses

#	Initial	Final	Diff.
1	60.33	57.80	-2.53
2	56.02	54.13	-1.89
3	52.07	42.71	-9.39
4	57.83	48.11	-9.72
5	54.75	53.01	-1.74
6	59.21	48.06	-11.15
7	53.90	55.58	1.68
8	53.21	48.28	-4.93
9	47.76	52.42	4.66
10	52.62	40.99	-11.63

Testing Criteria: Better than or comparable to control.

Appendix XV: Statistical comparison of test and control results for Total Reflection of Cooper Clear™ lenses with formula (b)(4) Confidential

Test	Control
-9.89	-2.53
2.22	-1.89
-2.27	-9.39
-1.01	-9.72
-11.72	-1.74
11.13	-11.15
-1.73	1.68
-3.17	-4.93
-3.91	4.66
-4.46	-11.63
-3.17	
2.8	
-4.79	
-2.35	
-6.25	
-1.39	
-3.24	
-2.78	
-5.32	
-4.02	

t-Test: Two-Sample Assuming Unequal Variances

	Variable 1	Variable 2
Mean	-2.766	-4.664
Variance	21.86285	31.83827
Observations	20	10
Hypothesized Mean Difference	0	
df	15	
t Stat	0.917758	
P(T<=t) one-tail	0.186634	
t Critical one-tail	1.753051	
P(T<=t) two-tail	0.373267	
t Critical two-tail	2.131451	

Appendix XVI: Purite/HA Rewetter (b)(4) Confidential

Table 13

Diameter (mm)

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Delta
1	14.30	14.20	0.10
2	14.30	14.10	0.20
3	14.35	14.20	0.15
4	14.10	14.00	0.10
5	14.20	14.10	0.10
6	14.30	14.10	0.20
7	14.35	14.25	0.10
8	14.65	14.50	0.15
9	14.35	14.15	0.20
10	14.15	14.10	0.05
11	14.25	14.05	0.20
12	14.20	14.05	0.15
13	14.45	14.50	0.05
14	14.20	14.10	0.10
15	14.85	14.70	0.15
16	14.50	14.35	0.15
17	14.05	14.00	0.05
18	14.30	14.10	0.20
19	14.30	14.15	0.15
20	14.25	14.15	0.10
		$\bar{x} =$	0.13
		sd =	0.05

Control Lenses

#	Initial	Final	Delta
1	14.00	13.95	0.05
2	14.20	14.10	0.10
3	14.05	13.85	0.20
4	14.10	14.05	0.05
5	14.25	14.10	0.15
6	14.45	14.25	0.20
7	14.20	14.10	0.10
8	14.40	14.20	0.20
9	14.20	14.05	0.15
10	14.70	14.55	0.15
		$\bar{x} =$	0.14
		sd =	0.06

Testing Criteria: ± 0.20 mm

1 045
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Appendix XVII: Purite/HA Rewetter (b)(4) Confidential

Table 14

Power (D)

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Delta
1	-7.63	-7.63	0.00
2	-3.00	-3.13	0.13
3	+5.13	+5.25	0.12
4	-3.50	-3.25	0.25
5	-2.25	-2.38	0.13
6	-7.50	-7.50	0.00
7	+3.88	+4.00	0.12
8	-2.13	-2.00	0.13
9	-3.13	-3.00	0.13
10	-2.75	-2.75	0.00
11	-7.50	-7.75	0.25
12	-2.75	-2.63	0.12
13	+1.88	+2.00	0.12
14	-7.50	-7.38	0.12
15	-3.13	-3.13	0.00
16	+3.88	+4.13	0.25
17	-7.25	-7.38	0.13
18	+4.00	+4.13	0.13
19	-3.13	-3.13	0.00
20	-7.63	-7.63	0.00
		$\bar{x} =$	0.11
		sd =	0.08

Control Lenses

#	Initial	Final	Delta
1	-3.13	-3.25	0.12
2	-3.13	-3.25	0.12
3	0.00	0.00	0.00
4	-2.50	-2.50	0.00
5	-7.25	-7.38	0.13
6	-2.63	-2.50	0.13
7	-2.88	-2.88	0.00
8	+3.75	+3.88	0.13
9	-3.13	-3.25	0.12
10	-2.88	-3.00	0.12
		$\bar{x} =$	0.09
		sd =	0.06

Testing Criteria: ± 0.25 D

Appendix XVIII: Purite/HA Rewetter, (b)(4) Confidential

Table 15

Base Curve (mm)

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Delta
1	7.67	7.84	0.17
2	7.69	7.57	0.08
3	7.40	7.41	0.01
4	7.84	7.95	0.11
5	8.01	8.17	0.16
6	8.07	8.25	0.18
7	7.29	7.37	0.08
8	8.24	8.07	0.17
9	8.28	8.43	0.15
10	8.06	7.97	0.09
11	8.41	8.45	0.04
12	7.98	7.86	0.12
13	8.29	8.35	0.06
14	8.56	8.63	0.07
15	8.67	8.70	0.03
16	7.77	7.85	0.08
17	8.15	8.18	0.03
18	8.25	8.40	0.15
19	7.64	7.75	0.11
20	8.44	8.32	0.12
		$\bar{x} =$	0.10
		sd =	0.05

Control Lenses

#	Initial	Final	Delta
1	8.12	8.04	0.08
2	8.10	8.02	0.08
3	8.48	8.17	0.31
4	8.12	8.08	0.04
5	8.60	8.55	0.05
6	8.17	8.03	0.14
7	7.73	7.83	0.10
8	7.96	8.04	0.08
9	8.21	8.23	0.02
10	7.96	7.95	0.01
		$\bar{x} =$	0.09
		sd =	0.09

Testing Criteria: ± 0.20 mm

Appendix XIX: Purite/HA Rewetter (b)(4) Confidential

Table 16

Total Reflection

Group 4, BioCurve Soft DW

Test Lenses

#	Initial	Final	Diff.
1	60.36	52.87	-7.49
2	57.02	52.38	-4.64
3	68.42	58.52	-9.90
4	58.77	46.99	-11.78
5	56.50	58.26	1.76
6	57.52	54.46	-3.06
7	60.43	60.35	-0.08
8	63.78	61.18	-2.60
9	92.03	86.81	-5.22
10	101.44	97.45	-3.99
11	60.20	49.94	-10.26
12	95.42	93.21	-2.21
13	62.46	54.18	-8.28
14	58.24	46.76	-11.48
15	97.93	91.38	-6.55
16	69.76	62.51	-7.25
17	58.87	53.01	-5.86
18	62.63	57.84	-4.79
19	57.78	54.58	-3.20
20	61.34	50.73	-10.61

Control Lenses

#	Initial	Final	Diff.
1	91.58	85.75	-5.83
2	94.36	93.62	-0.74
3	57.56	61.59	4.03
4	92.87	98.63	5.76
5	63.79	62.77	-1.02
6	57.72	62.51	4.79
7	98.18	99.00	0.82
8	63.65	58.74	-4.91
9	58.78	59.19	0.41
10	84.40	92.42	8.02

Testing Criteria: Better than or comparable to control.

Appendix XX: Statistical comparison of test and control results for Total Reflection of BioCurve lenses with formula (b)(4) Confidential

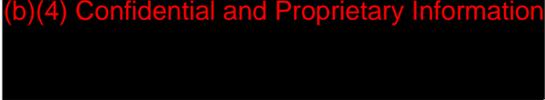
Test	Control
-7.49	-5.83
-4.64	-0.74
-9.9	4.03
-11.78	5.76
1.76	-1.02
-3.06	4.79
-0.08	0.82
-2.6	-4.91
-5.22	0.41
-3.99	8.02
-10.26	
-2.21	
-8.28	
-11.48	
-6.55	
-7.25	
-5.86	
-4.79	
-3.2	
-10.61	

t-Test: Two-Sample Assuming Unequal Variances

	Variable 1	Variable 2
Mean	-5.8745	1.133
Variance	14.35108	20.48573
Observations	20	10
Hypothesized Mean Difference	0	
df	16	
t Stat	-4.21334	
P(T<=t) one-tail	0.00033	
t Critical one-tail	1.745884	
P(T<=t) two-tail	0.00066	
t Critical two-tail	2.119905	

Lens Compatibility (RGP lenses)

(b)(4) Confidential and Proprietary Information

A solid black rectangular redaction box covers the text below the FOIA exemption code.

June 10, 2003

ADVANCED MEDICAL OPTICS

BRAND SUPPORT TECHNOLOGIES

Lens Compatibility Study of Purite/HA Rewetter, Formula's 9464X and 9467X with RGP Contact Lenses for Regulatory Registration

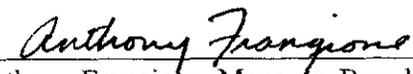
Technical Report No.: 2261

BST Study No.: 2003-012

Issued: Date of Last Signature

Author:  6/10/03
Anh La, Associate Professional, Brand Support Technologies Date

Reviewed by:  6/10/03
Marcel Van Leuven, Senior Professional, Brand Support Technologies Date

Approved by:  6-10-03
Anthony Frangione, Manager, Brand Support Technologies Date

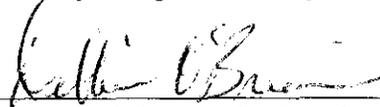
Approved by:  6-10-03
Debbie O'Brien, Senior Regulatory Professional, Regulatory Affairs Date

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Information

1.0 SUMMARY

The purpose of this study was to demonstrate the compatibility of two formulations (9464X and 9467X) of the Purite/HA (Hyaluronic Acid) Rewetter with RGP contact lenses. In this study, diameter, power, base curve, as well as physical appearance of the lenses were monitored during thirty (30) regimen cycles. The control, Refresh Contacts™, was run concurrently. Silicone Acrylate lenses and Fluorosilicone Acrylate RGP lenses were used. The averaged results for the changes in measurements of diameter, power, and base curve for the test lenses were within the established acceptance criteria. Also, the results of the test lenses showed a trend that was comparable to that of the control lenses. In addition, the results for physical appearance did not show any evidence of surface deposits, discoloration and/or deformities with any of the lenses tested. The results of this study demonstrate that the Purite/HA Rewetter products (9464X and 9467X) are compatible with RGP contact lenses and perform equivalent to the control.

KEY WORDS: Compatibility, Purite/HA Rewetter contact lenses, Silicone Acrylate, Fluorosilicone Acrylate, Refresh Contacts™

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(b)(4) Confidential and Proprietary Information

2.0 INTRODUCTION/PURPOSE

The purpose of this study was to demonstrate the compatibility of two formulations (9464X and 9467X) of the Purite/HA (Hyaluronic Acid) Rewetter with RGP contact lenses. The comparability of the two formulations to the control solution will also be noted. Trans Aire lenses represented the silicone acrylate group and FluoroPerm® 60 represented the fluorosilicone acrylate group. This study is intended to support the regulatory submission of the Purite/HA Rewetter.

3.0 MATERIALS/EQUIPMENT

3.1 MATERIALS

- Purite/HA Rewetter, 9464X (0.15% sodium hyaluronate), Lot # 02RD45A
- Purite/HA Rewetter, 9467X (0.075% sodium hyaluronate, 0.075% HPMC), Lot # 02RD47A
- Refresh Contacts™ (Refresh Tears®), Contact Lens Comfort Drops, 9329X, Lot # 20082
- Wet & Soak (DURACARE™), Wetting and Storing solution, 5885X, Lot # E09327
- DURACLEAN®, Daily Lens Cleaner, 7529X, Lot # E17308
- Lens Plus® Sterile Saline solution, 7317X, Lot # 22792
- TransAire (SA), RGP Contact Lens, Lot # A061097
- FluoroPerm® 60 (FSA), RGP Contact Lens, Lot # 423108
- RGP Barrel Lens Case
- Artificial Tear Solution

3.2 EQUIPMENT

- (b)(4) Confidential and Proprietary Information
- [REDACTED]
- [REDACTED]
- [REDACTED]

4.0 PROCEDURES

Compatibility testing was performed according to (b)(4) Confidential and Proprietary Information guidelines of ISO 11981. Silicone Acrylate and Fluorosilicone Acrylate lenses were used in this study. The lenses were cycled 30 times through a regimen of Artificial Tear and DURACLEAN®/

(b)(4) Confidential and Proprietary Information

DURACARE™, with the test products (9464X and 9467X) being applied during the Artificial Tear soak.

The procedure was as follows:

- All lenses (test and control) were cleaned (rubbed/rinsed) with Lens Plus® Sterile Saline solution.
- All lenses were conditioned in Lens Plus® Sterile Saline solution for at least forty-eight hours.
- All lenses were inspected for initial appearance, i.e. cleanliness, color, shape and integrity.
- Initial measurements of diameter, power and base curve were made for all lenses.
- The test lenses (10 per group, per test product), were exposed to the following **test regimen**:
 1. Soak the lenses in 3 mL of Artificial Tear solution at 37°C for 8 hours.
 2. During the soak, remove the lens from the Artificial Tear solution and apply 2-3 drops of the respective test solution to the anterior side of the lens. Return the lens to the Artificial Tear solution.
 3. Repeat the application (step 2) every 2 hours.
 4. After 8 hours in Artificial Tear, remove the lenses from solution.
 5. Apply 2-3 drops of DURACLEAN® and rub for 20 seconds.
 6. Rinse with DURACARE™, 10 seconds on each side of the lens.
 7. Place the lenses in the RGP Barrel Lens Case filled with DURACARE™ and allow to soak for 16-18 hours (overnight).
 8. Repeat cycle 30 times.
- Measurements of diameter, power and base curve for all lenses were made after completion of the final cycle. The lenses were visually examined for cleanliness and possible evidence of discoloration and deformities.
- The control lenses (5 per group) were exposed to the **control regimen**, which was identical to the test regimen, except that Refresh Contacts® was substituted for the test product.

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- The difference between final and initial measurements for all lenses was calculated and the averaged value was compared to the acceptance standards.
- Acceptance criteria:

The test solutions, Purite/HA Rewetter (b)(4) Confidential and Proprietary Information will be acceptable for use with RGP contact lenses if the lenses tested are within the limits of the standards for clinically significant parameter changes for RGP lenses (see below). If any one of the criteria is not met, the solutions may still be considered acceptable if the test results compare favorably with the control results.

Parameter-standards of acceptance:

Diameter	:	± 0.20 mm
Power	:	± 0.25 Diopter
Base Curve	:	± 0.04 mm

5.0 RESULTS

The results of measurements of diameter, power and base curve can be found in Appendices I through VI. Missing values in appendices I, III, and V were caused by loss of the lens due to handling. Results for physical appearance did not show any evidence of lens surface deposits, discoloration and/or deformities with any of the lenses tested.

6.0 DISCUSSION

The averaged results for the changes in measurements of diameter, power and base curve for the lenses tested with 9464X and 9467X formulations were within the limits of the established parameter standards. They also showed a trend that was comparable to that of the control lenses. These results, including the observations for physical appearance, met the acceptance criteria as stated in the protocol for this study. Therefore, FDA and ISO requirements were met.

7.0 CONCLUSION

The results of this study demonstrate that the two formulations of the Purite/HA Rewetter, 9464X and 9467X, are compatible with RGP contact lenses.

(b)(4) Confidential and Proprietary Information

8.0 REFERENCES

1. SOP #PDBST-M-03, Method for Lens Compatibility Testing (version 2.0)
2. SOP #PDBST-M-04, Method to Measure the Power of Soft Hydrophilic/RGP Contact Lenses (version 2.0)
3. SOP #PDBST-I-15, Calibration and Use of the Optimec Contact Lens Dimension Analyzer (version 2.0)
4. SOP #PDBST-I-12, Calibration and Use of the Marco Radiusgauge (version 2.0)
5. ISO 11981, Assessment of Physical Compatibility of Contact Lenses with their Care Products
6. AMO Laboratory Notebook # 684, pgs.38-44, 80-82, and #703, pg. 44
7. Protocol for the Compatibility Study of Purite/HA Rewetter, Formula's 9464X and 9467X with RGP Contact Lenses for Regulatory Registration, (b)(4) Study #2003-012

9.0 APPENDICES

- Appendix I: Diameter Measurements of Trans Aire (SA)
- Appendix II: Diameter Measurements of FluoroPerm®60 (FSA)
- Appendix III: Power Measurements of Trans Aire (SA)
- Appendix IV: Power Measurements of FluoroPerm®60 (FSA)
- Appendix V: Base Curve Measurements of Trans Aire (SA)
- Appendix VI: Base Curve Measurements of FluoroPerm®60 (FSA)

(b)(4) Confidential and Proprietary Information

Appendix I: Diameter Measurements of Trans Aire (SA)

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	9.00	9.00	0.00
2	8.95	8.95	0.00
3	9.00	9.00	0.00
4	9.00	9.00	0.00
5	9.00	9.00	0.00
6	9.00	9.00	0.00
7	8.95	8.95	0.00
8	9.00	9.00	0.00
9	8.90	8.90	0.00
10	9.00	9.00	0.00
		\bar{x}	0.00
		sd	0.00

Purite/HA Rewetter (b)(4) Confidential

#	Initial	Final	Delta
1	9.00	9.00	0.00
2	9.00	9.00	0.00
3	8.95	8.95	0.00
4	9.05	9.05	0.00
5	9.00	9.00	0.00
6	9.00	9.00	0.00
7	9.00	-	-
8	9.00	9.05	0.05
9	9.00	9.00	0.00
10	9.00	9.00	0.00
		\bar{x}	0.01
		sd	0.02

Control -- Refresh Contacts™

#	Initial	Final	Delta
1	9.05	9.05	0.00
2	8.95	8.95	0.00
3	9.00	9.00	0.00
4	9.05	9.05	0.00
5	9.00	9.00	0.00
		\bar{x}	0.00
		sd	0.00

Acceptance Criteria: ± 0.20 mm

(b)(4) Confidential and Proprietary Information

Appendix II: Diameter Measurements of FluoroPerm®60 (FSA)

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	9.00	9.00	0.00
2	9.00	9.05	0.05
3	8.95	8.95	0.00
4	9.00	9.05	0.05
5	9.00	9.00	0.00
6	9.00	9.00	0.00
7	9.00	9.00	0.00
8	8.95	8.95	0.00
9	9.00	9.00	0.00
10	9.00	9.00	0.00
		\bar{x}	0.01
		sd	0.02

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	9.00	9.00	0.00
2	9.00	9.00	0.00
3	9.00	9.00	0.00
4	9.05	9.05	0.00
5	9.00	9.00	0.00
6	9.00	9.00	0.00
7	9.00	9.00	0.00
8	9.00	9.00	0.00
9	9.05	9.05	0.00
10	9.00	9.00	0.00
		\bar{x}	0.00
		sd	0.00

Control – Refresh Contacts™

#	Initial	Final	Delta
1	8.95	8.95	0.00
2	9.05	9.00	0.05
3	9.00	8.95	0.05
4	8.95	8.95	0.00
5	9.00	9.00	0.00
		\bar{x}	0.02
		sd	0.03

Acceptance Criteria: ± 0.20 mm

Appendix III: Power Measurements of Trans Aire (SA)

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	-3.88	-3.88	0.00
2	+6.25	+6.25	0.00
3	+6.25	+6.25	0.00
4	+4.13	+4.25	0.12
5	+6.25	+6.25	0.00
6	-6.00	-6.00	0.00
7	+2.13	+2.13	0.00
8	-6.00	-6.00	0.00
9	-5.88	-5.88	0.00
10	+4.13	+4.13	0.00
		\bar{x}	0.01
		sd	0.04

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	+2.00	+2.00	0.00
2	+2.13	+2.13	0.00
3	+2.00	+2.00	0.00
4	-4.00	-4.00	0.00
5	-4.00	-4.00	0.00
6	-1.88	-1.88	0.00
7	-4.00	-	-
8	-1.88	-1.88	0.00
9	-1.88	-1.88	0.00
10	-3.88	-3.88	0.00
		\bar{x}	0.00
		sd	0.00

Control – Refresh Contacts™

#	Initial	Final	Delta
1	-2.00	-2.00	0.00
2	-1.88	-1.88	0.00
3	+4.13	+4.13	0.00
4	+4.13	+4.25	0.12
5	+2.00	+2.00	0.00
		\bar{x}	0.02
		sd	0.05

Acceptance Criteria: ± 0.25 Diopter

(b)(4) Confidential and Proprietary Information

Appendix V: Base Curve Measurements of Trans Aire (SA)

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	8.55	8.55	0.00
2	8.50	8.52	0.02
3	8.50	8.53	0.03
4	8.52	8.52	0.00
5	8.52	8.53	0.01
6	8.60	8.59	0.01
7	8.53	8.54	0.01
8	8.52	8.56	0.04
9	8.63	8.62	0.01
10	8.51	8.47	0.04
		\bar{x}	0.02
		sd	0.01

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	8.49	8.51	0.02
2	8.53	8.55	0.02
3	8.48	8.49	0.01
4	8.54	8.55	0.01
5	8.55	8.56	0.01
6	8.59	8.57	0.02
7	8.48	-	-
8	8.55	8.58	0.03
9	8.61	8.58	0.03
10	8.61	8.61	0.00
		\bar{x}	0.02
		sd	0.01

Control – Refresh Contacts™

#	Initial	Final	Delta
1	8.53	8.51	0.02
2	8.53	8.53	0.00
3	8.48	8.48	0.00
4	8.54	8.55	0.01
5	8.49	8.49	0.00
		\bar{x}	0.01
		sd	0.01

Acceptance Criteria: ±0.04 mm

(b)(4) Confidential and Proprietary Information

Appendix VI: Base Curve Measurements of FluoroPerm® 60 (FSA)

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	8.60	8.59	0.01
2	8.59	8.58	0.01
3	8.53	8.56	0.03
4	8.54	8.55	0.01
5	8.53	8.55	0.02
6	8.52	8.51	0.01
7	8.61	8.60	0.01
8	8.61	8.58	0.03
9	8.55	8.54	0.01
10	8.53	8.53	0.00
		\bar{x}	0.01
		sd	0.01

Purite/HA Rewetter, (b)(4) Confidential

#	Initial	Final	Delta
1	8.56	8.56	0.00
2	8.56	8.57	0.01
3	8.50	8.46	0.04
4	8.52	8.52	0.00
5	8.57	8.55	0.02
6	8.52	8.52	0.00
7	8.50	8.53	0.03
8	8.50	8.51	0.01
9	8.50	8.50	0.00
10	8.52	8.52	0.00
		\bar{x}	0.01
		sd	0.01

Control – Refresh Contacts™

#	Initial	Final	Delta
1	8.56	8.57	0.01
2	8.56	8.58	0.02
3	8.60	8.59	0.01
4	8.55	8.54	0.01
5	8.57	8.56	0.01
		\bar{x}	0.01
		sd	0.00

Acceptance Criteria: ±0.04 mm

Solution Compatibility

(b)(4) Confidential and Proprietary Information

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June 5, 2003

ADVANCED MEDICAL OPTICS

**RESEARCH AND DEVELOPMENT
ANALYTICAL CHEMISTRY**

TECHNICAL REPORT

(b)(4) Confidential and
Proprietary Information

Report for Purite[®] HA Rewetter

(b)(4) Confidential and Proprietary
Information

Compatibility

ISSUED: Date of Last Signature

Author: Celeste Lim 06/05/03
Celeste Lim, Associate Professional, Formulation Development Date

Reviewed by: Stuart 06/05/03
Lam Tran, Senior Professional, Formulation Development Date

Approved by: James Cook 06/05/03
James Cook, Manager, Formulation Development and Analytical Chemistry Date

1.0 PURPOSE

The compatibility of the Purite[®] HA Rewetter (9464X and 9467X) with leading contact lens care products on the market was determined in this study.

2.0 MATERIALS AND METHODS

Changes in physical appearance, pH and osmolality were monitored 10 minutes after the addition of Purite[®] HA Rewetter (9464X and 9467X) to each of the following solutions.

2.1 MATERIALS

<u>Product Name</u>	<u>Lot No.</u>	<u>Exp. Date</u>
Complete [®] C (9451X)	(b)(4) Confidential and Proprietary Information	09/2004
Ultra Care [®] (neutralized solution) Neutralizing Tablet		09/2004 09/2004
Bausch & Lomb ReNu Multi-Plus [®]		09/2004
Alcon OptiFree [®] Express [®] MPDS		09/2004
CIBA SOLO-Care Plus with Aqualube MPS		10/2004
Boston [®] Simplicity Multi-Action Solution		04/2005

2.2 METHODS

Ten drops of Purite[®] HA Rewetter (9464X or 9467X) were added to 1 ml of each commercial product (except for in Ultra Care[®], where 10 drops of 9464X or 9467X were added to 10ml of neutralized solution). After ten minutes, the physical appearance of the mixtures was observed for any visible change (discoloration or precipitate formation) and the pH and osmolality were measured and recorded.

3.0 RESULTS

3.1 Compatibility of (b)(4) Confidential commercial products

- 3.1.1 The addition of 9464X caused no visible change in physical appearance. No discoloration or precipitate formation was seen.
- 3.1.2 Figures 1 and 2 outline how the pH and osmolality of the six commercial products tested was affected by the addition of 9464X.

Figure 1: The graph demonstrates that the addition of 10 drops of 9464X to each solution causes a slight drop in each solution's pH (except for in Complete C, where the pH remained unchanged). The largest shift in pH was a decrease of 0.11 pH units for SOLO-Care/9464X combination.

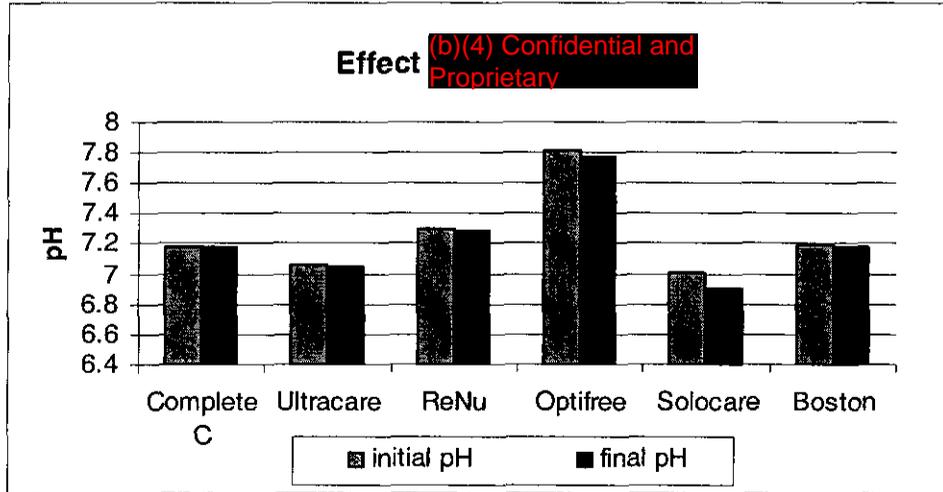
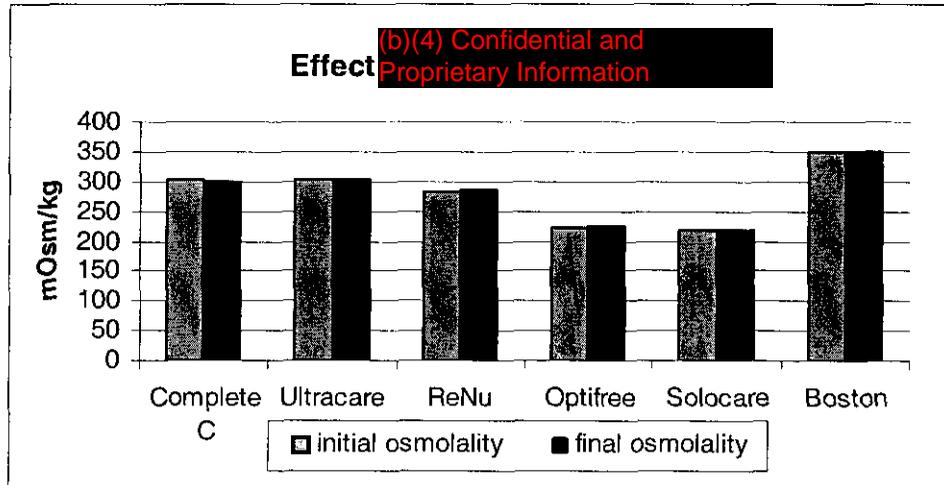


Figure 2: The osmolality of each commercial product was altered minimally after the addition of 10 drops of 9464X.



3.2 Compatibility of (b)(4) Confidential with commercial products

- 3.2.1 The addition of 9467X caused no visible changes in physical appearance. No discoloration or precipitate formation was seen.
- 3.2.2 Figures 3 and 4 outline how the pH and osmolality of the six commercial products tested was affected by the addition of 9467X.

Figure 3: The addition of 10 drops of 9467X to each commercial product caused both an increase and decrease in pH. The highest change (pH drop of 0.11 units) occurred in the SOLO-Care/9467X combination.

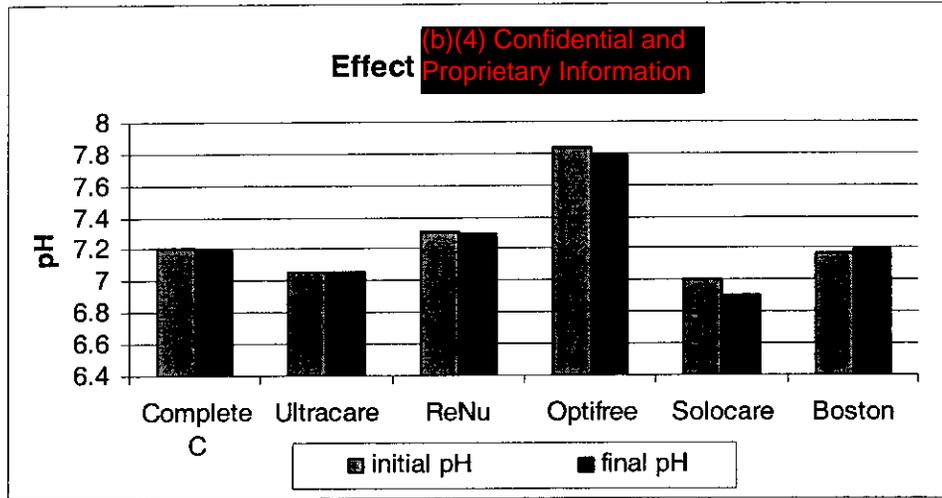
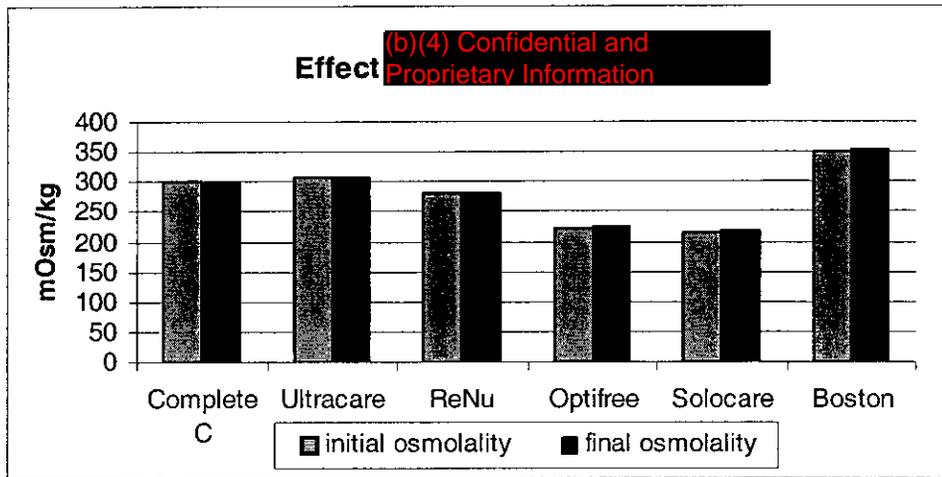


Figure 4: An osmolality change within ± 6 mOsm/kg was seen after 10 drops of 9467X was added to each product.



4.0 DISCUSSION

4.1 Compatibility of (b)(4) Confidential with commercial products

No change was seen in the physical appearance of each commercial product after 9464X was added. Slight drops in pH were seen in all commercial products, except in Complete C. The pH in Complete C after the addition of 9464X remained unchanged from its original pH. The highest drop in pH occurred in the SOLO-Care/9464X combination solution. All solutions demonstrated a small change in osmolality after the addition of 9464X. The

osmolalities of the combination solutions were within ± 3 mOsm/kg from the original osmolalities.

4.2 Compatibility of (b)(4) with commercial products

No change was seen in the physical appearance of each commercial product after 9467X was added. Minimal changes in pH were seen and all variations occurred within ± 0.11 pH units. Similar to 9464X, the highest drop in pH also occurred in the SOLO-Care/ 9467X combination solution. The osmolality of the combination solutions varied within ± 6 mOsm/kg.

5.0 CONCLUSION

All the commercial products tested showed minimal change in physical appearance, pH and osmolality due to the addition of Purite[®] HA Rewetter (b)(4) Confidential and Proprietary Information. The care solution parameters tested remained within safe ranges for the eye following interaction with the Purite[®] HA Rewetter formulations. These results, therefore, indicate that both (b)(4) Confidential and Proprietary Information are compatible with leading contact lens care products.

6.0 REFERENCES

6.1 AMO Laboratory Notebook: CL683_56-58

Preservative Uptake/Release

(b)(4) Confidential and Proprietary Information

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June 13, 2003

ADVANCED MEDICAL OPTICS

**RESEARCH AND DEVELOPMENT
ANALYTICAL CHEMISTRY**

***Report for the Preservative Uptake and Release of Purite[®] from Purite[®] HA
Rewetter (b)(4) Confidential and Proprietary Information) with Hydrophilic and Rigid Gas Permeable
Contact Lenses***

TECHNICAL REPORT

(b)(4) Confidential and
Proprietary Information

ISSUED: Date of Last Signature

Author:	<u>Celeste Lim</u>	<u>06/13/03</u>
	Celeste Lim, Associate Professional, Formulation Development	Date
Reviewed by:	<u>Shuan</u>	<u>06/13/03</u>
	Lam Tran, Senior Professional, Formulation Development	Date
Approved by:	<u>James Cook</u>	<u>6-13-03</u>
	James Cook, Manager, Formulation Development and Analytical Chemistry	Date

1.0 PURPOSE

The uptake and release of the preservative (Purite[®]) in Purite[®] HA Rewetter (b)(4) Confidential with hydrophilic and rigid gas permeable (RGP) contact lenses was determined in this study.

2.0 INTRODUCTION

For safety reasons, contact lens care products in multi-use containers contain substances with antimicrobial activity. The absorption and release of these preservatives by the contact lens may cause irritation and sensitization to the eyes. It is, therefore, necessary to be able to estimate the extent of preservative uptake and release by contact lenses for new contact lens care products and new or modified contact lens materials.

3.0 MATERIALS AND METHODS

3.1 Materials

- Group 1 contact lenses: Optima FW, Bausch & Lomb, Polymacon, 38.6% water, Dia 14.0mm, BC 8.7, PWR – 7.00, lot W31904110, exp 03/2006
- Group 4 contact lenses: SUREVUE[®], Johnson and Johnson, Etafilcon A, 58% water, Dia 14.0, BC 8.8, PWR – 7.00, lot 255302, exp 09/2007
- RGP: Transaire, Rand Scientific Research, Silicone Acrylate, Dia 9.0, BC 8.50, PWR +4.00, lot A061097
- RGP: Fluoroperm 60, Paragon Vision Sciences, Fluoro/Silicone Acrylate, BC 8.50, Dia 9.0, PWR +4.00, lot 423108
- Purite[®] HA Rewetter, 9464X, lot# 02RD24A, DOM: 10/23/03
- Purite[®] HA Rewetter, 9467X, lot # 02RD27A, DOM: 10/24/03
- Isotonic Phosphate Buffered Saline Solution, prepared as per ISO 10344
- Glass scintillation vials

3.2 Methods

Group 1 (low water, nonionic) and Group 4 (high water, ionic) hydrophilic contact lenses and two RGP lens types (Silicone Acrylate and Fluoro/Silicone Acrylate) were used to represent all contact lens groups in a worst case scenario. The preservative uptake and release method described below is in accordance with ISO 11986:1999.

3.2.1 Uptake of Purite[®] (b)(4) Confidential and Proprietary Information

3.2.1.1 In five glass scintillation vials, 10ml of 9464X was added into each vial. Ten lenses of each lens group were added into four

(b)(4) Confidential and Proprietary Information

vials (one lens group per vial). The only exception occurred in the Transaire vial, where seven lenses were added into 7ml of (b)(4) Confidential. The fifth vial containing no lenses served as the solution control vial. All test vials were stored in a small box in the dark at 25 ± 2 °C with occasional shakes to ensure adequate mixing.

3.2.1.2 Another set of five glass scintillation vials were filled with 10ml of (b)(4) Confidential. Ten lenses of each lens group were added into four vials. Once again, the only exception occurred in the Transaire vial, where six lenses were added into 6ml of 9467X. The fifth vial containing no lenses served as the solution control vial. All test vials were stored in a small box in the dark at 25 ± 2 °C with occasional shakes to ensure adequate mixing.

3.2.1.3 The matrix of samples tested is shown below:

Lens Type	Brand	Test Solutions	
		9464X	9467X
Soft-Group 1	Optima FW	10 lenses/10ml	10 lenses/10ml
Soft-Group 4	SureVue	10 lenses/10ml	10 lenses/10ml
RGP*	TransAire	7 lenses/7ml	6 lenses/6ml
RGP	FluoroPerm 60	10 lenses/10ml	10 lenses/10ml

* Note: The number of lenses used was reduced due to a limited number available for the study.

At the designated time intervals, 100µl aliquot portions (n=3) of the test solutions were taken and assayed for Purite® content. Aliquot portions (100 µl, n=3) of the solution control vials with no lenses were also assayed for Purite® baseline content. The assay was performed according to the current version of Method # AC-024-A. The procedure was continued until the uptake reached a plateau.

3.2.1.4 Time points: 4, 8, 24 and 48 hours.

3.2.1.5 The uptake values were calculated as follows:

Hydrogel Lenses

$$\text{uptake } (\mu\text{g}/\text{mg lens}) = \frac{[\text{purite}(\text{ppm}) \text{ in control vial} - \text{purite}(\text{ppm}) \text{ in test vial}] \times \text{volume (ml) in vial}}{\text{total dry weight (mg) of the lenses}}$$

RGP Lenses

$$\text{uptake } (\mu\text{g}/\text{cm}^2) = \frac{[\text{purite}(\text{ppm}) \text{ in control vial} - \text{purite}(\text{ppm}) \text{ in test vial}] \times \text{volume (ml) in vial}}{\text{total surface area (cm}^2\text{) of the lenses}}$$

3.2.2 Release of Purite® (b)(4) Confidential and Proprietary Information

- 3.2.2.1 10ml of un-preserved isotonic phosphate buffered saline solution was added into a scintillation vial.
- 3.2.2.2 The hydrophilic Group 1 test lenses were removed from the 9464X soak solution and excess solution was removed from each lens by gently touching the lens with a Kimwipe® absorbent tissue.
- 3.2.2.3 The ten lenses were immersed in the saline vial and stored at 37 ± 2 °C for 48 hours in a small box in the dark with occasional shakes.
- 3.2.2.4 At the designated time intervals, 100µl aliquot portions (n=3) of the test solution were taken and assayed for Purite® content. The assay was performed according to the current version of Method # AC-024-A. The procedure was continued until the release reached a plateau.
- 3.2.2.5 Time points: 4, 8, 24 and 48 hours.
- 3.2.2.6 Steps 3.2.2.1 to 3.2.2.5 were repeated for hydrophilic Group 4 lenses and the two RGP lens types.
- 3.2.2.7 Steps 3.2.2.1 to 3.2.2.6 were repeated for formula 9467X.
- 3.2.2.8 The release of purite® was calculated as follows:

Hydrogel Lenses

$$\text{release } (\mu\text{g}/\text{mg lens}) = \frac{\text{purite (ppm) in saline vial} \times \text{volume (ml) in vial}}{\text{total dry weight (mg) of the lenses}}$$

RGP Lenses

$$\text{release } (\mu\text{g}/\text{cm}^2 \text{ lens}) = \frac{\text{purite(ppm) in saline vial} \times \text{volume (ml) in vial}}{\text{total surface area (cm}^2\text{) of the lenses}}$$

4.0 RESULTS

4.1 (b)(4) Confid - Uptake and Release

4.1.1 Group 1 Hydrogel Lenses

The Purite[®] uptake and release data for the Group 1 (Optima) hydrogel lenses are graphed in Figures 1 and 2 respectively. The calculated uptake and release values are tabulated in Table 1.

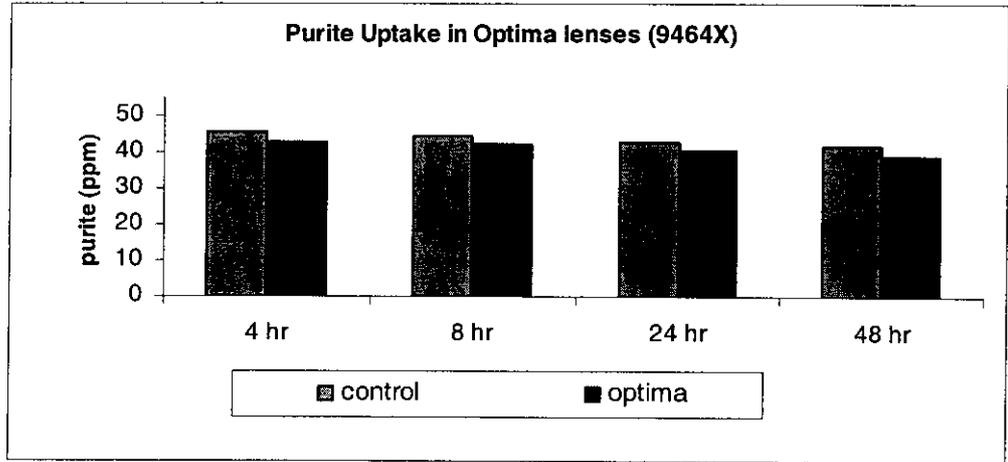


Figure 1: The uptake of Purite[®] in Optima lenses that were soaked in 9464X.

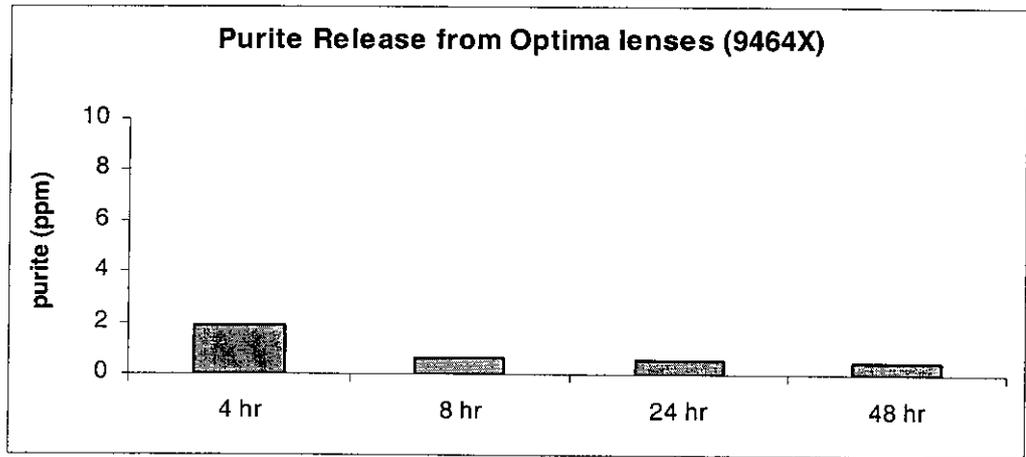


Figure 2: Purite[®] release from Optima lenses into saline, following soak in 9464X.

Table 1: Calculated uptake and release values following soaking Group 1 (Optima) hydrogel lenses in 9464X. The average total dry weight of the lenses was 208.4 mg.

Time Point (hr)	Uptake ($\mu\text{g}/\text{mg}$ lens)	Release ($\mu\text{g}/\text{mg}$ lens)
4	0.140	0.091
8	0.095	0.029
24	0.088	0.027
48	0.136	0.022

(b)(4) Confidential and Proprietary Information

4.1.2 Group 4 Hydrogel Lenses

The Purite[®] uptake and release data for the Group 4 (Surevue) hydrogel lenses are graphed in Figures 3 and 4 respectively. The calculated uptake and release values are tabulated in Table 2.

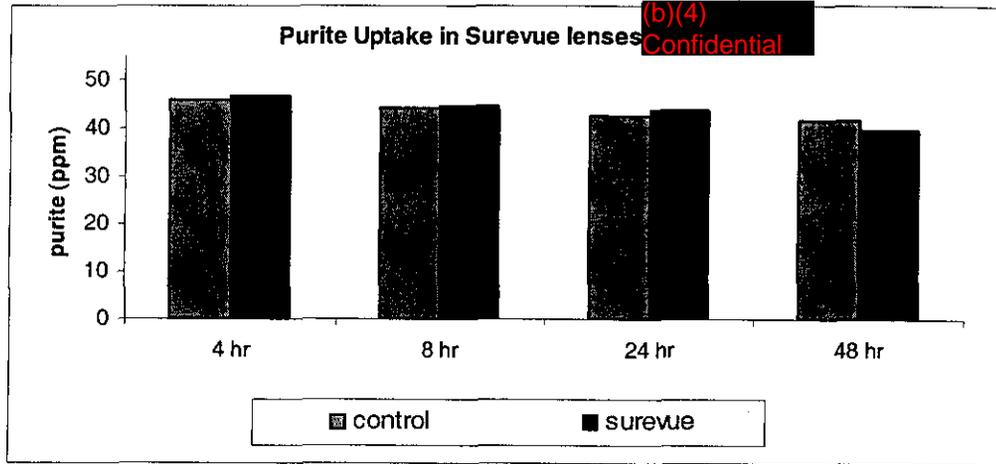


Figure 3: The uptake of Purite[®] in Surevue lenses that were soaked in 9464X.

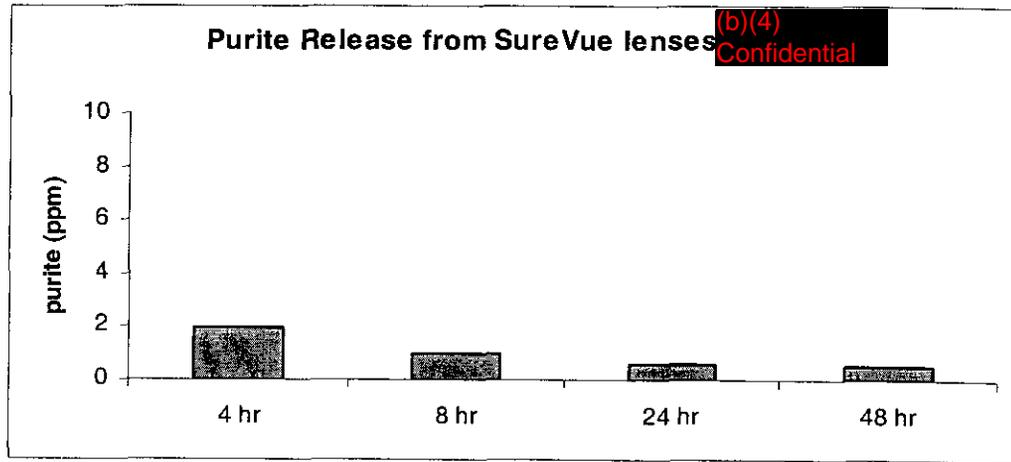


Figure 4: Purite[®] release from Surevue lenses into saline, following soak in 9464X.

Table 2: Calculated uptake and release values following soaking Group 4 (Surevue) hydrogel lenses in 9464X. The average total dry weight of the lenses was 160.7 mg.

Time Point (hr)	Uptake ($\mu\text{g}/\text{mg}$ lens)	Release ($\mu\text{g}/\text{mg}$ lens)
4	-0.050	0.120
8	-0.026	0.062
24	-0.078	0.039
48	0.131	0.030

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4.1.3 Silicone Acrylate RGP Lenses

The Purite[®] uptake and release data for the Silicone Acrylate RGP (Transaire) lenses are graphed in Figures 5 and 6 respectively. The calculated uptake and release values are tabulated in Table 3.

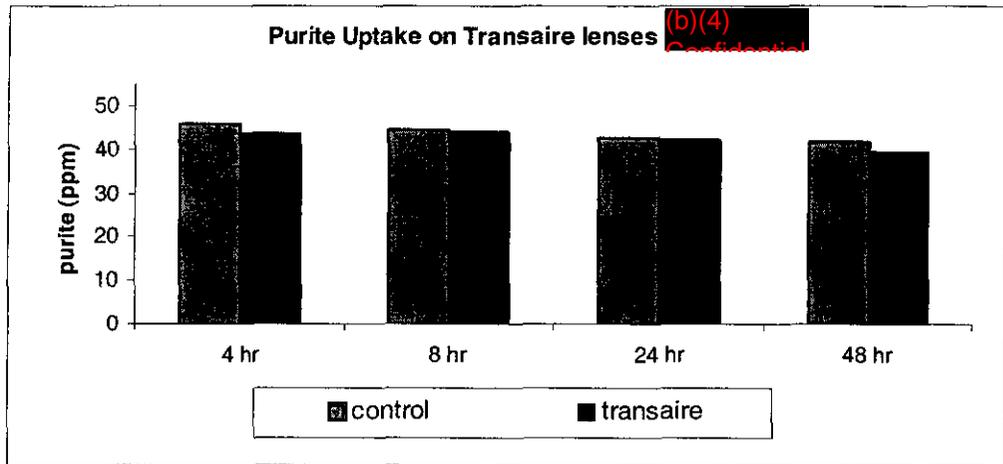


Figure 5: The uptake of Purite[®] on Transaire lenses that were soaked in 9464X.

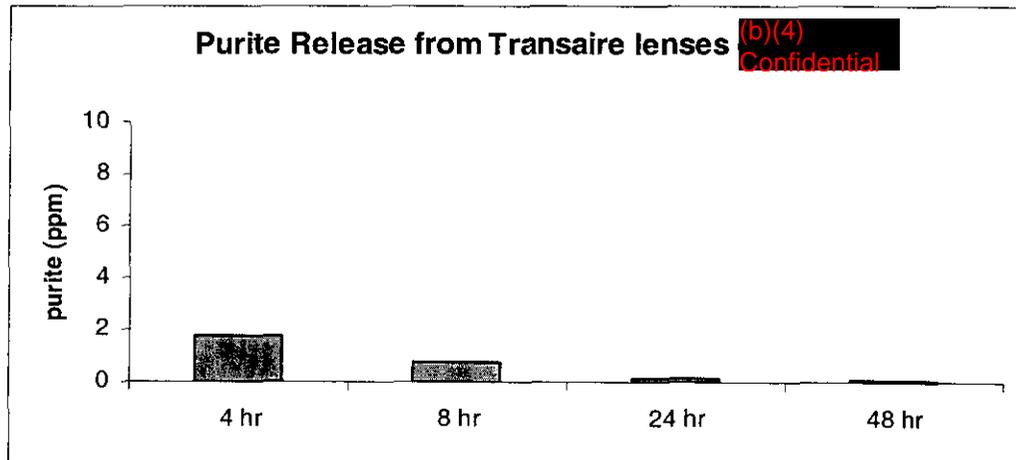


Figure 6: Purite[®] release from Transaire lenses into saline, following soak in 9464X.

Table 3: Calculated uptake and release values following soaking Silicone Acrylate RGP (Transaire) lenses in (b)(4). The average total surface area of the lenses was 9.19 cm².

Time Point (hr)	Uptake (μg/cm ² lens)	Release (μg/mg lens)
4	1.35	1.90
8	-0.524	0.806
24	-1.02	0.163
48	-0.287	0.092

4.1.4 Fluoro/Silicone Acrylate RGP Lenses

The Purite[®] uptake and release data for the Fluoro/Silicone Acrylate RGP (Fluoroperm) lenses are graphed in Figures 7 and 8 respectively. The calculated uptake and release values are tabulated in Table 4.

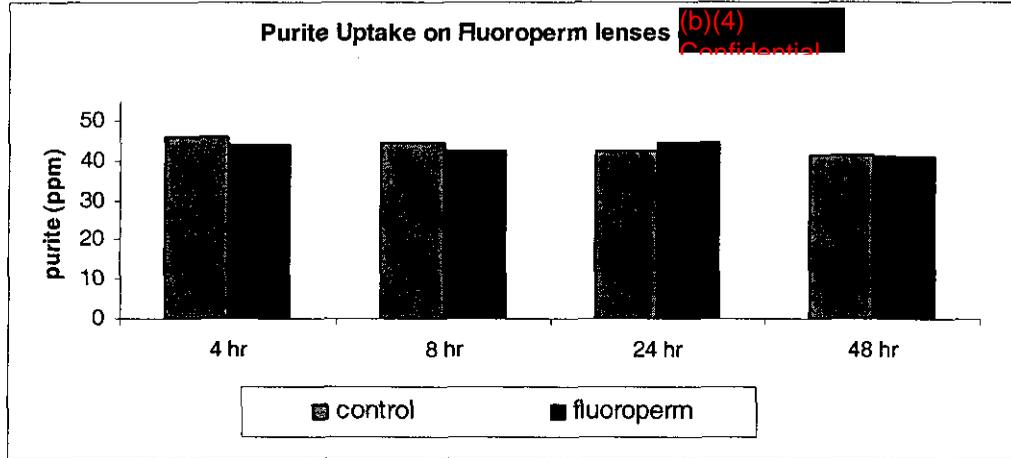


Figure 7: The uptake of Purite[®] on Fluoroperm lenses that were soaked in 9464X.

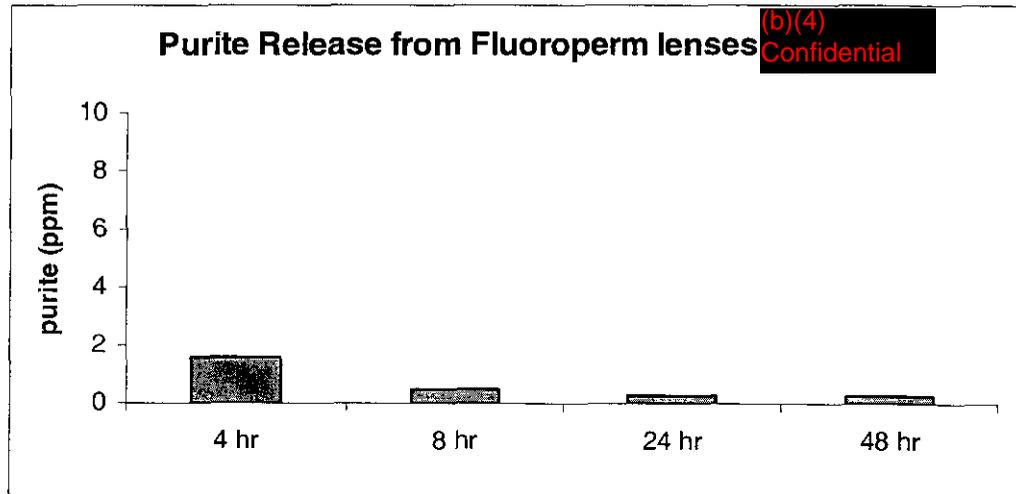


Figure 8: Purite[®] release from Fluoroperm lenses into saline, following soak in 9464X.

Table 4: Calculated uptake and release values following soaking Fluoro/Silicone Acrylate RGP (Fluoroperm) lenses in 9464X. The average total surface area of the lenses was 12.7 cm².

Time Point (hr)	Uptake ($\mu\text{g}/\text{cm}^2$ lens)	Release ($\mu\text{g}/\text{mg}$ lens)
4	1.33	1.35
8	1.49	0.433
24	-1.32	0.197
48	0.651	0.236

4.2 (b)(4) Confidential – Uptake and Release

4.2.1 Group 1 Hydrogel Lenses

The Purite® uptake and release data for the Group 1 (Optima) hydrogel lenses are graphed in Figures 9 and 10 respectively. The calculated uptake and release values are tabulated in Table 5.

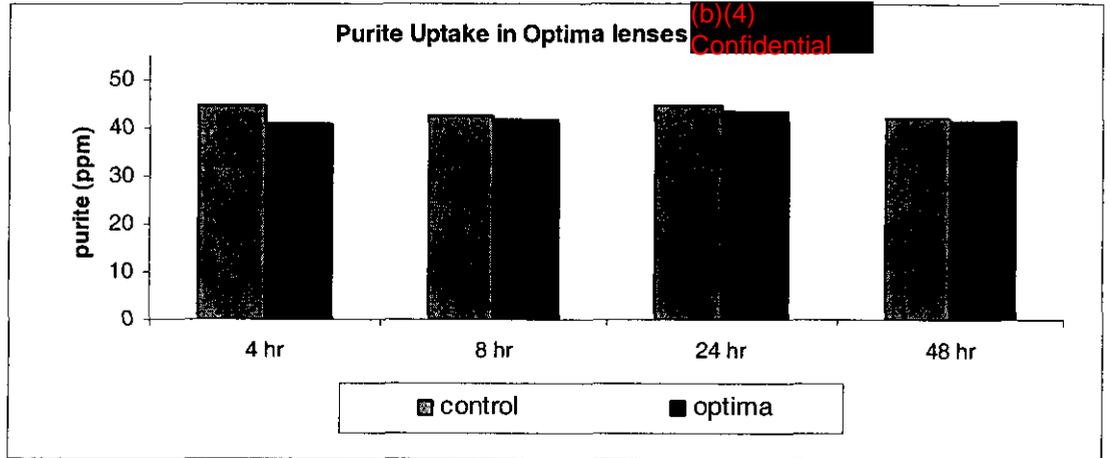


Figure 9: The uptake of Purite® in Optima lenses that were soaked in 9467X.

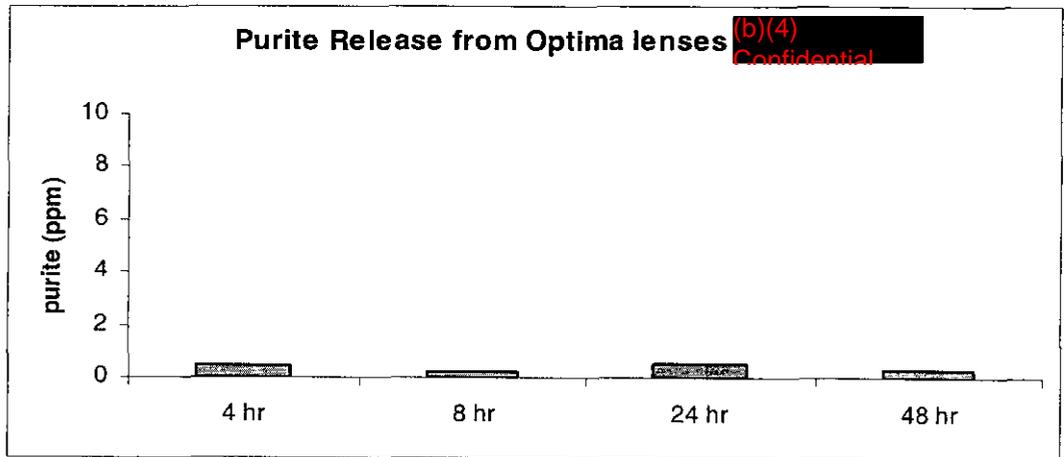


Figure 10: Purite® release from Optima lenses into saline, following soak in 9467X.

Table 5: Calculated uptake and release values following soaking Group 1 (Optima) hydrogel lenses in 9467X. The average total dry weight of the lenses was 225.3 mg.

Time Point (hr)	Uptake (µg/mg lens)	Release (µg/mg lens)
4	0.167	0.020
8	0.034	0.010
24	0.054	0.023
48	0.041	0.012

4.2.2 Group 4 Hydrogel Lenses

The Purite[®] uptake and release data for the Group 4 (Surevue) hydrogel lenses are graphed in Figures 11 and 12 respectively. The calculated uptake and release values are tabulated in Table 6.

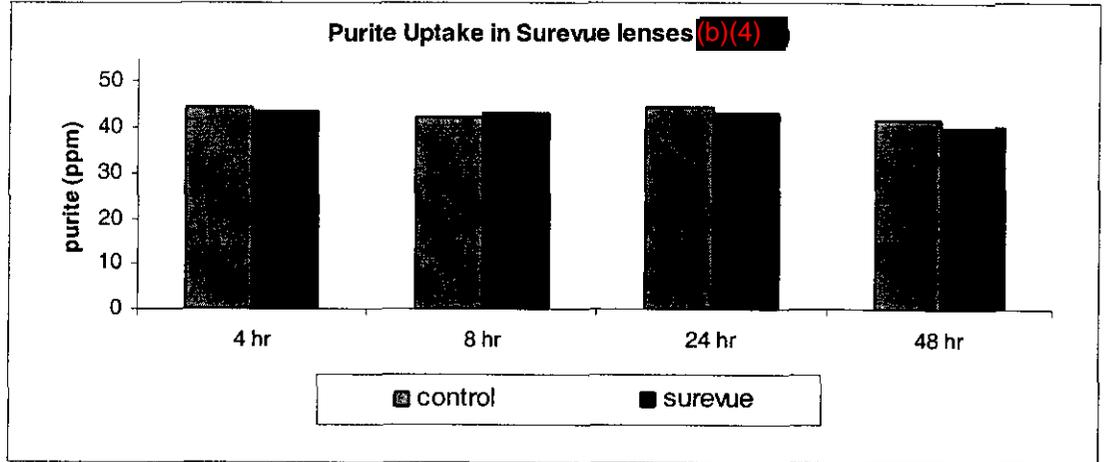


Figure 11: The uptake of Purite[®] in Surevue lenses that were soaked in (b)(4) Confidential and

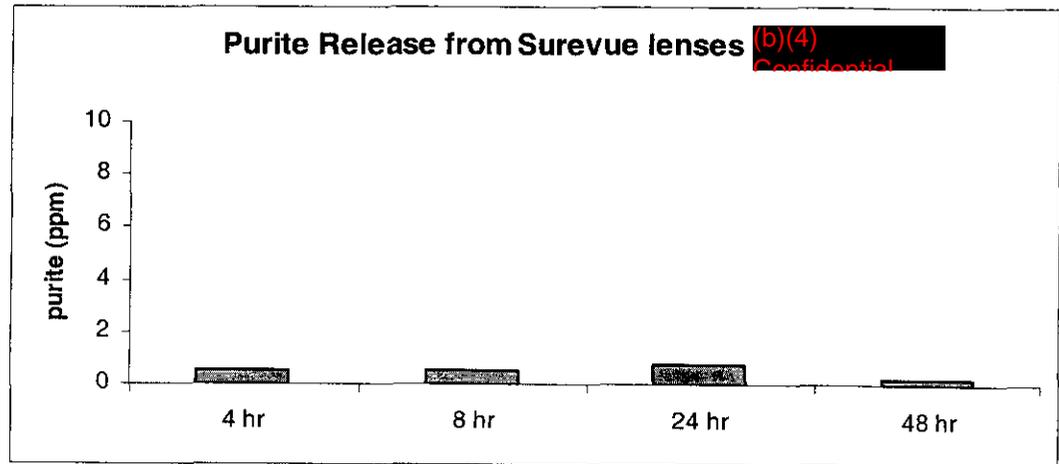


Figure 12: Purite[®] release from Surevue lenses into saline, following soak in 9467X.

Table 6: Calculated uptake and release values following soaking Group 4 (Surevue) hydrogel lenses in 9467X. The average total dry weight of the lenses was 164.1 mg.

Time Point (hr)	Uptake ($\mu\text{g}/\text{mg}$ lens)	Release ($\mu\text{g}/\text{mg}$ lens)
4	0.057	0.031
8	-0.048	0.031
24	0.073	0.046
48	0.114	0.013

4.2.3 Silicone Acrylate RGP Lenses

The Purite[®] uptake and release data for the Silicone Acrylate RGP (Transaire) lenses are graphed in Figures 13 and 14 respectively. The calculated uptake and release values are tabulated in Table 7.

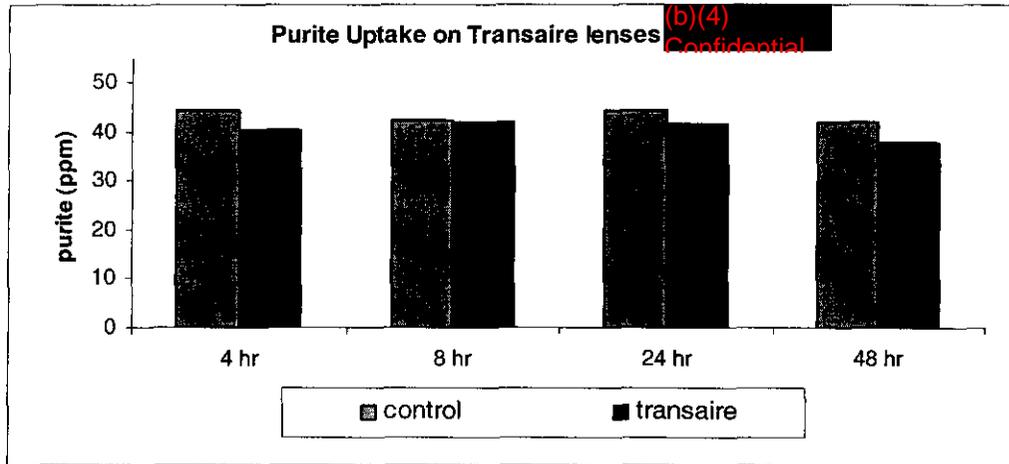


Figure 13: The uptake of Purite[®] on Transaire lenses that were soaked in

(b)(4) Confidential

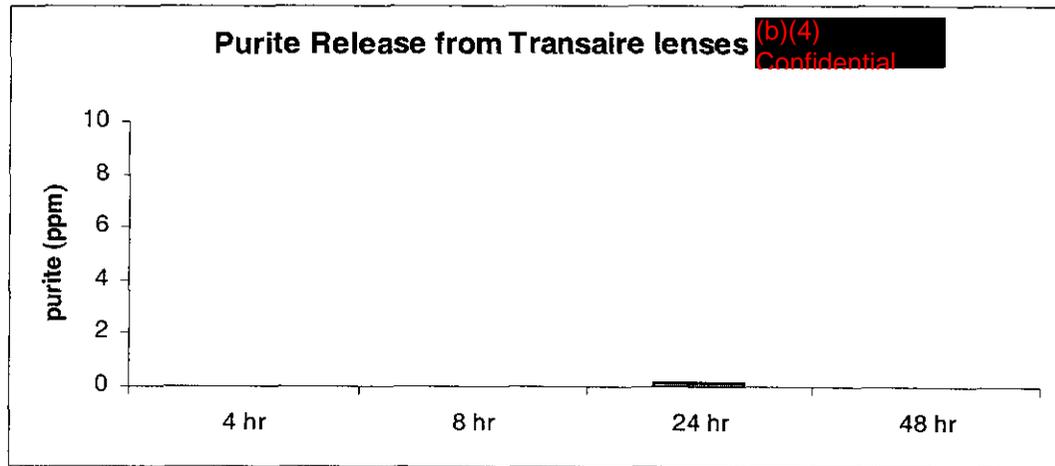


Figure 14: Purite[®] release from Transaire lenses into saline, following soak in

(b)(4) Confidential

Table 7: Calculated uptake and release values following soaking Silicone Acrylate RGP (Transaire) lenses in 9467X. The average total surface area of the lenses was 8.5 cm².

Time Point (hr)	Uptake ($\mu\text{g}/\text{cm}^2$ lens)	Release ($\mu\text{g}/\text{mg}$ lens)
4	2.26	0
8	-1.11	0
24	-0.098	0.180
48	0.237	0

4.2.4 Fluoro/Silicone Acrylate RGP Lenses

The Purite[®] uptake and release data for the Fluoro/Silicone Acrylate RGP (Fluorperm) lenses are graphed in Figures 15 and 16 respectively. The calculated uptake and release values are tabulated in Table 8.

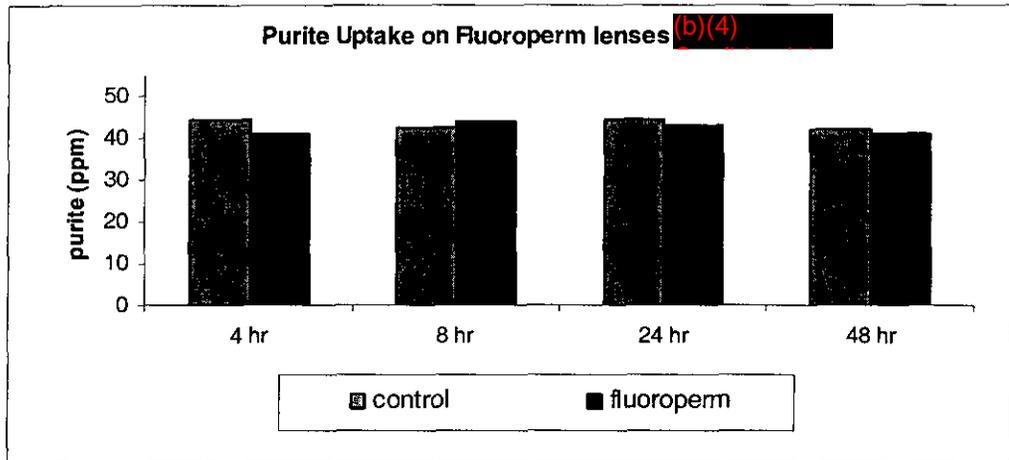


Figure 15: The uptake of Purite[®] on Fluorperm lenses that were soaked in (b)(4) Confidential

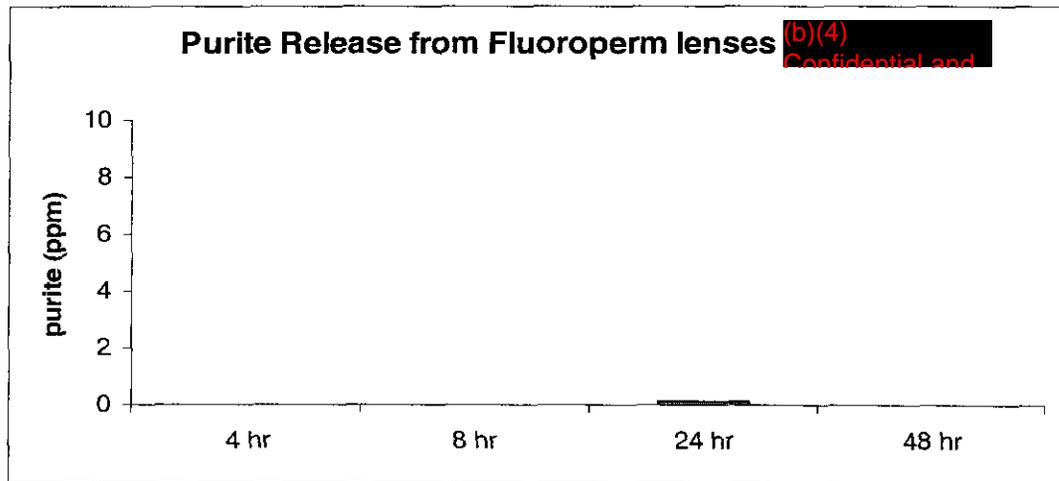


Figure 16: Purite[®] release from Fluorperm lenses into saline, following soak in (b)(4) Confidential

Table 8: Calculated uptake and release values following soaking Fluoro/Silicone Acrylate RGP (Fluorperm) lenses in 9467X. The average total surface area of the lenses was 12.7 cm².

Time Point (hr)	Uptake ($\mu\text{g}/\text{cm}^2$ lens)	Release ($\mu\text{g}/\text{mg}$ lens)
4	2.79	0
8	-1.19	0
24	0.946	0.095
48	0.591	0

5.0 DISCUSSION

The uptake data compare the Purite[®] levels between the sample and the control vial at several time points during soaks of Optima, Surevue, Transaire and Fluoroperm lenses in the test solutions. The control vial represents the baseline Purite[®] concentration in the solution. Uptake of Purite[®] is calculated as the difference between the Purite[®] concentration in the sample vials and the Purite[®] concentration in the control vial. Uptake is tabulated in units of $\mu\text{g}/\text{mg}$ of dry lens for hydrogel lenses and in $\mu\text{g}/\text{cm}^2$ of lens surface for RGP lenses. The release data demonstrate the Purite[®] levels released by the lenses into the saline solution. Release is also tabulated in units of $\mu\text{g}/\text{mg}$ of dry lens for hydrogel lenses and in $\mu\text{g}/\text{cm}^2$ of lens surface for RGP lenses.

5.1 9464X – Uptake and Release

An uptake of no greater than $0.14\mu\text{g}/\text{mg}$ of dry lens was found for hydrogel lenses soaked in (b)(4) (Tables 1 and 2). An uptake of no greater than $1.49\mu\text{g}/\text{cm}^2$ of lens surface was found for RGP lenses soaked in (b)(4) (Tables 3 and 4). For all lens types but the Group 1 hydrogel lenses, there were time points indicating a negative uptake, due to the control solution measurement having a lower value than the sample solution measurement. These results indicate that there was no uptake of preservative into or on these lenses.

A maximum release of $0.12\mu\text{g}/\text{mg}$ of dry lens was determined for hydrogel lenses soaked in 9464X. A maximum release of $1.90\mu\text{g}/\text{cm}^2$ of lens surface was calculated for RGP lenses soaked in 9464X. The maximum release values are very close to the maximum uptake values indicating that any very low levels of preservative taken up are quickly released.

5.2 9467X – Uptake and Release

A maximum uptake of $0.17\mu\text{g}/\text{mg}$ of dry lens was determined for hydrogel lenses soaked in 9467X (Tables 5 and 6) and a maximum uptake of $2.79\mu\text{g}/\text{cm}^2$ of lens surface was calculated for the RGP lenses (Tables 7 and 8). For all lens types but the Group 1 hydrogel lenses, there were time points indicating a negative uptake, due to the control solution measurement having a lower value than the sample solution measurement. These results indicate that there was no uptake of preservative into or on these lenses.

Maximum release was calculated to be $0.05\mu\text{g}/\text{mg}$ of dry lens for hydrogel lenses and $0.18\mu\text{g}/\text{cm}^2$ of lens surface for RGP lenses.

6.0 CONCLUSION

Based on the very low, if any, amounts of Purite[®] uptake onto or in the various types of lenses it is concluded that there is no strong chemical or non-chemical propensity for the Purite[®] preservative in the Purite[®] HA Rewetter formulations (9464X and 9467X) to absorb or adsorb to contact lenses. The results indicate the Purite[®] preservative in formulations 9464X and 9467X to be compatible with all lens types tested, and thus, the formulations are acceptable for use with all hydrogel and RGP lenses.

7.0 REFERENCES

- 7.1 ISO 11986:1999, Ophthalmic Optics – Contact lenses and contact lens care products – Guidelines for determination of preservative uptake and release
- 7.2 ISO 10344, Optics and Optical Instruments – Contact lenses – Saline solution for contact lens testing
- 7.3 AMO Laboratory Notebook (b)(4) Confidential and Proprietary Information

Contact Lens Wetting Angle (RGP lenses)

(b)(4) Confidential and Proprietary Information

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June 19, 2003

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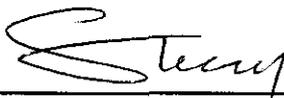
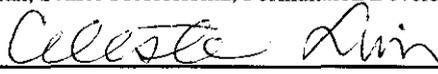
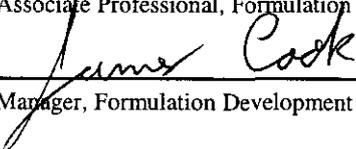
**RESEARCH AND DEVELOPMENT
ANALYTICAL CHEMISTRY**

***Report for the Measurement of Wetting Angles of RGP Lenses in Association
With Purite® HA Rewetter***

(b)(4) Confidential
and Proprietary

(b)(4) Confidential and Proprietary Information

ISSUED: Date of Last Signature

Author:		<u>6/19/03</u>
	Lam Tran, Senior Professional, Formulation Development	Date
Reviewed by:		<u>6/19/03</u>
	Celeste Lim, Associate Professional, Formulation Development	Date
Approved by:		<u>6/19/03</u>
	James Cook, Manager, Formulation Development and Analytical Chemistry	Date

1 086

1.0 PURPOSE

To evaluate the wetting angle on RGP contact lenses in association with Purite® HA Rewetter (9464X) and other products.

2.0 INTRODUCTION

The surface of most Rigid Gas Permeable (RGP) contact lenses exhibits hydrophobic behavior. The effectiveness of different rewetter products in enhancing the wettability of RGP lenses can be evaluated by measuring the wetting angles using the Sessile Drop Method.

3.0 MATERIALS AND METHODS

3.1 MATERIALS

- SA-18, Silicone Acrylate buttons, Kolfocon, Lagado Corp., lot#1348-1
- Boston 7, Fluorosilicone Acrylate buttons, Satafocon, Polymer Technology, lot #35886
- Purite® HA Rewetter (b)(4) Confidential and Proprietary Information
- Refresh Contacts™ (b)(4) Confidential and Proprietary Information
- Focus AQuify™, Ciba Vision, lot #27170
- Isotonic Phosphate Buffered Saline, lab batch lot # 683-51
- Deionized water
- FTA100 Dynamic Contact Angle Analyzer by First Ten Angstroms (Portsmouth, Virginia)

3.2 METHODS

- 3.2.1 The procedure used for the set-up of FTA100 Dynamic Contact Angle Analyzer and the measurement of contact angles is described in Protocol # (b)(4) Confidential and Proprietary Information
- 3.3.2 Three RGP lens material buttons of each polymer type (Silicone Acrylate and Fluorosilicone acrylate) were tested for wetting angle in association with the test solutions.
- 3.2.3 A static (sessile) drop of each test solution was placed on each button and contact angle measurements taken at 0, 5, 10 and 20 minutes.
- 3.2.4 At each time point, the relative changes in base areas of the drops were additionally recorded.

3.2.5 Additionally measured for comparison, by the method of pendant drop shape assessment, was the surface tension of each test solution.

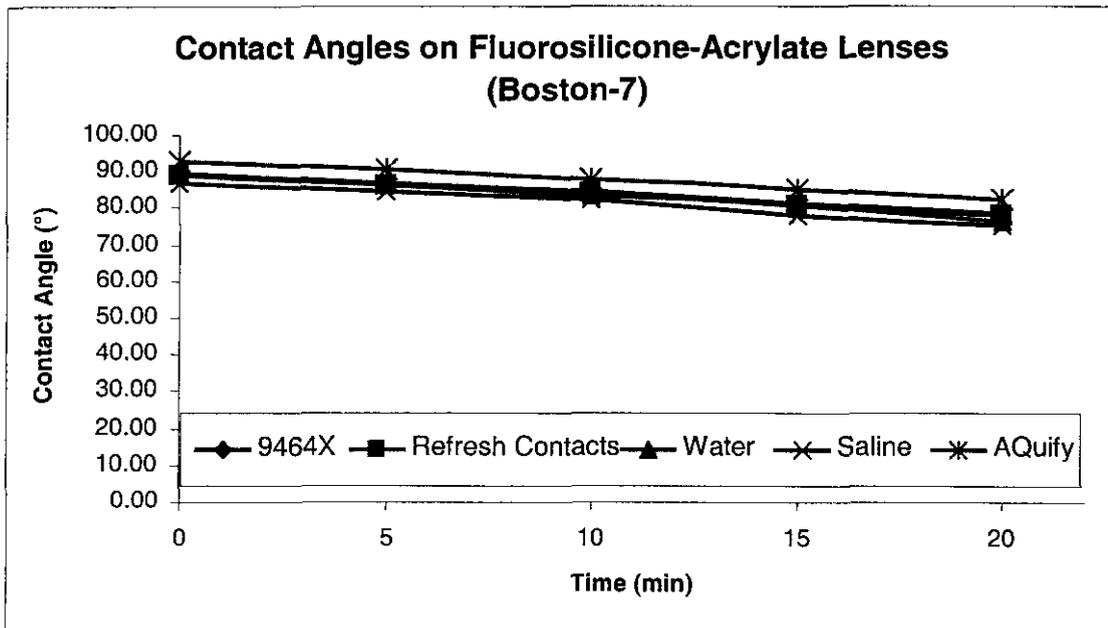
4.0 RESULTS

4.1 Surface Tension Measurements

(b)(4) Confidential and	Refresh Contacts™	Water	Saline	AQuify™
72.23	72.10	72.81	72.80	72.45

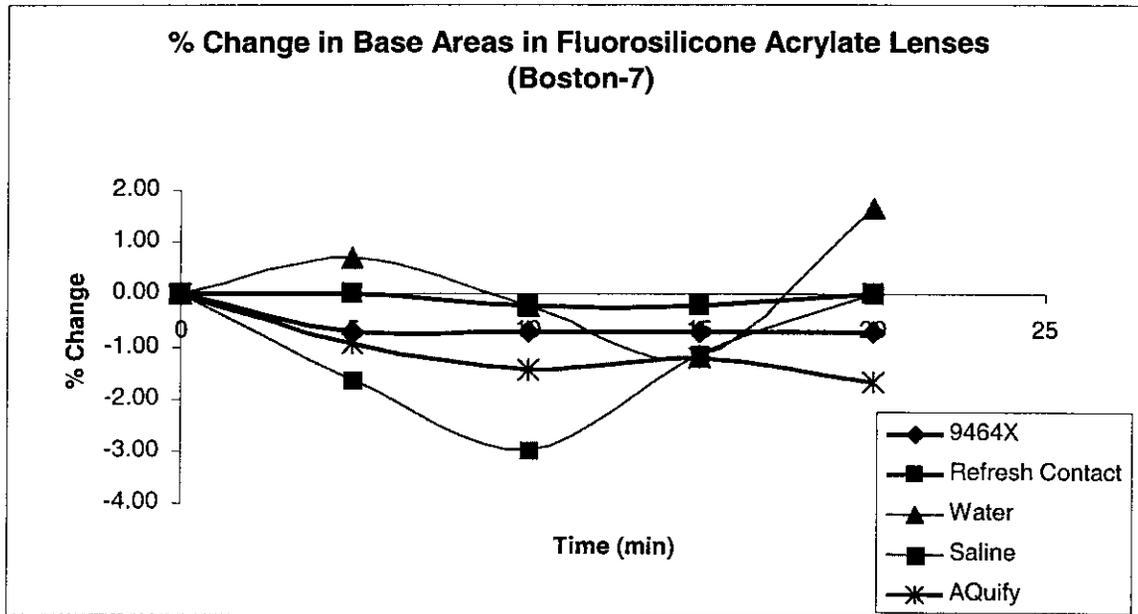
4.2 Contact Angle vs Time (min) in Boston-7 Lenses

Time(min)	9464X	Refresh Contacts™	Water	Saline	AQuify™
0	89.44	89.28	89.26	86.58	92.78
5	87.06	86.22	86.36	84.48	90.61
10	84.40	83.92	83.52	82.55	88.17
15	81.55	80.82	80.82	78.21	85.41
20	78.51	77.76	76.35	75.40	82.52



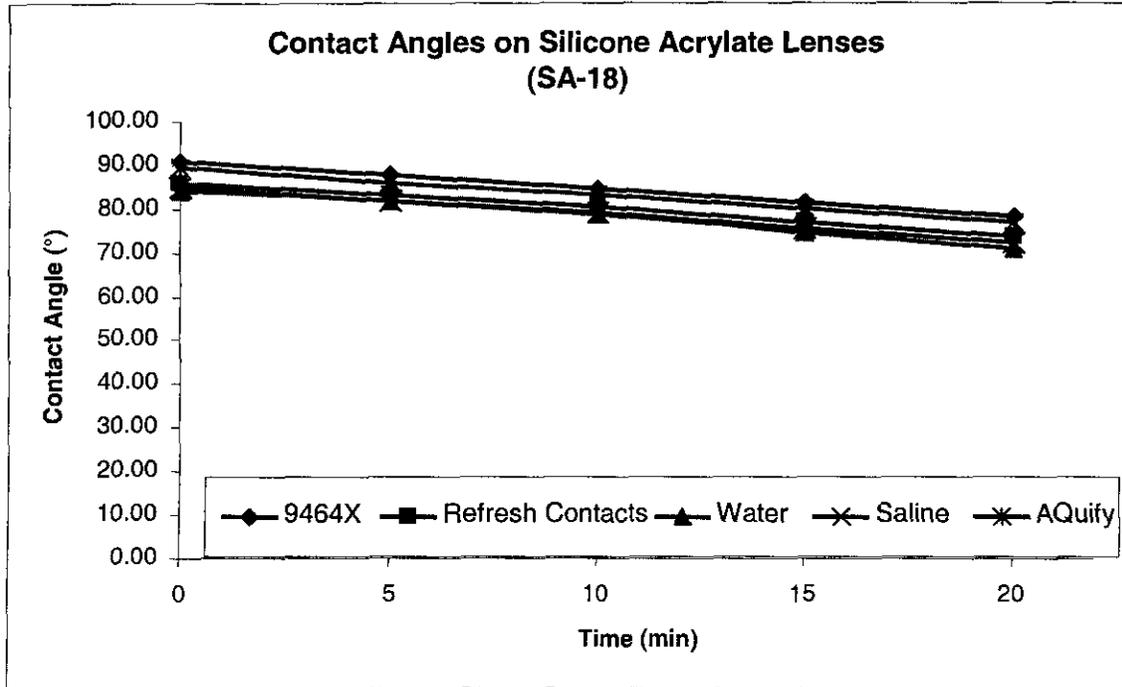
4.3 % Change in Base Areas vs Time (min) in Boston-7 Lenses

Time(min)	9464X	Refresh Contacts™	Water	Saline	AQuify™
0	0.00	0.00	0.00	0.00	0.00
5	-0.70	0.00	0.71	-1.61	-0.95
10	-0.70	-0.23	-0.23	-2.96	-1.44
15	-0.70	-0.23	-1.15	-1.15	-1.19
20	-0.70	0.00	1.65	0.01	-1.67



4.4 Contact Angle vs Time(min) in SA-18 Lenses

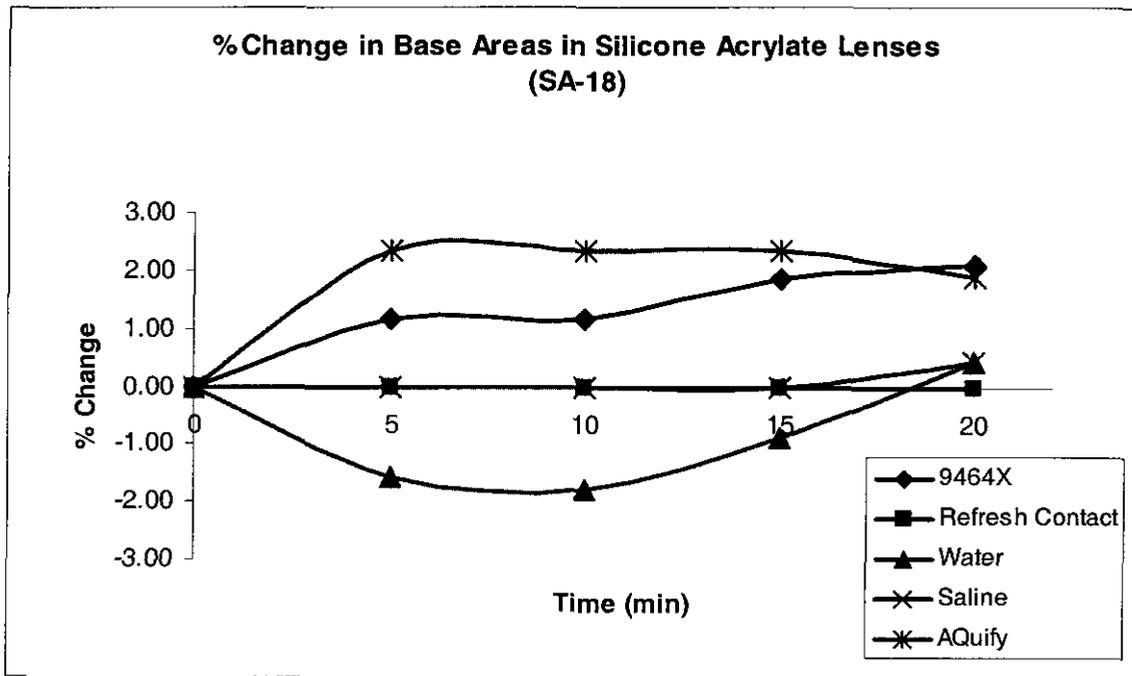
Time(min)	9464X	Refresh Contact™	Water	Saline	AQuify™
0	90.69	86.02	84.01	84.82	89.71
5	87.49	83.22	81.64	81.95	85.78
10	84.65	80.15	78.72	78.87	82.95
15	81.33	76.93	74.65	75.55	79.98
20	78.04	73.42	70.97	72.23	76.80



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4.5 % Change in Base Area vs Time(min) in SA-18 Lenses

Time(min)	% change				
	9464X	Refresh Contact™	Water	Saline	AQuify™
0	0.00	0.00	0.00	0.00	0.00
5	1.16	0.00	-1.57	0.00	2.34
10	1.16	0.00	-1.79	0.00	2.34
15	1.86	0.00	-0.90	0.00	2.34
20	2.09	0.00	0.44	0.44	1.87



5.0 DISCUSSION

All solutions tested in this study exhibited high contact angles on dried and untreated surfaces of both Silicone Acrylate and Fluorosilicone Acrylate lens materials. All of the solutions tested had measured surface tensions very similar to that tested for deionized water (72.81 dynes/cm). It was therefore not expected that the lens buttons would wet easily, as might be expected for solutions with lower surface tension (< 60 dynes/cm), or show significant differences in wetting angle in comparison to each other.

The measurement of the drop base areas was also included in this study because the change in the base areas in time may indicate the contraction or dispersion of the solutions on the lens surface, thus potentially providing another measurable wetting property. The results from this study show that Purite® HA Rewetter(9464X) and

AQuify™ spread very slightly on the Silicone Acrylate surface while other solutions remained stationary (saline and Refresh Contacts™), or even contracted (deionized water) on the same surface. No spreading was observed with the Fluorosilicone Acrylate lens material.

6.0 CONCLUSION

On dried and untreated rigid gas permeable lens material surfaces, no differences are observed in wetting angle between Purite HA Rewetter (b)(4) Confidential, Refresh Contacts™, and AQuify™. The wetting angles on these materials are very similar to water as expected by comparison of the surface tensions of the solutions, which are also very similar to water.

Purite HA Rewetter (b)(4) Confidential and AQuify™, both containing Sodium Hyaluronate, appear to have slightly better wetting properties than Refresh Contacts™, as exhibited by increasing base area on Silicone Acrylate lens material.

7.0 REFERENCES

1. First Ten Angstroms FTA100 Series Contact Angle Analyzer manual.
2. Contact Angle Measurements Using the Drop Shape Method, R.P. Woodward, First Ten Angstroms, Internal Publication, FTA 100 Manual
3. Surface Tension Measurements Using the Drop Shape Method, R.P. Woodward, First Ten Angstroms, Internal Publication, FTA 100 Manual
4. Advanced Medical Optics Laboratory Notebook 652-61 pp 61-66

STABILITY

Study Type	Page
Summary	1 094
Six Month Interim Stability Report for <i>blink</i> [™] CL Lubricant Eye Drops, (9464X)	1 095

NONCLINICAL REPORT SUMMARIES

Department: Analytical Chemistry
Study Type: Stability
Title: Six Month Interim Stability Report for *blink*TM CL Lubricant Eye Drops, Formulation 9464X, Justification for Expiration Dating

Study Date: June 18, 2003

Study Number: (b)(4) [REDACTED]

Study Summary: Three lots of *blink*TM CL Lubricant Eye Drops, 9464X, were filled into 15 mL bottles (12 mL fill volume) and three lots into 6 mL bottles (2 mL fill volume). Each lot has been stored for 6 months at 25°C/40% relative humidity (RH), 30°C/60% RH and 40°C/20% RH. The following parameters were monitored during this time period:

Parameter	Specification
Physical Appearance	(b)(4) Confidential and Proprietary Information
pH	
Potential Chlorine Dioxide	
Sodium Hyaluronate (HA) Concentration	
Osmolality	
Viscosity	
Sterility, Current USP	
Preservative Effectiveness, ISO 14730:2000	

All data remained within the proposed specifications. Based on an evaluation of the 40°C data, the recommended expiration dating is nine (9) months. The protocol used for and the resultant data generated from this ongoing R&D stability study will be used to extend expiration dating when these data are sufficient to support an extension.

Six Month Interim Stability Report ***blink*TM CL Lubricant Eye Drops** **Formulation 9464X**

(b)(4) Confidential and Proprietary Information

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June 18, 2003

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STABILITY REPORT

(b)(4) Confidential and Proprietary
Information

6 MONTH INTERIM STABILITY REPORT FOR *blink*TM CL LUBRICANT EYE
DROPS FORMULATION 9464X

Justification for Expiration Dating

ISSUED: DATE OF LAST SIGNATURE

Author:	<u><i>Lauren Crawford</i></u>	<u>06-17-03</u>
	Lauren Crawford, Scientist, Analytical Chemistry	Date
Approved by:	<u><i>James Cook</i></u>	<u>6-17-03</u>
	James Cook, Manager, Formulation Development and Analytical Chemistry	Date
Approved by:	<u><i>Debbie O'Brien</i></u>	<u>6-17-03</u>
	Debbie O'Brien, Professional, Regulatory Affairs	Date
Approved by:	<u><i>John Worsley</i></u>	<u>6-18-03</u>
	John Worsley, Project Manager, Worldwide Quality Assurance	Date

1 096

SUMMARY

This 6-month interim report presents data from storage stability testing completed to date on *blink*TM CL Lubricant Eye Drops, Formula 9464X. Chemistry data available following 6-months storage under real-time and accelerated conditions are presented. Microbiology (preservative efficacy test (PET)) data available following 3-months storage at accelerated conditions are presented.

Three lots (b) (4) of *blink*TM CL Lubricant Eye Drops (b) (4) filled in 15-mL LDPE teal bottles (12 mL fill volume) and three lots (b) (4) (b) (4) CL Lubricant Eye Drops (9464X) filled in (b) (4) (b) (4) were evaluated. Each lot was subjected to storage at 25°C/40% RH, 30°C/60% RH, and 40°C/20%RH. Each lot was monitored for the following parameters: sodium hyaluronate, potential chlorine dioxide, physical appearance, pH, osmolality, viscosity, sterility and preservative efficacy.

Data from all chemistry testing following 6-months storage at 25°C/40% RH, 30°C/60% RH, and 40°C/20%RH remain within proposed specifications. Additionally, PET testing, following 3-months storage at 40°C/20%RH passes specifications. All studies at each of the three storage conditions remain in progress.

Based on the evaluation of the interim chemistry accelerated data, an expiration dating period of 18 month is justified. The available microbiology (PET) accelerated data support an expiration dating period of 9 months; however, based on the stability of the preservative ingredient Purite® (stabilized oxychloro complex) remaining well within specifications, it is expected that the expiration dating will be extended to 18 months upon receipt of additional PET data from the 6-month time point. The expiration dating period may be amended at a future date as additional data is obtained from continued storage at 25°C/40% RH, 30°C/60% RH, and 40°C/20%RH.

STABILITY CONDITIONS

Proposed Product Specifications

The proposed product shelf specifications for *blink*TM CL Lubricant Eye Drops, Formula 9464X, are listed in the following table.

Parameter	Specification
Sodium Hyaluronate (or Hyaluronic Acid (HA))	(b)(4) Confidential and Proprietary Information
Potential Chlorine Dioxide	
Physical Appearance	
pH	
Osmolality	
Viscosity	
Sterility (USP)	
Presevative Efficacy Test (ISO 14730: 2000)	

(b) (4)

(b)(4) Confidential and Proprietary Information

Lot Descriptions/Study Conditions

All lots were manufactured according to current good manufacturing practices (cGMPs) at a pilot-scale contract manufacturing facility, Prima Pharm, Inc., located in San Diego, CA. The bottles were made of low density polyethylene (LDPE) resin with teal colorant. The tips were made of low density polyethylene (LDPE) resin with teal colorant. The caps were made of polystyrene with teal colorant. Lot numbers (b) (4) and (b) (4) were packaged into the 12-mL fill volume/15-mL capacity configuration. Lot numbers (b) (4) were packaged into the 2-mL fill volume/6-mL capacity configuration.

Specific manufacturing and storage information for each lot is listed in the following table.

Lot Descriptions

Lot Number	Container Configuration (fill volume/fill capacity)	(b)(4) Confidential and Proprietary Information	Storage Condition (°C/%RH)	Mfg. Date	Stability Start Date	Age of Study (mo)
02RD24A	12 mL / 15 mL	(b)(4) Confidential and Proprietary Information	25/40	23 Oct 2002	23 Oct 2002	6
			30/60		16 Dec 2002	6
			40/20		16 Dec 2002	6
02RD45A	12 mL / 15 mL	(b)(4) Confidential and Proprietary Information	25/40	12 Dec 2002	12 Dec 2002	6
			30/60		18 Dec 2002	6
			40/20		18 Dec 2002	6
02RD51A	12 mL / 15 mL	(b)(4) Confidential and Proprietary Information	25/40	17 Dec 2002	17 Dec 2002	6
			30/60		20 Dec 2002	6
			40/20		20 Dec 2002	6
02RD24B	2 mL / 6 mL	(b)(4) Confidential and Proprietary Information	25/40	23 Oct 2002	23 Oct 2002	6
			30/60		16 Dec 2002	6
			40/20		16 Dec 2002	6
02RD45B	2 mL / 6 mL	(b)(4) Confidential and Proprietary Information	25/40	12 Dec 2002	12 Dec 2002	6
			30/60		20 Dec 2002	6
			40/20		20 Dec 2002	6
02RD51B	2 mL / 6 mL	(b)(4) Confidential and Proprietary Information	25/40	17 Dec 2002	17 Dec 2002	6
			30/60		20 Dec 2002	6
			40/20		20 Dec 2002	6

Test Schedule

Parameters were tested at the scheduled time intervals listed in the tables on the following pages.

For lot numbers (b) (4), each parameter except PET and sterility was tested in triplicate (one sample from each of three separate bottles) at release (0-time) and in duplicate at the subsequent designated time points. For the PET and sterility tests, the appropriate numbers of bottles to complete the tests were pooled and one value reported.

For lot numbers (b) (4) the sodium hyaluronate, viscosity, potential chlorine dioxide, PET and sterility tests required sample bottles to be pooled due to limited volume available for the tests. With the exception of the viscosity test

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and Proprietary(b)(4) Confidential and Proprietary
Information

results at the 4 and 6-month time points, and the sodium hyaluronate results at 0-time (lot number 02RD24B only), one value from each of the tests requiring pooling was reported. Two replicate measurements from the same pooled sample were reported for the viscosity test at 4 and 6 months. Three replicate values were reported for sodium hyaluronate at 0-time for lot number 02RD24B. For all other parameters, testing was conducted in triplicate (one sample from each of three separate bottles) at release (0-time) and in duplicate at subsequent time points.

Test Schedule for the 25°C/40% RH Storage Condition

Test Parameter	Test Interval (Months)							
	0	3	6	9	12	18	24	36
Physical Appearance	X	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X	X
Potential Chlorine Dioxide	X	X	X	X	X	X	X	X
Sodium Hyaluronate Concentration	X	X	X	X	X	X	X	X
Osmolality	X	X	X	X	X	X	X	X
Viscosity	X	X	X	X	X	X	X	X
Sterility (USP)	X				X		X	X
PET (ISO 14730: 2000)	X		X		X		X	X

Test Schedule for the 30°C/60% RH Storage Condition

Test Parameter	Test Interval (Months)									
	0	1	2	3	4	6	9	12	18	24
Physical Appearance	X	X	X	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X	X	X	X
Potential Chlorine Dioxide	X	X	X	X	X	X	X	X	X	X
Sodium Hyaluronate Concentration	X	X	X	X	X	X	X	X	X	X
Osmolality	X	X	X	X	X	X	X	X	X	X
Viscosity	X	X	X	X	X	X	X	X	X	X
Sterility (USP)	X							X		X
PET (ISO 14730: 2000)	X					X		X		X

Test Schedule for the 40°C/20% RH Storage Condition

Test Parameter	Test Interval (Months)						
	0	1	2	3	4	6	9
Physical Appearance	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X
Potential Chlorine Dioxide	X	X	X	X	X	X	X
Sodium Hyaluronate Concentration	X	X	X	X	X	X	X
Osmolality	X	X	X	X	X	X	X
Viscosity	X	X	X	X	X	X	X
Sterility (USP)	X						X
PET (ISO 14730: 2000)	X			X		X	X

DISCUSSION OF THE STABILITY DATA

The six lots of Formulation 9464X have been tested for sodium hyaluronate, potential chlorine dioxide, physical appearance, pH, osmolality, viscosity, sterility and preservative efficacy. All test data for the six lots remain within proposed product specifications for chemistry following 6-months storage at 25°C/40% RH, 30°C/60% RH, and 40°C/20%RH and for microbiology following 3 months storage at 40°C/20%RH. The stability results are presented in data tables in Appendix A.

For establishment of shelf-life dating, focus is placed on the following stability-limiting parameters: viscosity, potential chlorine dioxide, pH, sodium hyaluronate and osmolality.

The viscosity results exhibit a downward slope but stay within specifications for 6 months when stored at 25°C/40% RH, 30°C/60% RH, and 40°C/20%RH. The potential chlorine dioxide data decrease only slightly, remaining well above the lower specification limit. Plots of the viscosity and the potential chlorine dioxide stability results from storage at 40°C/20% RH are presented in Appendix B.

The pH results over the course of the study were virtually unchanged, decreasing only slightly (<2%). Values stayed well within specifications for 6 months when stored at 25°C/40% RH, 30°C/60% RH, and 40°C/20%RH.

Both osmolality and sodium hyaluronate concentration exhibit a slight upward drift when stored at 40°C/20%RH in the 2 mL fill/6 mL capacity bottle configuration; however they remain within specifications for the test period. No changes in the osmolality or sodium hyaluronate parameters were observed for the 12 mL fill/15 mL capacity bottle configuration.

All other parameters tested show little change and remain within respective specifications when stored for 6 months at 25°C/40% RH, 30°C/60% RH, and 40°C/20%RH.

PROPOSED EXPIRATION DATING

The determination of expiration dating is based upon evaluation of shelf life projection plots of the main stability-indicating parameter (viscosity). Additionally, all parameters tested over the evaluation period at all storage conditions must meet specifications. *blink™* CL Lubricant Eye Drops, Formula (b) (4), has been shown to remain within proposed product specifications through 6 months accelerated (40°C/20% RH and 30°C/60% RH) and 6 months real-time (25°C/40% RH) testing. As sufficient real-time stability data are not yet available, the accelerated data results have been used to determine an expiration dating period for the product according to the May 1, 1997 Guidance for Industry “Pre-market Notification (510(k)) Guidance Document for Contact Lens Care Products”. Per the guidance document, the acceleration factor is based on the temperature difference between the elevated temperature storage condition (40°C) and ambient temperature (25°C), which is 15°C. The acceleration factor is calculated as $2.0^{(1.5)} = 2.83$. After rounding this factor to 3, and then multiplying by the length of accelerated testing (6 months for chemistry and 3 months for PET), the product is projected to be stable for at least 18 months based on chemistry data and 9 months based on microbiology data when stored under room temperature conditions. The preservative ingredient, Purite®, as measured by the potential chlorine dioxide test, remained well within specifications following 6-months product storage at accelerated condition (40°C/20% RH). It is therefore expected that the expiration dating will be extended based on receipt of additional PET data from the 6-month time point.

CONCLUSION

All chemistry parameters measured through 6 months of real-time and accelerated storage for *blink™* CL Lubricant Eye Drops, Formula (b) (4) remain within specifications. Microbiology (PET) testing through 3 months accelerated storage additionally remain within specifications. Based on an evaluation of the 40°C/20% RH accelerated storage data, the recommended expiration dating period is 9 months for *blink™* CL Lubricant Eye Drops, Formula (b) (4). The expiration dating will be extended to 18 months pending satisfactory PET results from the 6-month time point.

APPENDICES

APPENDIX A: Stability Data for Formulation (b) (4)

APPENDIX B: Data Plots of viscosity, potential chlorine dioxide for Formulation (b) (4)

APPENDIX A

Stability Data for *blink*™ CL Lubricant Eye Drops, Formula 9464X

1 102
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Abbreviations Used in Data Tables:

PA	Physical Appearance	OSM	Osmolality
PH	Solution pH	VIS	Viscosity
PCLO	Potential Chlorine Dioxide	STR	Sterility
HA	Sodium Hyaluronate (or Hyaluronic Acid)	PET	Preservative Efficacy Test

Contents of Appendix A

Table 1	Stability Raw Data for Batch 02RD24B, 25°C/40% RH Storage, 2 mL Fill
Table 2	Stability Raw Data for Batch 02RD45B, 25°C/40% RH Storage, 2 mL Fill
Table 3	Stability Raw Data for Batch 02RD51B, 25°C/40% RH Storage, 2 mL Fill
Table 4	Stability Raw Data for Batch 02RD24A, 25°C/40% RH Storage, 12 mL Fill
Table 5	Stability Raw Data for Batch 02RD45A, 25°C/40% RH Storage, 12 mL Fill
Table 6	Stability Raw Data for Batch 02RD51A, 25°C/40% RH Storage, 12 mL Fill
Table 7	Stability Raw Data for Batch 02RD24B, 30°C/60% RH Storage, 2 mL Fill
Table 8	Stability Raw Data for Batch 02RD45B, 30°C/60% RH Storage, 2 mL Fill
Table 9	Stability Raw Data for Batch 02RD51B, 30°C/60% RH Storage, 2 mL Fill
Table 10	Stability Raw Data for Batch 02RD24A, 30°C/60% RH Storage, 12 mL Fill
Table 11	Stability Raw Data for Batch 02RD45A, 30°C/60% RH Storage, 12 mL Fill
Table 12	Stability Raw Data for Batch 02RD51A, 30°C/60% RH Storage, 12 mL Fill
Table 13	Stability Raw Data for Batch 02RD24B, 40°C/20% RH Storage, 2 mL Fill
Table 14	Stability Raw Data for Batch 02RD45B, 40°C/20% RH Storage, 2 mL Fill
Table 15	Stability Raw Data for Batch 02RD51B, 40°C/20% RH Storage, 2 mL Fill
Table 16	Stability Raw Data for Batch 02RD24A, 40°C/20% RH Storage, 12 mL Fill
Table 17	Stability Raw Data for Batch 02RD45A, 40°C/20% RH Storage, 12 mL Fill
Table 18	Stability Raw Data for Batch 02RD51A, 40°C/20% RH Storage, 12 mL Fill

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 25°C/40%RH

Table 1

Product Name/Strength: *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 6 ML BOTTLES
 Lot Number: 02RD24B
 Date Manufactured: 23Oct2002
 Date Packaged: 23Oct2002
 Storage Condition: 25°C/40%RH
 Shelf Life (Months): 36

Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Packaging/Site: [REDACTED]
 Storage Orientation: INVERTED

Date Study Started: 23Oct2002
 Container Supplier: [REDACTED]
 Fill Volume: 2 ML
 Fill Capacity: 6 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification Low High	0	3	6
PA	TM 4382	[REDACTED]	CLEAR COLORLESS SOLUTION Assay Date: 7Nov2002 NB Ref: TP659 NB Page: 57-58	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 6May2003 NB Ref: TK693 NB Page: 80
PH (pH units)	USP 26 <791>	[REDACTED]	7.2 7.2 7.2 Assay Date: 5Nov2002 NB Ref: CL670 NB Page: 20-21	7.2 7.2 Assay Date: 24Jan2003 NB Ref: CL682 NB Page: 3	7.1 7.1 Assay Date: 1May2003 NB Ref: TK693 NB Page: 71
PCLO (ppm)	TM 4381	[REDACTED]	49 Assay Date: 1Nov2002 NB Ref: CL670 NB Page: 19-25	47 Assay Date: 24Jan2003 NB Ref: CL682 NB Page: 2	47 Assay Date: 7May2003 NB Ref: TK693 NB Page: 80
HA (%w/v)	TM 4386	[REDACTED]	0.15 0.16 0.16 Assay Date: 30Oct2002 NB Ref: TP659 NB Page: 42-44	0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 25°C/40%RH

Table 1

Attributes	Method SOP#	Specification Low High	0	3	6	
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	284	282	288	
			283	282	286	
			286	Assay Date: 24Jan2003 NB Ref: CL682 NB Page: 4	Assay Date: 1May2003 NB Ref: TK693 NB Page: 71	
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	6.6	6.3	5.8	
			Assay Date: 4Nov2002 NB Ref: LT652 NB Page: 18	Assay Date: 23Jan2003 NB Ref: LT652 NB Page: 31-33	Assay Date: 5May2003 NB Ref: TK693 NB Page: 75	
			USP=PASS			
STR	USP	(b)(4) Confidential and Proprietary Information	Assay Date: 7Nov2002 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 90-97			
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information	FDA, Mod. USP = PASS Assay Date: 11Dec2002 NB Ref: NA673 NB Page: 16-17			

Table 2

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 25°C/40%RH

Product Name/Strength: *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 6 ML BOTTLES
 Batch Number: 02RD45B
 Date Manufactured: 12Dec2002
 Date Packaged: 12Dec2002
 Storage Condition: 25°C/40%RH
 Shelf Life (Months): 36
 Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Packager/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 12Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 2 ML
 Fill Capacity: 6 ML
 Closure Supplier: [REDACTED]
 Seal Supplier: [REDACTED]

Attributes	Method SOP#	Specification Low High	0	3	6	
PA	TM 4382	[REDACTED]	CLEAR COLORLESS SOLUTION Assay Date: 2Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 12Mar2003 NB Ref: TP681 NB Page: 60	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33	
PH (pH units)	USP 26 <791>	[REDACTED]	7.2 7.2 7.2 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 54-55	7.2 7.2 7.2 Assay Date: 17Mar2003 NB Ref: CL682 NB Page: 61	7.2 7.2 7.2 Assay Date: 6Jun2003 NB Ref: TK706 NB Page: 30	
PCLO (ppm)	TM 4381	[REDACTED]	48 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 51-53	47 Assay Date: 20Mar2003 NB Ref: CL682 NB Page: 62	47 Assay Date: 11Jun2003 NB Ref: TK693 NB Page: 37	
HA (%w/v)	TM 4386	[REDACTED]	0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.15 Assay Date: 12Mar2003 NB Ref: TP681 NB Page: 57	0.15 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54	

(b)(4) Confidential and Proprietary Information

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 25°C/40%RH

Table 2

Attributes	Method SOP#	Specification Low High	0	3	6	
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	272 272 272 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 56-57	276 276 Assay Date: 17Mar2003 NB Ref: CL682 NB Page: 61	277 273 Assay Date: 6Jun2003 NB Ref: TK706 NB Page: 30	
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	5.1 Assay Date: 6Jan2003 NB Ref: LT652 NB Page: 27	4.8 Assay Date: 17Mar2003 NB Ref: LT652 NB Page: 46	4.5 4.5 Assay Date: 6Jun2003 NB Ref: TK706 NB Page: 30	
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 27Dec2002 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test log book No. 2 QC-40, pages 112-121			
PEP	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information	USP=PASS EP=PASS Assay Date: 23Jan2003 NB Ref: NA673 NB Page: 38-39			

Product Name/Strength
Purpose of Study
Batch Number
Date Manufactured
Date Packaged
Storage Condition
Shelf Life (Months)

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RDS1B, 25°C/40%RH
 Formulation Number 09464X
 STABILITY OF blink™ CL LUBRICANT EYE DROPS IN 6 ML BOTTLES
 02RDS1B
 17Dec2002
 17Dec2002
 25°C/40%RH
 36

Batch Size
Manufacturer/Site
Packager/Site
Storage Orientation
 12,000 GRAMS
 [REDACTED]
 INVERTED
 Date Study Started
Container Supplier
Fill Volume
Fill Capacity
Closure Supplier
Seal Supplier
 17Dec2003
 [REDACTED]
 2 ML
 6 ML
 [REDACTED]

Table 3

Attributes	Method SOP#	Specification		0	3	6	(b) (4)
		Low	High				
PA	TM 4382	[REDACTED]		CLEAR COLORLESS SOLUTION Assay Date: 21Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 18Mar2003 NB Ref: 681 NB Page: 69	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33	[REDACTED]
PH (pH units)	USP 26 <791>	7.2	7.2	7.1	7.1	7.1	
		7.2	7.2	7.1	7.1	7.1	
		Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 60	Assay Date: 17Mar2003 NB Ref: CL682 NB Page: 59	Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36			
PCLO (ppm)	TM 4381	48	47	47	47		
		Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 58-59	Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 59	Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37			
HA (%w/v)	TM 4386	0.15	0.16	0.16	0.16		
		Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72	Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54			

(b)(4) Confidential and Proprietary Information

Table 3
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 25°C/40%RH

Attributes	Method SOP#	Specification Low High	0	3	6	
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	274 274 273 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 61	273 272 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59	276 274 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35	
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	7.0 Assay Date: 8Jan2003 NB Ref: LT652 NB Page: 28	6.5 Assay Date: 21Mar2003 NB Ref: LT652 NB Page: 48	6.1 6.1 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35	
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 21Jan2003 NB Ref: (b)(4) Confidential and Proprietary Information sterility log book No. 2; QC-40; pages 122-127			
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information	USP=PASS EP=PASS Assay Date: 30Jan2003 NB Ref: NA673 NB Page: 42,43			

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 25°C/40%RH

Table 4

Product Name/Strength: *blink*™ CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*™ CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Batch Number: 02RD24A
 Date Manufactured: 23Oct2002
 Date Packaged: 23Oct2002
 Storage Condition: 25°C/40%RH
 Shelf Life (Months): 36
 Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Package/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 23Oct2002
 Container Supplier: [REDACTED]
 Fill Volume: 12 ML
 Fill Capacity: 15 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification		
		Low	High	0
PA	TM 4382	(b)(4) Confidential and Proprietary Information		
PH (pH units)	USP 26 <791>	7.2 7.2 7.2 Assay Date: 5Nov2002 NB Ref: CL670 NB Page: 20-21	7.2 7.2 7.2 Assay Date: 24Jan2003 NB Ref: CL682 NB Page: 3	7.1 7.1 7.1 Assay Date: 1May2003 NB Ref: TK693 NB Page: 71
PCLO (ppm)	TM 4381	50 49 49 Assay Date: 1Nov2002 NB Ref: CL670 NB Page: 19-25	48 48 48 Assay Date: 24Jan2003 NB Ref: CL682 NB Page: 2	47 47 47 Assay Date: 6May2003 NB Ref: TK693 NB Page: 80
HA (%w/v)	TM 4386	0.15 0.15 0.15 Assay Date: 30Oct2002 NB Ref: TP659 NB Page: 42-44	0.15 0.15 0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.14 0.14 0.14 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2

Table 4
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 25°C/40%RH

Attributes	Method SOP#	Specification		0	3	6	
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		288	280	283	
				276	280	285	
				288	Assay Date: 24Jan2003 NB Ref: CL682 NB Page: 4	Assay Date: 1May2003 NB Ref: TK693 NB Page: 71	
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information		6.6	6.4	6.0	
				6.6	6.4	6.0	
				6.6	Assay Date: 23Jan2003 NB Ref: LT652 NB Page: 31-33	Assay Date: 5May2003 NB Ref: TK693 NB Page: 75	
STR	USP	(b)(4) Confidential and Proprietary Information		USP=PASS			
				Assay Date: 7Nov2002 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test log book No. 2; OC 40; pages 90-97			
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information		USP=PASS			
				BP=PASS			
				Assay Date: 11Dec2002 NB Ref: NA673 NB Page: 16-17			

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 25°C/40%RH

Table 5

blink™ CL LUBRICANT EYE DROPS
STABILITY OF blink™ CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Formulation Number: 09464X
 Batch Number: 02RD45A
 Date Manufactured: 12Dec2002
 Date Packaged: 12Dec2002
 Storage Condition: 25°C/40%RH
 Shelf Life (Months): 36
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: (b)(4)
 Packager/Site: (b)(4)
 Storage Orientation: INVERTED
 Date Study Started: 12Dec2002
 Container Supplier: (b)(4)
 Fill Volume: 12 ML
 Fill Capacity: 16 ML
 Closure Supplier: (b)(4)

Attributes	Method SOT#	Specification	
		Low	High
PA	TM 4382	0	3
PH (pH units)	USP 26 <791>	7.2	7.2
PCLO (ppm)	TM 4381	49	47
HA (%w/v)	TM 4386	0.15	0.15

(b)(4) Confidential and Proprietary Information

CLEAR COLORLESS SOLUTION	Assay Date: 21Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION	Assay Date: 12Mar2003 NB Ref: 681 NB Page: 60	CLEAR COLORLESS SOLUTION	Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33
Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 54-55	Assay Date: 17Mar2003 NB Ref: CL682 NB Page: 61	Assay Date: 6Jun2003 NB Ref: TK706 NB Page: 30	Assay Date: 12Jun2003 NB Ref: TK706 NB Page: 37		
Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 51-53	Assay Date: 17Mar2003 NB Ref: CL682 NB Page: 62	Assay Date: 12Jun2003 NB Ref: TK706 NB Page: 37			
Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	Assay Date: 12Mar2003 NB Ref: TP681 NB Page: 57	Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54			

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 25°C/40%RH

Table 5

Attributes	Method SOP#	Specification		0	3	6	
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			271	273	270	
				271	279	271	
				271	Assay Date: 17Mar2003 NB Ref: CL682 NB Page: 61	Assay Date: 6Jun2003 NB Ref: TK706 NB Page: 30	
VIS (cp)	TM 4384			5.2	4.8	4.6	
				5.2	4.9	4.6	
				5.2	Assay Date: 17Mar2003 NB Ref: LT652 NB Page: 46	Assay Date: 6Jun2003 NB Ref: TK706 NB Page: 30	
STR	USP			USP=PASS			
				Assay Date: 27Dec2002 NB Ref: (b)(4) Sterility test log book No. 2; QC-40; Pages 112-121			
				USP=PASS			
PET	Current FDA/Modified USP/ISO 14730:2000			USP=PASS			
				Assay Date: 11Dec2002 NB Ref: NA673			
				Assay Date: 38, 39			

(b)(4) Confidential and Proprietary Information

Table 6
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51A, 25°C /40%RH

Product Name/Strength: *blink*™ CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*™ CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Batch Number: 02RD51A
 Date Manufactured: 17Dec2002
 Date Packaged: 17Dec2002
 Storage Condition: 25°C /40%RH
 Shelf Life (Months): 36

Formulation Number: 09464X
 Batch Size: 12.000 GRAMS
 Manufacturer/Site: (b) (4)
 Package/Site: (b) (4)
 Storage Orientation: INVERTED
 Date Study Started: 17Dec2002
 Container Supplier: (b) (4)
 Fill Volume: 12 MIL
 Fill Capacity: 15.4 ML
 Closure Supplier: (b) (4)

Attributes	Method SOP#	Specification		
		Low	High	
PA	TM 4382	0	3	6
PH (pH units)	USP 26 <791>	7.2 7.2 7.2	7.1 7.1	7.1 7.1
PCLO (ppm)	TM 4381	48 49 48	47 47	47 47
HA (%w/v)	TM 4386	0.15 0.15 0.15	0.16 0.15	0.16 0.16

(b)(4) Confidential and Proprietary Information

Table 6

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RDS1A, 25°C/40%RH

Attributes	Method SOP#	Specification Low High	0	3	6	
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	273 274 273 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 61	273 271 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59	270 271 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35	
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	7.0 7.0 7.0 Assay Date: 8Jan2003 NB Ref: LT652 NB Page: 28	6.5 6.5 Assay Date: 21Mar2003 NB Ref: LT652 NB Page: 48	5.9 5.9 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35	
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 21Jan2003 NB Ref: (b)(4) Confidential and Proprietary Information sterility log book No. 2; QC-40; pages 122-127			
PET	Current FDA/Modified USP/ ISO 14730:2000	(b)(4) Confidential and Proprietary Information	USP=PASS EP=PASS Assay Date: 23Jan2003 NB Ref: NA673 NB Page: 42, 43			

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 30°C/60%RH

Table 7

Product Name/Strength *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 6 ML BOTTLES
 Lot Number 02RD24B
 Date Manufactured 23Oct2002
 Date Packaged 23Oct2002
 Storage Condition 30°C/60%RH
 Shelf Life (Months) 36

Formulation Number 09464X

Batch Size 12,000 GRAMS
 Manufacturer/Site [REDACTED]
 Packaging/Site [REDACTED]
 Storage Orientation INVERTED

Date Study Started 16Dec2002
 Container Supplier [REDACTED]
 Fill Volume 2 ML
 Fill Capacity 6 ML
 Closure Supplier [REDACTED]

Attributes	Method SOP#	Specification Low High	0	1	2	3
PA	TM 4382	[REDACTED]	CLEAR COLORLESS SOLUTION Assay Date: 7Nov2002 NB Ref: TP659 NB Page: 57-58	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP693 NB Page: 67
PH (pH units)	USP 26 <791>	[REDACTED]	7.2 7.2 7.2 Assay Date: 7Nov2002 NB Ref: CL670 NB Page: 20-21	7.2 7.2 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 86-87	7.2 7.2 Assay Date: 27Feb2003 NB Ref: CL682 NB Page: 33	7.1 7.1 Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 63
PCLO (ppm)	TM 4381	[REDACTED]	49 Assay Date: 1Nov2002 NB Ref: CL670 NB Page: 19-25	48 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 88-89	48 Assay Date: 27Feb2003 NB Ref: CL682 NB Page: 31-32	46 Assay Date: 20Mar2003 NB Ref: CL682 NB Page: 64
HA (%w/v)	TM 4386	[REDACTED]	0.15 0.16 0.16 Assay Date: 30Oct2002 NB Ref: TP659 NB Page: 42-44	0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.16 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.14 0.14 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 30°C/60%RH

Table 7

Attributes	Method SOP#	Specification Low High	0	1	2	3
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	284 283 286 Assay Date: 5Nov2002 NB Ref: CL670 NB Page: 20-21, 25	282 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 91	287 288 Assay Date: 27Feb2003 NB Ref: CL682 NB Page: 34	289 291 Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 63
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	6.6 Assay Date: 4Nov2002 NB Ref: LT652 NB Page: 18	6.2 Assay Date: 16Jan2003 NB Ref: LT652 NB Page: 31	6.1 Assay Date: 24Feb2003 NB Ref: LT652 NB Page: 36	5.9 Assay Date: 17Mar2003 NB Ref: LT652 NB Page: 47
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 7Nov2002 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 90-97			
PET	Current FDA/Modified USP/ ISO 14730:2000	(b)(4) Confidential and Proprietary Information	FDA, Mod. USP = PASS Assay Date: 11Dec2002 NB Ref: NA673 NB Page: 16-17			

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 30°C/60%RH

Table 7

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 23Apr2003 NB Ref: TK693 NB Page: 54,55,60	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK693 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.1 7.1 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	7.1 7.1 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	47 Assay Date: 28Apr2003 NB Ref: TK693 NB Page: 56	46 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.16 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.15 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

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221

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02R24B, 30°C/60%RH

Table 7

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			289 289 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	287 288 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384			5.8 5.9 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	5.7 5.7 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 36		
STR	USP						
PEI	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information					

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 30°C/60%RH

Table 8

Product Name/Strength: **blink™ CL LUBRICANT EYE DROPS**
 Purpose of Study: **STABILITY OF blink™ CL LUBRICANT EYE DROPS IN 6 ML BOTTLES**
 Lot Number: **02RD45B**
 Date Manufactured: **12Dec2002**
 Date Packaged: **12Dec2002**
 Storage Condition: **30°C/60%RH**
 Shelf Life (Months): **36**

Formulation Number: **09464X**
 Batch Size: **12,000 CAPSULES**
 Manufacturer/Site: **[REDACTED]**
 Packager/Site: **[REDACTED]**
 Storage Orientation: **INVERTED**
 Date Study Started: **20Dec2002**
 Container Supplier: **[REDACTED]**
 Fill Volume: **2 ML**
 Fill Capacity: **6 ML**
 Closure Supplier: **[REDACTED]**

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
PA	TM 4382			CLEAR COLORLESS SOLUTION Assay Date: 21Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP681 NB Page: 67
PH (pH units)	USP 26 <791>			7.2 7.2 7.2 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 54-55	7.3 7.3 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.2 7.2 7.2 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.2 7.2 7.2 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 65
PCLO (ppm)	TM 4381			48 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 51-53	48 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	48 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	47 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 66
HA (%w/v)	TM 4386			0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.15 Assay Date: 21Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.15 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

Table 8

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 30°C/60%RH

Attributes	Method SOP#	Specification Low High	0	1	2	3
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	272 272 272 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 56-57	269 269 Assay Date: 21Jan2003 NB Ref: CL670 NB Page: 97-99	272 272 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 37	276 273 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 65
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	5.1 Assay Date: 6Jan2003 NB Ref: LT652 NB Page: 27	4.9 Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	4.8 Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	4.9 Assay Date: 19Mar2003 NB Ref: LT652 NB Page: 47
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 27Dec2002 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 112-121			
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information	FDA, Mod. USP = PASS Assay Date: 23Jan2003 NB Ref: NA673 NB Page: 38-39			

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 30°C/60%RH

Table 8

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.2 7.2 Assay Date: 25Apr2003 NB Ref: TK693 NB Page: 61	7.2 7.2 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	46 Assay Date: 6May2003 NB Ref: TK693 NB Page: 78	45 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.16 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.15 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 30°C/60%RH

Table 8

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		274 277 Assay Date: 25Apr2003 NB Ref: TK693 NB Page: 61	275 274 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information		4.3 4.3 Assay Date: 28Apr2003 NB Ref: TK693 NB Page: 63	4.3 4.3 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information					
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information					

Table 9

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 30°C /60%RH

Product Name/Strength: *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 6 ML BOTTLES
 Lot Number: 02RD51B
 Date Manufactured: 17Dec2002
 Date Packaged: 17Dec2002
 Storage Condition: 30°C /60%RH
 Shelf Life (Months): 36

Formulation Number: 09464X
 Batch Size: 12,000
 Manufacturer/Site: [REDACTED]
 Package/Site: [REDACTED]
 Storage Orientation: INVERTED

Date Study Started: 20Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 2 ML
 Fill Capacity: 6 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification Low High	0	1	2	3
PA	TM 4382		CLEAR COLORLESS SOLUTION Assay Date: 2Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 18Mar2003 NB Ref: TP681 NB Page: 69
PH (pH units)	USP 26 <791>		7.2 7.2 7.2 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 60	7.2 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.2 7.2 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.1 7.1 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
PCLO (ppm)	TM 4381		48 Assay Date: 30Dec2002 NB Ref: CL670 NB Page: 58-59	48 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	48 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	47 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 59
HA (%w/v)	TM 4386		0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.16 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.16 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 30°C/60%RH

Table 9

Attributes	Method SOP#	Specification Low High	0	1	2	3
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	274 274 273 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 61	272 275 Assay Date: 21Jan2003 NB Ref: CL670 NB Page: 97-99	271 272 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 37	273 273 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
VIS (cp)	TM 4384	(b)(4) Confidential and Proprietary Information	7.0 Assay Date: 8Jan2003 NB Ref: LT652 NB Page: 28	6.6 Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	6.4 Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	6.0 Assay Date: 21Mar2003 NB Ref: LT652 NB Page: 48
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 21Jan2003 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 122-127			
PET	Current FDA/Modified USP ISO 14730:2000	(b)(4) Confidential and Proprietary Information	FDA, Mod. USP = PASS Assay Date: 30Jan2003 NB Ref: NA673 NB Page: 42, 43			

Table 9
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 30°C /60%RH

Attributes	Method SOP#	Specification Low High	4	6			
PA	TM 4382	(b)(4) Confidential and Proprietary Information		CLEAR COLORLESS SOLUTION Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33		
PH (pH units)	USP 26 <791>			7.1 7.1	7.1 7.1		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information		46 Assay Date: 2May2003 NB Ref: TK693 NB Page: 74,78	46 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386			0.16 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.16 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 30°C/60%RH

Table 9

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		275 274 Assay Date: 25Apr2003 NB Ref: TK693 NB Page: 61	276 276 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information		5.8 5.8 Assay Date: 28Apr2003 NB Ref: TK693 NB Page: 63	5.7 5.6 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information					
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information					

Table 10

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 30°C/60%RH

Product Name/Strength: *blink*[™] CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*[™] CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Lot Number: 02RD24A
 Date Manufactured: 23Oct2002
 Date Packaged: 23Oct2002
 Storage Condition: 30°C/60%RH
 Shelf Life (Months): 36

Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Package/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 16Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 12 ML
 Fill Capacity: 15 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification Low High	0	1	2	3
PA	TM 4382	[REDACTED]	CLEAR COLORLESS SOLUTION Assay Date: 7Nov2002 NB Ref: TP659 NB Page: 57-58	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP693 NB Page: 67
PH (pH units)	USP 26 <791>	[REDACTED]	7.2 7.2 7.2 Assay Date: 5Nov2002 NB Ref: CL670 NB Page: 20-21	7.2 7.2 7.2 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 86-87	7.2 7.2 7.2 Assay Date: 27Feb2003 NB Ref: CL682 NB Page: 33	7.1 7.1 7.1 Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 63
PCLO (ppm)	TM 4381	[REDACTED]	50 49 49 Assay Date: 1Nov2002 NB Ref: CL670 NB Page: 19-25	49 49 49 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 88-89	49 49 49 Assay Date: 27Feb2003 NB Ref: CL682 NB Page: 31-32	47 47 47 Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 64
HA (%w/v)	TM 4386	[REDACTED]	0.15 0.15 0.15 Assay Date: 30Oct2002 NB Ref: TP659 NB Page: 42-44	0.15 0.15 0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.16 0.16 0.16 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.14 0.14 0.14 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 30°C/60%RH

Table 10

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			288	280	283	286
				276	280	282	285
				288	Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 91	Assay Date: 27Feb2003 NB Ref: CL682 NB Page: 34	Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 63
VIS (cP)	TM 4384			6.6	6.3	6.2	6.0
				6.6	6.2	6.2	6.0
				6.6	Assay Date: 16Jan2003 NB Ref: LT652 NB Page: 31	Assay Date: 24Feb2003 NB Ref: LT652 NB Page: 36	Assay Date: 17Mar2003 NB Ref: LT652 NB Page: 46
STR	USP						
		(b)(4) Confidential and Proprietary Information		USP=PASS Assay Date: 7Nov2002 NB Ref: (b)(4) Sterility test book no. 2 QC-40; pages 90-97			
PFT	Current FDA/Modified USP/ISO 14730:2000			FDA, Mod. USP = PASS Assay Date: 11Dec2002 NB Ref: NA673 NB Page: 16-17			

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 30°C /60%RH

Table 10

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 22Apr2003 NB Ref: TK693 NB Page: 54,55,60	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK693 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.1 7.1 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	7.1 7.1 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
PCL O (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	47 47 Assay Date: 22Apr2003 NB Ref: TK693 NB Page: 53, 54	46 46 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.16 0.15 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.15 0.16 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 30°C /60%RH

Table 10

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		286 286 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	284 283 Assay Date: 17Jun2003 NB Ref: TK706 NB Page: 35		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information		5.8 5.9 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	5.7 5.6 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information					
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information					

(b)(4) Confidential and Proprietary Information

Table II

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 30°C/60%RH

Product Name/Strength
Purpose of Study
Lot Number
Date Manufactured
Date Packaged
Storage Condition
Shelf Life (Months)

*blink*TM CL LUBRICANT EYE DROPS
STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
02RD45A
12Dec2002
12Dec2002
30°C/60%RH
36

Formulation Number 09464X
12,000 GRAMS
Batch Size
Manufacturer/Site
Packager/Site
Storage Orientation
INVERTED

Date Study Started
Container Supplier
Fill Volume
Fill Capacity
Closure Supplier
18Dec2002
12 ML
15 ML

Attributes	Method SOP#	Specification Low High	0	1	2	3
PA	TM 4382		CLEAR COLORLESS SOLUTION Assay Date: 2Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP681 NB Page: 67
PH (pH units)	USP 26 <791>		7.2 7.2 7.2 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 54-55	7.2 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.2 7.2 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.2 7.2 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 65
PCLO (ppm)	TM 4381		49 48 48 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 51-53	48 49 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	48 48 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	47 47 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 66
HA (%w/v)	TM 4386		0.15 0.15 0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.15 0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 0.15 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.15 0.15 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

Table II
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 30°C/60%RH

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		271	266	276	274
				271	266	274	272
				271	266	274	272
VIS (gP)	Tm 4384	(b)(4) Confidential and Proprietary Information		Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 56-57	Assay Date: 21Jan2003 NB Ref: CL670 NB Page: 97-99	Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 37	Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 65
				5.2	4.9	4.8	4.9
				5.2	5.0	4.7	4.9
STR	USP	(b)(4) Confidential and Proprietary Information		Assay Date: 6Jan2003 NB Ref: LT652 NB Page: 27	Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	Assay Date: 19Mar2003 NB Ref: LT652 NB Page: 47
				USP=PASS			
				Assay Date: 27Dec2002 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 112-121			
PEF	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information		FDA, Mod. USP = PASS Assay Date: 23Jan2003 NB Ref: NA673 NB Page: 38-39			

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236

Table 11
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 30°C/60%RH

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33		
PH (pH units)	USP 26 <7/91>	(b)(4) Confidential and Proprietary Information	7.2 7.2 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 58	7.2 7.2 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	48 48 Assay Date: 6May2003 NB Ref: TK693 NB Page: 78	47 48 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.15 0.15 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.14 0.14 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 30°C/60%RH

Table 11

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		273 270 Assay Date: 25Apr2003 NB Ref: TK693 NB Page: 61	272 271 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information		4.3 4.3 Assay Date: 25Apr2003 NB Ref: TK693 NB Page: 61, 63	4.2 4.1 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information					
PET	Current FDAM/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information					

Table 12
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51A, 30°C/60%RH

blink™ CL LUBRICANT EYE DROPS
STABILITY OF blink™ CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Formulation Number 09464X
 Lot Number 02RD51A
 Date Manufactured 17Dec2002
 Date Packaged 17Dec2002
 Storage Condition 30°C /60%RH
 Shelf Life (Months) 36
 Batch Size 12,000 GRAMS
 Manufacturer/Site [REDACTED]
 Package/Site [REDACTED]
 Storage Orientation INVERTED
 Date Study Started 20Dec2002
 Container Supplier [REDACTED]
 Fill Volume 12 ML
 Fill Capacity 15 ML
 Closure Supplier [REDACTED]

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
PA	TM 4382	[REDACTED]		CLEAR COLORLESS SOLUTION Assay Date: 2Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 18Mar2003 NB Ref: TP681 NB Page: 69
PH (pH units)	USP 26 <791>	[REDACTED]		7.2 7.2 7.2 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 60	7.2 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.2 7.2 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.1 7.1 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
PCL0 (ppm)	TM 4381	[REDACTED]		48 49 48 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 58-59	48 48 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	49 49 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	46 47 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 59
HA (%w/v)	TM 4386	[REDACTED]		0.15 0.15 0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.16 0.16 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 0.15 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.16 0.16 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

Table 12
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51A, 30°C/60%RH

Attributes	Method SOP#	Specification Low	0	1	2	3
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	273 274 273 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 61	271 273 Assay Date: 21Jan2003 NB Ref: CL670 NB Page: 97-99	275 270 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 37	271 271 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	7.0 7.0 7.0 Assay Date: 8Jan2003 NB Ref: LT652 NB Page: 28	6.7 6.7 Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	6.5 6.5 Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	5.8 6.0 Assay Date: 21Mar2003 NB Ref: LT652 NB Page: 48
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 21Jan2003 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 122-127			
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information	FDA, Mod. USP = PASS Assay Date: 30Jan2003 NB Ref: NA673 NB Page: 42, 43			

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51A, 30°C/60%RH

Table 12

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 29 Apr 2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9 Jun 2003 NB Ref: TK706 NB Page: 31, 33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.1 7.1 Assay Date: 24 Apr 2003 NB Ref: TK693 NB Page: 58	7.1 7.1 Assay Date: 11 Jun 2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	46 46 Assay Date: 2 May 2003 NB Ref: TK693 NB Page: 74, 78	47 47 Assay Date: 11 Jun 2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.16 0.16 Assay Date: 24 Apr 2003 NB Ref: TP701 NB Page: 2	0.16 0.16 Assay Date: 10 Jun 2003 NB Ref: TP701 NB Page: 54		

Table 12
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RDS1A, 30°C/60%RH

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			270 270 Assay Date: 25Apr2003 NB Ref: TK693 NB Page: 61	273 272 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384			5.6 5.6 Assay Date: 28Apr2003 NB Ref: TK693 NB Page: 63	5.2 5.2 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP						
PEP	Current FDA/Modified USP/ISO 14730:2000						

(b)(4) Confidential and Proprietary Information

Table 13
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 40°C/20%RH

Product Name/Strength: *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 6 ML BOTTLES
 Lot Number: 02RD24B
 Date Manufactured: 23Oct2002
 Date Packaged: 23Oct2002
 Storage Condition: 40°C/20%RH
 Shelf Life (Months): 36
 Formulation Number: 09464X
 Batch Size: 12,000 GP/AMS
 Manufacturer/Site: [REDACTED]
 Package/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 14Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 2 ML
 Fill Capacity: 6 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
PA	TM 4382			CLEAR COLORLESS SOLUTION Assay Date: 7Nov2002 NB Ref: TP659 NB Page: 57-58	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP681 NB Page: 67
PH (pH units)	USP 26 <7/91>			7.2 7.2 7.2 Assay Date: 5Nov2002 NB Ref: CL670 NB Page: 20-21	7.2 7.2 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 86-87	7.1 7.1 Assay Date: 14Feb2003 NB Ref: CL682 NB Page: 33-34	7.1 7.1 Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 63
PCLO (ppm)	TM 4381			49 Assay Date: 1Nov2002 NB Ref: CL670 NB Page: 19-25	47 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 88-89	47 Assay Date: 14Feb2003 NB Ref: CL682 NB Page: 31-32	44 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 64
HA (%w/v)	TM 4386			0.15 0.16 0.16 Assay Date: 30Oct2002 NB Ref: TP659 NB Page: 42-44	0.16 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.16 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.15 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

Table 13
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 40°C/20%RH

Attributes	Method SOP#	Specification		0	1	2	3	
		Low	High					
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		284	288	299	300	
				283	Assay Date: 17Jan2003	298	Assay Date: 14Feb2003	302
				286	NB Ref: CL670	NB Ref: CL682	Assay Date: 18Mar2003	NB Ref: CL682
				Assay Date: 5Nov2002	NB Page: 91	NB Page: 34	NB Page: 63	
VIS (gP)	TM 4384	6.6	5.8	5.5	5.1			
		Assay Date: 4Nov2002	Assay Date: 20Jan2003	Assay Date: 18Feb2003	Assay Date: 18Mar2003			
		NB Ref: LT652	NB Ref: LT652	NB Ref: LT652	NB Ref: LT652			
		NB Page: 18	NB Page: 31	NB Page: 36	NB Page: 47			
STR	USP	USP=PASS						
		Assay Date: 7Nov2002						
		NB Ref: (b)(4)						
		Sterility Test book no. 2						
		QC-40, pages 90-97						
PET	Current FDA/Modified USP/ ISO 14730:2000	FDA, Mod. USP = PASS						
		Assay Date: 11Dec2002						
		NB Ref: NA673						
		NB Page: 16-17						
		FDA, Mod. USP = PASS						
		Assay Date: 21Apr2003						
		NB Ref: NA690						
		NB Page: 16-17						

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244

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 40°C/20%RH

Table 13

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 23Apr2003 NB Ref: TK693 NB Page: 54,55,60	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK693 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.1 7.1 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	7.1 7.1 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	43 Assay Date: 28Apr2003 NB Ref: TK693 NB Page: 56	41 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.17 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.17 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24B, 40°C/20%RH

Table 13

Attributes	Method SOP#	Specification Low High	4	6		
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	305 306 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 50	315 316 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	4.7 4.7 Assay Date: 21Apr2003 NB Ref: TK693 NB Page: 52	4.5 4.5 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information				
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information				

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Table 14

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 40°C/20%RH

Product Name/Strength: *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 6 ML BOTTLES
 Lot Number: 02RD45B
 Date Manufactured: 12Dec2002
 Date Packaged: 12Dec2002
 Storage Condition: 40°C/20%RH
 Shelf Life (Months): 36
 Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Package/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 20Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 2 ML
 Fill Capacity: [REDACTED]
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification Low High	0	1	2	3
PA	TM 4382	[REDACTED]	CLEAR COLORLESS SOLUTION Assay Date: 2Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP681 NB Page: 67
PH (pH units)	USP 26 <791>	[REDACTED]	7.2 7.2 7.2 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 54-55	7.2 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.2 7.2 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.1 7.1 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 65
PCLO (ppm)	TM 4381	[REDACTED]	48 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 51-53	47 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	46 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	43 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 66
HA (%w/v)	TM 4386	[REDACTED]	0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.16 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RP45B, 40°C/20%RH

Table 14

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			272 272 272	274 273	288 285	286 289
				Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 56-57	Assay Date: 21Jan2003 NB Ref: CL670 NB Page: 97-99	Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 37	Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 66
VIS (cP)	TM 4384			5.1	4.5	4.2	4.0
				Assay Date: 6Jan2003 NB Ref: LT652 NB Page: 27	Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	Assay Date: 19Mar2003 NB Ref: LT652 NB Page: 47
STR	USP			USP=PASS Assay Date: 27Dec2002 NB Ref: (b)(4) Sterility test book no. 2 QC-40; pages 112-121			
PET	Current FDA/Modified USP ISO 14730:2000			FDA, Mod. USP = PASS Assay Date: 23Jan2003 NB Ref: NA673 NB Page: 38-39			FDA, Mod. USP = PASS Assay Date: 28Apr2003 NB Ref: NA690 NB Page: 30-32

(b)(4) Confidential and Proprietary Information

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Table 14
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 40°C/20%RH

Attributes	Method SOP#	Specification		4	6		
		Low	High				
PA	TM 4382	(b)(4) Confidential and Proprietary Information		CLEAR COLORLESS SOLUTION Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information		7.1 7.1 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 58	7.2 7.1 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information		42 Assay Date: 6May2003 NB Ref: TK693 NB Page: 78	41 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information		0.15 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.16 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45B, 40°C/20%RH

Table 14

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		295 294 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 57	303 303 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information		3.6 3.6 Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 67	3.4 3.4 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information					
PET	Current FDA/Modified USP/ ISO 14730.2000	(b)(4) Confidential and Proprietary Information					

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 40°C/20%RH

Table 15

Attributes	Method SOP#	Specification Low High	0	1	2	3
Product Name/Strength						
Purpose of Study						
Lot Number						
Date Manufactured						
Date Packaged						
Storage Condition						
Shelf Life (Months)						
blink™ CL LUBRICANT EYE DROPS STABILITY OF blink™ CL LUBRICANT EYE DROPS IN 6 ML BOTTLES Formulation Number 09464X Batch Size 12,000 GRAMS Manufacturer/Site [REDACTED] Package/Site [REDACTED] Storage Orientation INVERTED Date Study Started 20Dec2002 Container Supplier [REDACTED] Fill Volume 2 ML Fill Capacity 6 ML Closure Supplier [REDACTED]						
PA	TM 4382		CLEAR COLORLESS SOLUTION Assay Date: 21Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 18Mar2003 NB Ref: TP681 NB Page: 69
PH (pH units)	USP 26 <791>		7.2 7.2 7.2 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 60	7.2 7.2 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.1 7.1 7.1 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.1 7.1 7.1 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
PCLO (ppm)	TM 4381		48 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 58-59	47 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	46 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	45 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 59
HA (%w/v)	TM 4386		0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.16 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.16 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72
(b)(4) Confidential and Proprietary Information						

Table 15
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02NRD51B, 40°C/20%RH

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information		274	272	280	287
				274	273	291	289
				273	Assay Date: 21Jan2003 NB Ref: CL670 NB Page: 97-99	Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 37	Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
VIS (cp)	TM 4384	(b)(4) Confidential and Proprietary Information		7.0	6.1	5.6	4.9
				Assay Date: 8Jan2003 NB Ref: LT652 NB Page: 28	Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	Assay Date: 21Mar2003 NB Ref: LT652 NB Page: 48
				USP=PASS Assay Date: 21Jan2003 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 122-127			
STR	USP	(b)(4) Confidential and Proprietary Information					
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information		FDA, Mod. USP = PASS Assay Date: 30Jan2003 NB Ref: NA673 NB Page: 42, 43			FDA, Mod. USP = PASS Assay Date: 28Apr2003 NB Ref: NA690 NB Page: 30-32

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 40°C/20%RH

Table 15

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.0 7.1 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 58	7.1 7.1 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	45 Assay Date: 6May2003 NB Ref: TK693 NB Page: 78	43 Assay Date: 12Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.16 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.18 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

Table 15
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51B, 40°C/20%RH

Attributes	Method SOP#	Specification Low High	4	6		
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	293 293 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 57	302 303 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	4.6 4.6 Assay Date: 30Apr2003 NB Ref: TK693 NB Page: 69	4.1 4.1 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information				
PET	Current FDAM/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information				

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Table 16
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 40°C/20%RH

Product Name/Strength: *blink*[™] CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*[™] CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Lot Number: 02RD24A
 Date Manufactured: 23Oct2002
 Date Packaged: 23Oct2002
 Storage Condition: 40°C/20%RH
 Shelf Life (Months): 36
 Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Package/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 16Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 12 ML
 Fill Capacity: 15 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
PA	TM 4382			CLEAR COLORLESS SOLUTION Assay Date: 7Nov2002 NB Ref: TP659 NB Page: 57-58	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP693 NB Page: 67
PH (pH units)	USP 26 <791>			7.2 7.2 7.2 Assay Date: 5Nov2002 NB Ref: CL670 NB Page: 20-21	7.2 7.2 7.2 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 86-87	7.2 7.2 7.2 Assay Date: 14Feb2003 NB Ref: CL682 NB Page: 33-34	7.1 7.1 7.1 Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 63
PCLO (ppm)	TM 4381			50 49 49 Assay Date: 1Nov2002 NB Ref: CL670 NB Page: 19-25	48 47 47 Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 88-89	47 48 48 Assay Date: 14Feb2003 NB Ref: CL682 NB Page: 31-32	45 45 45 Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 64
HA (%w/v)	TM 4386			0.15 0.15 0.15 Assay Date: 30Oct2002 NB Ref: TP659 NB Page: 42-44	0.15 0.15 0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.16 0.16 0.16 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.14 0.14 0.14 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

1 151
255

Table 16
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RND24A, 40°C/20%RH

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			288	282	288	289
				276	286	286	287
				288	Assay Date: 17Jan2003 NB Ref: CL670 NB Page: 91	Assay Date: 14Feb2003 NB Ref: CL682 NB Page: 34	Assay Date: 18Mar2003 NB Ref: CL682 NB Page: 63
VIS (qP)	TM 4384			6.6	5.9	5.6	5.2
				6.6	6.0	5.6	5.3
				6.6	Assay Date: 16Jan2003 NB Ref: LT652 NB Page: 31	Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36	Assay Date: 18Mar2003 NB Ref: LT652 NB Page: 47
STR	USP			USP=PASS Assay Date: 7Nov2002 NB Ref: (b)(4) Sterility test book no. 2 QC-40; pages 90-97			
PET	Current FDAM/Modified USP/ISO 14730:2000			FDA, Mod. USP = PASS Assay Date: 11Dec2002 NB Ref: NA673 NB Page: 16-17			FDA, Mod. USP = PASS Assay Date: 21Apr2003 NB Ref: NA690 NB Page: 16-17

(b)(4) Confidential and Proprietary Information

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 40°C/20%RH

Table 16

Attributes	Method SOP#	Specification Low/High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 23Apr2003 NB Ref: TK693 NB Page: 54,55,60	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK693 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.1 7.1 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 49	7.1 7.1 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	45 45 Assay Date: 23Apr2003 NB Ref: TK693 NB Page: 54	44 45 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.17 0.16 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.15 0.15 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD24A, 40°C/20%RH

Table 16

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			287 288 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 50	289 289 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (CP)	TM 4384			4.9 4.9 Assay Date: 18Apr2003 NB Ref: TK693 NB Page: 52	4.5 4.5 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP						
PEP	Current FDA/Modified USP/ISO 14730:2000						

(b)(4) Confidential and Proprietary Information

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 40°C/20%RH

Table 17

Product Name/Strength: *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Lot Number: 02RD45A
 Date Manufactured: 12Dec2002
 Date Packaged: 12Dec2002
 Storage Condition: 40°C/20%RH
 Shelf Life (Months): 36

Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Packager/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 18Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 12 ML
 Fill Capacity: 15 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification Low High	0	1	2	3
PA	TM 4382	[REDACTED]	CLEAR COLORLESS SOLUTION Assay Date: 2Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 17Mar2003 NB Ref: TP681 NB Page: 67
PH (pH units)	USP 26 <7/91>	[REDACTED]	7.2 7.2 7.2 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 54-55	7.2 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.2 7.2 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.2 7.2 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 65
PCLO (ppm)	TM 4381	[REDACTED]	49 48 48 Assay Date: 19Dec2002 NB Ref: CL670 NB Page: 51-53	48 48 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	48 48 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	46 46 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 66
HA (%w/v)	TM 4386	[REDACTED]	0.15 0.15 0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.15 0.15 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 0.15 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.15 0.15 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

1 155 259

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 40°C/20%RH

Table 17

Attributes	Method SOP#	Specification									
		Low	High	0	1	2	3				
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information						271	269	275	276
								271	267	272	275
VIS (gP)	TM 4384	(b)(4) Confidential and Proprietary Information						5.2	4.6	4.4	4.0
								5.2	4.6	4.5	4.1
STR	USP	(b)(4) Confidential and Proprietary Information						Assay Date: 6Jan2003 NB Ref: LT652 NB Page: 27	Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	Assay Date: 19Mar2003 NB Ref: LT652 NB Page: 47
								USP=PASS Assay Date: 27Dec2002 NB Ref: [REDACTED] Sterility test book no. 2 QC-40; pages 112-121			
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information						FDA, Mod. USP = PASS Assay Date: 23Jan2003 NB Ref: NA673 NB Page: 38-39			FDA, Mod. USP = PASS Assay Date: 28Apr2003 NB Ref: NA690 NB Page: 30-32

1 156
260

Table 17
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 40°C/20%RH

Attributes	Method SOP#	Specification Low High	4	6		
PA	TM 4382	(b)(4) Confidential and Proprietary Information	CLEAR COLORLESS SOLUTION Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31,33		
PH (pH units)	USP 26 <791>	(b)(4) Confidential and Proprietary Information	7.2 7.1 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 58	7.2 7.2 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
PCLO (ppm)	TM 4381	(b)(4) Confidential and Proprietary Information	45 45 Assay Date: 13May2003 NB Ref: TK693 NB Page: 78	45 45 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 37		
HA (%w/v)	TM 4386	(b)(4) Confidential and Proprietary Information	0.14 0.14 Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	0.15 0.15 Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54		

1 157

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STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD45A, 40°C/20%RH

Table 17

Attributes	Method SOP#	Specification Low High	4	6		
OSM (mOsm/Kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	278 277 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 57	280 279 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	3.6 3.6 Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 67	3.5 3.4 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP	(b)(4) Confidential and Proprietary Information				
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information				

(b)(4) Confidential and Proprietary Information

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RD51A, 40° C/20%RH

Table 18

Product Name/Strength: *blink*TM CL LUBRICANT EYE DROPS
 Purpose of Study: STABILITY OF *blink*TM CL LUBRICANT EYE DROPS IN 15 ML BOTTLES
 Lot Number: 02RD51A
 Date Manufactured: 17Dec2002
 Date Packaged: 17Dec2002
 Storage Condition: 40° C/20%RH
 Shelf Life (Months): 36
 Formulation Number: 09464X
 Batch Size: 12,000 GRAMS
 Manufacturer/Site: [REDACTED]
 Package/Site: [REDACTED]
 Storage Orientation: INVERTED
 Date Study Started: 20Dec2002
 Container Supplier: [REDACTED]
 Fill Volume: 12 ML
 Fill Capacity: 15 ML
 Closure Supplier: [REDACTED]

Attributes	Method SOP#	Specification		0	1	2	3
		Low	High				
PA	TM 4382			CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP659 NB Page: 95-96	CLEAR COLORLESS SOLUTION Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 12-13	CLEAR COLORLESS SOLUTION Assay Date: 20Feb2003 NB Ref: TP681 NB Page: 40-42	CLEAR COLORLESS SOLUTION Assay Date: 18Mar2003 NB Ref: TP681 NB Page: 69
PH (pH units)	USP 26 <791>			7.2 7.2 7.2 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 60	7.2 7.2 Assay Date: 20Jan2003 NB Ref: CL670 NB Page: 95	7.2 7.2 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 35-36	7.1 7.1 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
PCLO (ppm)	TM 4381			48 49 48 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 58-59	48 48 Assay Date: 22Jan2003 NB Ref: CL670 & CL682 NB Page: 100 & 1	48 47 Assay Date: 19Feb2003 NB Ref: CL682 NB Page: 38-39	46 46 Assay Date: 21Mar2003 NB Ref: CL682 NB Page: 59
HA (%w/v)	TM 4386			0.15 0.15 0.15 Assay Date: 30Dec2002 NB Ref: TP659 NB Page: 91-92	0.16 0.16 Assay Date: 23Jan2003 NB Ref: TP681 NB Page: 5-9	0.15 0.14 Assay Date: 21Feb2003 NB Ref: TP681 NB Page: 43-45	0.16 0.16 Assay Date: 20Mar2003 NB Ref: TP681 NB Page: 72

(b)(4) Confidential and Proprietary Information

Table 18
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RDS1A, 40°C/20%RH

Attributes	Method SOP#	Specification Low High	0	1	2	3
OSM (mOsm/kg)	USP 26 <785>	(b)(4) Confidential and Proprietary Information	273 274 273 Assay Date: 27Dec2002 NB Ref: CL670 NB Page: 61	272 272 Assay Date: 21Jan2003 NB Ref: CL670 NB Page: 97-99	274 274 Assay Date: 18Feb2003 NB Ref: CL682 NB Page: 37	276 276 Assay Date: 19Mar2003 NB Ref: CL682 NB Page: 59
VIS (cP)	TM 4384	(b)(4) Confidential and Proprietary Information	7.0 7.0 7.0 Assay Date: 8Jan2003 NB Ref: LT652 NB Page: 28	6.1 Assay Date: 20Jan2003 NB Ref: LT652 NB Page: 31-33	5.5 5.5 Assay Date: 18Feb2003 NB Ref: LT652 NB Page: 36-38	4.8 4.8 Assay Date: 21Mar2003 NB Ref: LT652 NB Page: 48
STR	USP	(b)(4) Confidential and Proprietary Information	USP=PASS Assay Date: 21Jan2003 NB Ref: (b)(4) Confidential and Proprietary Information Sterility test book no. 2 QC-40; pages 122-127			
PET	Current FDA/Modified USP/ISO 14730:2000	(b)(4) Confidential and Proprietary Information	FDA, Mod. USP = PASS Assay Date: 30Jan2003 NB Ref: NA673 NB Page: 42, 43			FDA, Mod. USP = PASS Assay Date: 28Apr2003 NB Ref: NA690 NB Page: 30, 32

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264

Table 18
STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RDS1A, 40°C/20%RH

Attributes	Method SOP#	Specification		4	6		
		Low	High				
PA	TM 4382	(b)(4) Confidential and Proprietary Information		CLEAR COLORLESS SOLUTION Assay Date: 29Apr2003 NB Ref: TK693 NB Page: 65-67	CLEAR COLORLESS SOLUTION Assay Date: 9Jun2003 NB Ref: TK706 NB Page: 31, 33		
PH (pH units)	USP 26 <791>			7.1 7.1	7.1 7.1		
PCL O (ppm)	TM 4381			Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 58	Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
		46 45	44 44				
HA (%w/v)	TM 4386	Assay Date: 6May2003 NB Ref: TK693 NB Page: 74,78	Assay Date: 12Jun2003 NB Ref: TK706 NB Page: 37				
		0.16 0.16	0.16 0.16				
		Assay Date: 24Apr2003 NB Ref: TP701 NB Page: 2	Assay Date: 10Jun2003 NB Ref: TP701 NB Page: 54				

STABILITY RAW DATA FOR FORMULATION 09464X, LOT 02RDS1A, 40°C/20% RH

Table 18

Attributes	Method SOP#	Specification		4	6		
		Low	High				
OSM (mOsm/kg)	USP 26 <785>			274 276 Assay Date: 24Apr2003 NB Ref: TK693 NB Page: 57	278 279 Assay Date: 11Jun2003 NB Ref: TK706 NB Page: 36		
VIS (cP)	TM 4384			4.5 4.4 Assay Date: 30Apr2003 NB Ref: TK693 NB Page: 69	4.0 4.0 Assay Date: 10Jun2003 NB Ref: TK706 NB Page: 35		
STR	USP						
PEP	Current FDA/Modified USP/ ISO 14730:2000	(b)(4) Confidential and Proprietary Information					

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APPENDIX B

Stability Data Plots for *blink*[™] CL Lubricant Eye Drops, Formula 9464X

Abbreviations Used in Figures:

VIS	Viscosity
PCLO	Potential Chlorine Dioxide

Contents of Appendix B

- Figure 1 VIS Data Plot for Lot Number 02RD24B, 40°C/20% RH Storage, 2 mL Fill
- Figure 2 VIS Data Plot for Lot Number 02RD45B, 40°C/20% RH Storage, 2 mL Fill
- Figure 3 VIS Data Plot for Lot Number 02RD51B, 40°C/20% RH Storage, 2 mL Fill
- Figure 4 VIS Data Plot for Lot Number 02RD24A, 40°C/20% RH Storage, 12 mL Fill
- Figure 5 VIS Data Plot for Lot Number 02RD45A, 40°C/20% RH Storage, 12 mL Fill
- Figure 6 VIS Data Plot for Lot Number 02RD51A, 40°C/20% RH Storage, 12 mL Fill

- Figure 7 PCLO Data Plot for Lot Number 02RD24B, 40°C/20% RH Storage, 2 mL Fill
- Figure 8 PCLO Data Plot for Lot Number 02RD45B, 40°C/20% RH Storage, 2 mL Fill
- Figure 9 PCLO Data Plot for Lot Number 02RD51B, 40°C/20% RH Storage, 2 mL Fill
- Figure 10 PCLO Data Plot for Lot Number 02RD24A, 40°C/20% RH Storage, 12 mL Fill
- Figure 11 PCLO Data Plot for Lot Number 02RD45A, 40°C/20% RH Storage, 12 mL Fill
- Figure 12 PCLO Data Plot for Lot Number 02RD51A, 40°C/20% RH Storage, 12 mL Fill

Figure 1: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 2 mL
Viscosity Assay, 40°C/20%RH Lot: 02RD24B
(b)(4) Confidential and Proprietary Information

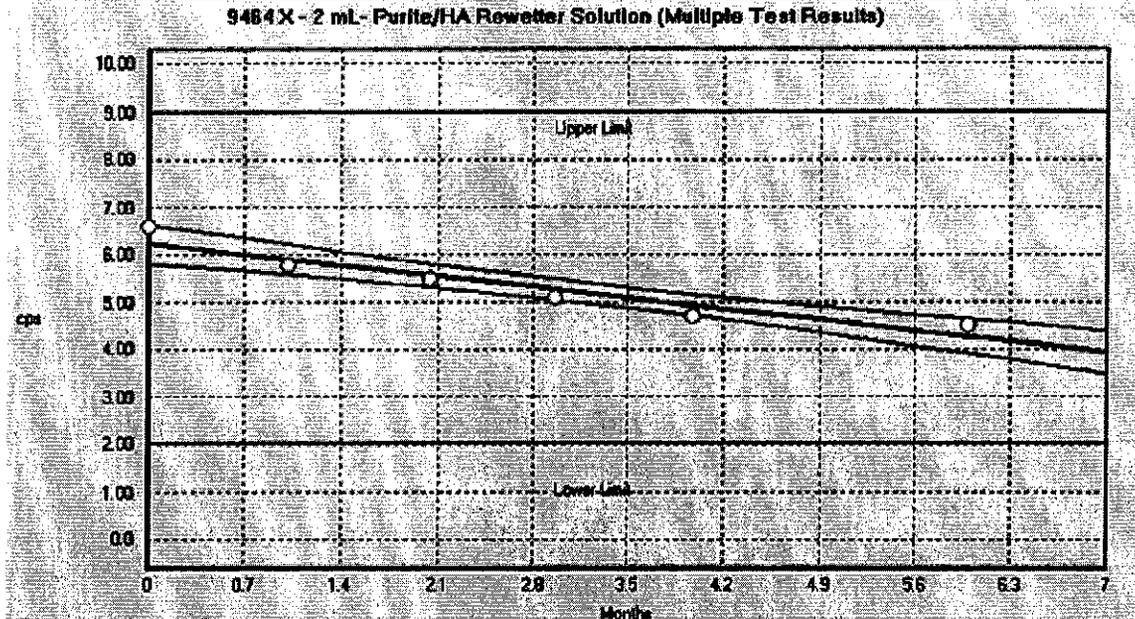


Figure 2: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 2 mL
Viscosity Assay, 40°C/20%RH Lot: 02RD45B
(b)(4) Confidential and Proprietary Information

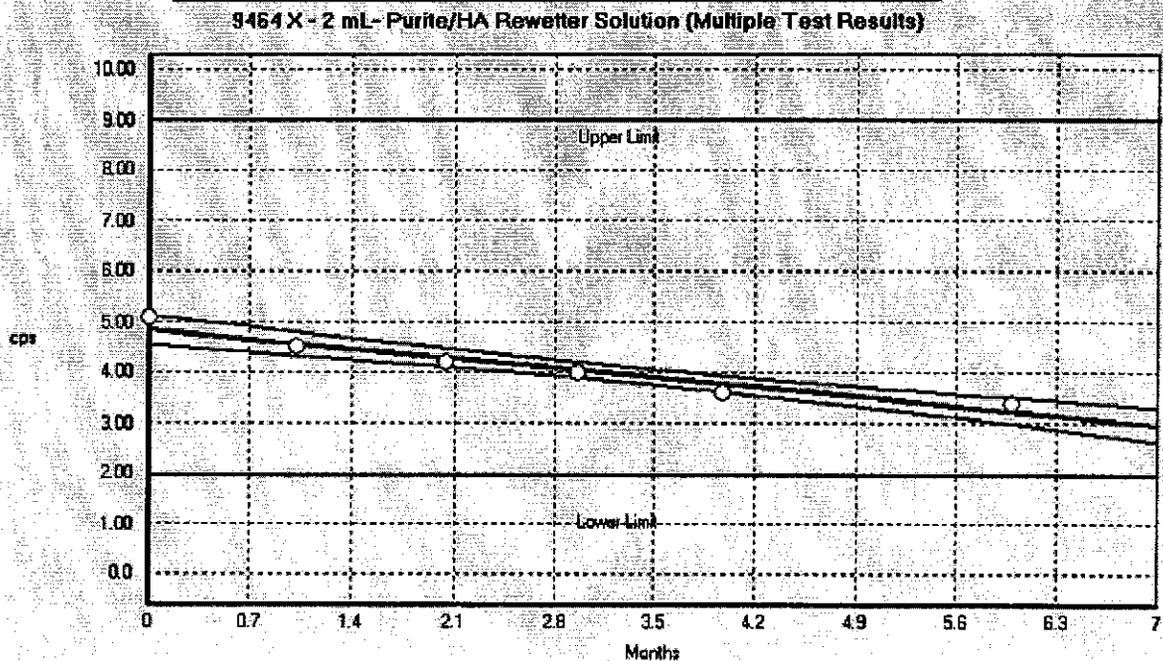


Figure 3: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 2 mL
Viscosity Assay, 40°C/20%RH Lot: 02RD51B
(b)(4) Confidential and Proprietary Information

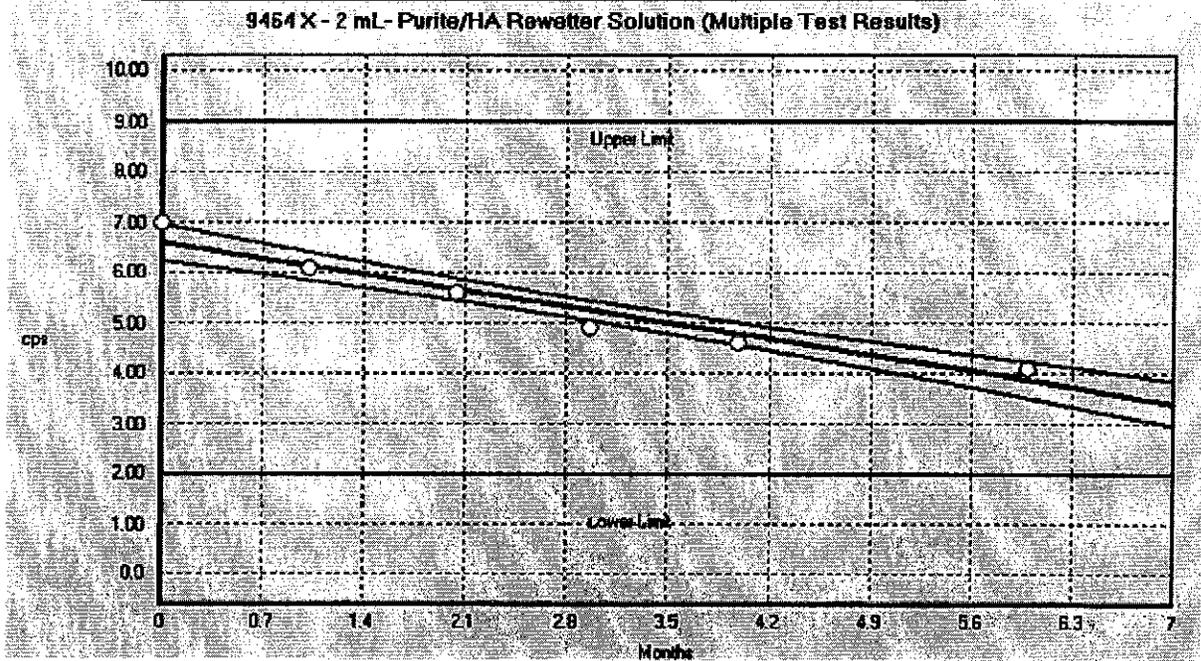


Figure 4: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 12 mL
Viscosity Assay, 40°C/20%RH Lot: 02RD24A
(b)(4) Confidential and Proprietary Information

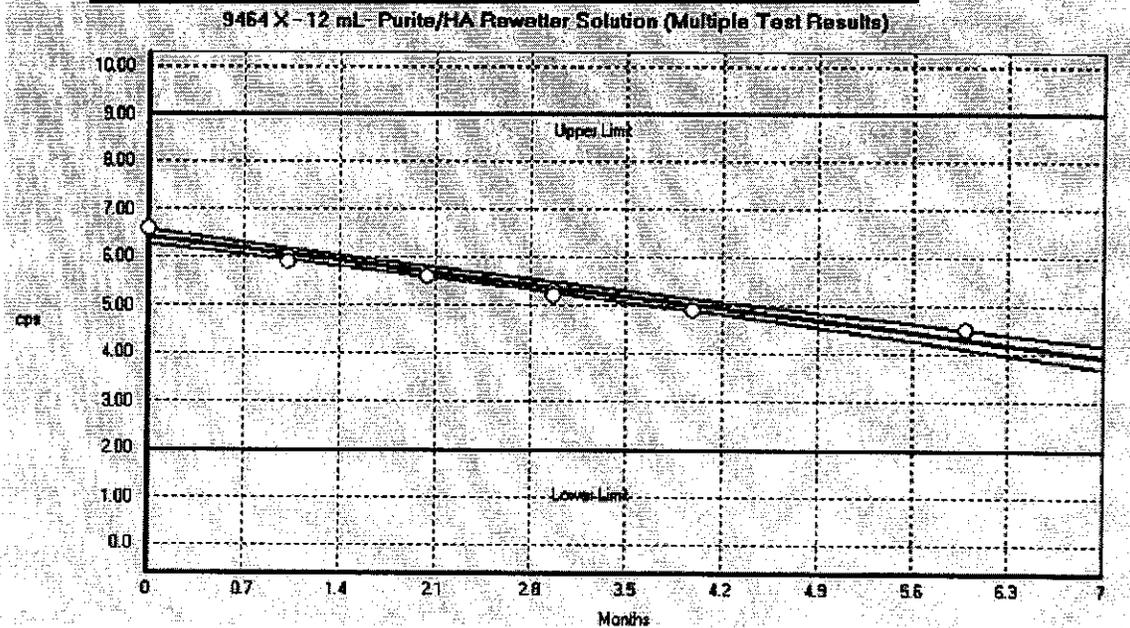


Figure 5: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 12 mL
Viscosity Assay, 40°C/20%RH Lot: 02RD45A
(b)(4) Confidential and Proprietary Information

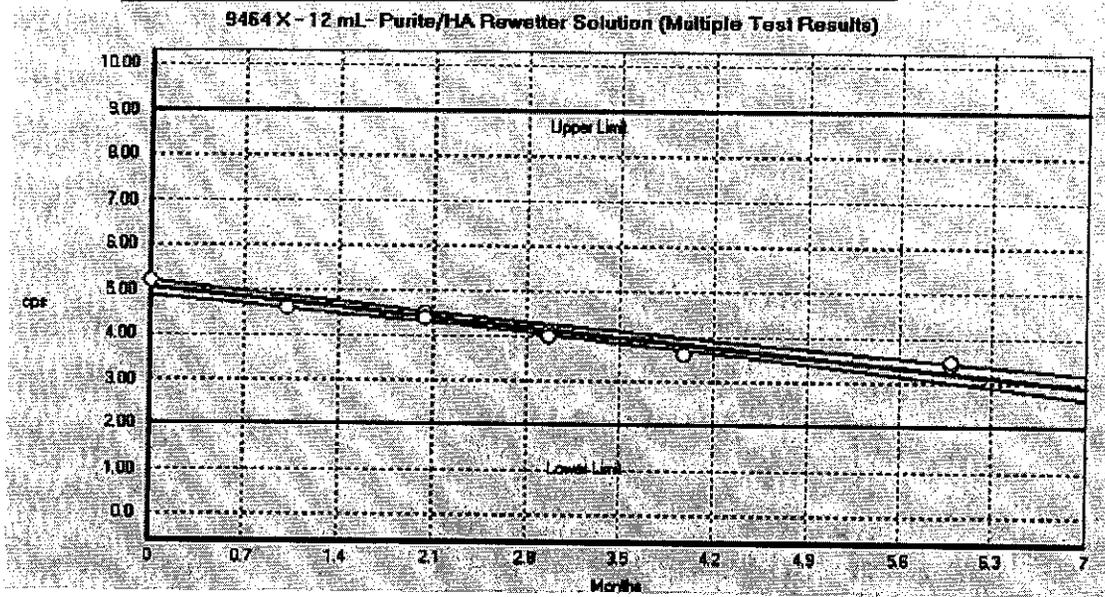
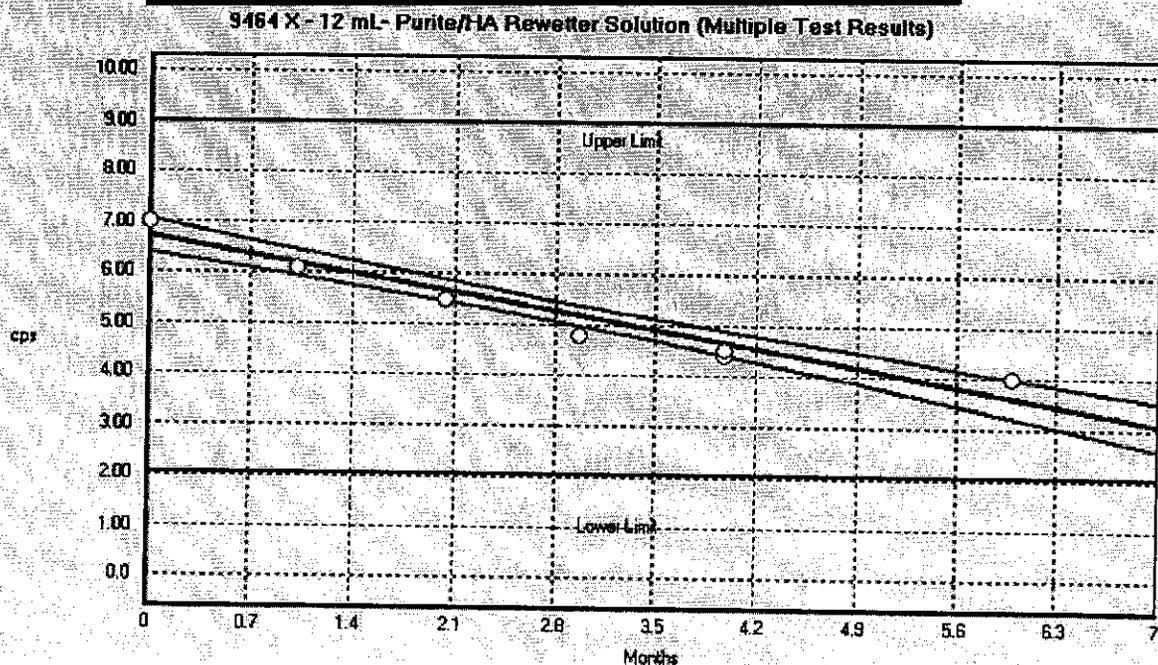


Figure 6: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 12 mL
Viscosity Assay, 40°C/20%RH Lot: 02RD51A
(b)(4) Confidential and Proprietary Information



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Figure 7: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 2 mL
Potential Chlorine Dioxide, 40°C/20%RH Lot: 02RD24B

(b)(4) Confidential and Proprietary Information

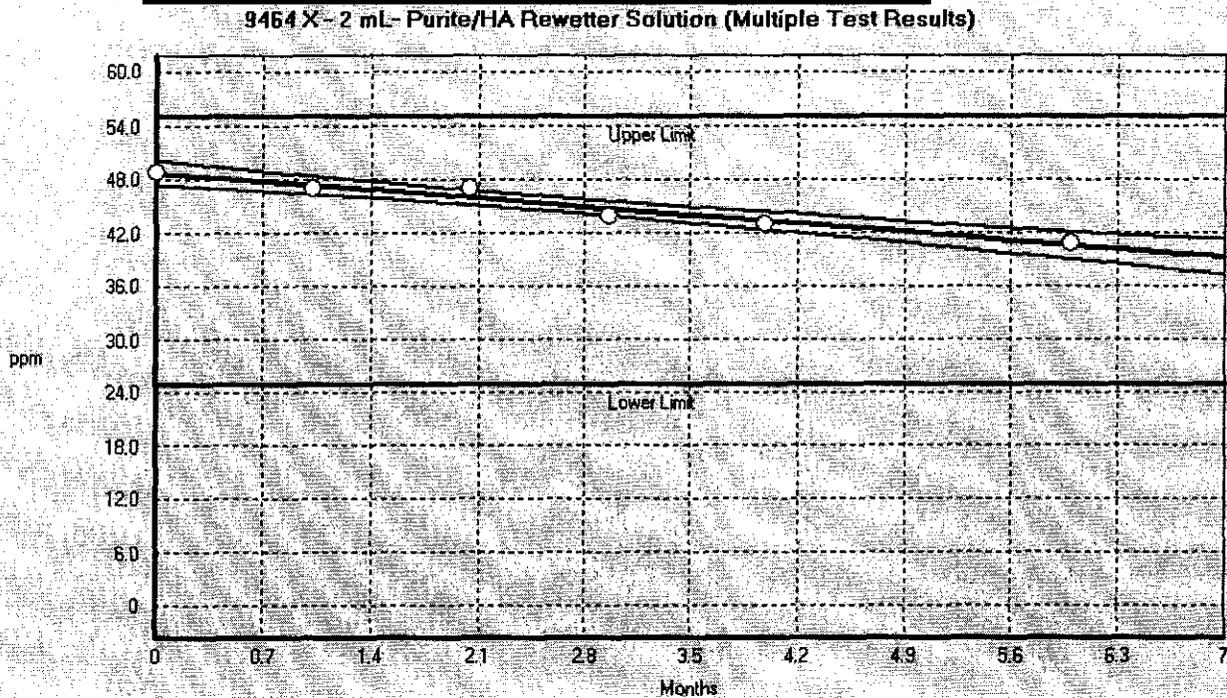


Figure 8: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 2 mL
Potential Chlorine Dioxide, 40°C/20%RH Lot: 02RD45B

(b)(4) Confidential and Proprietary Information

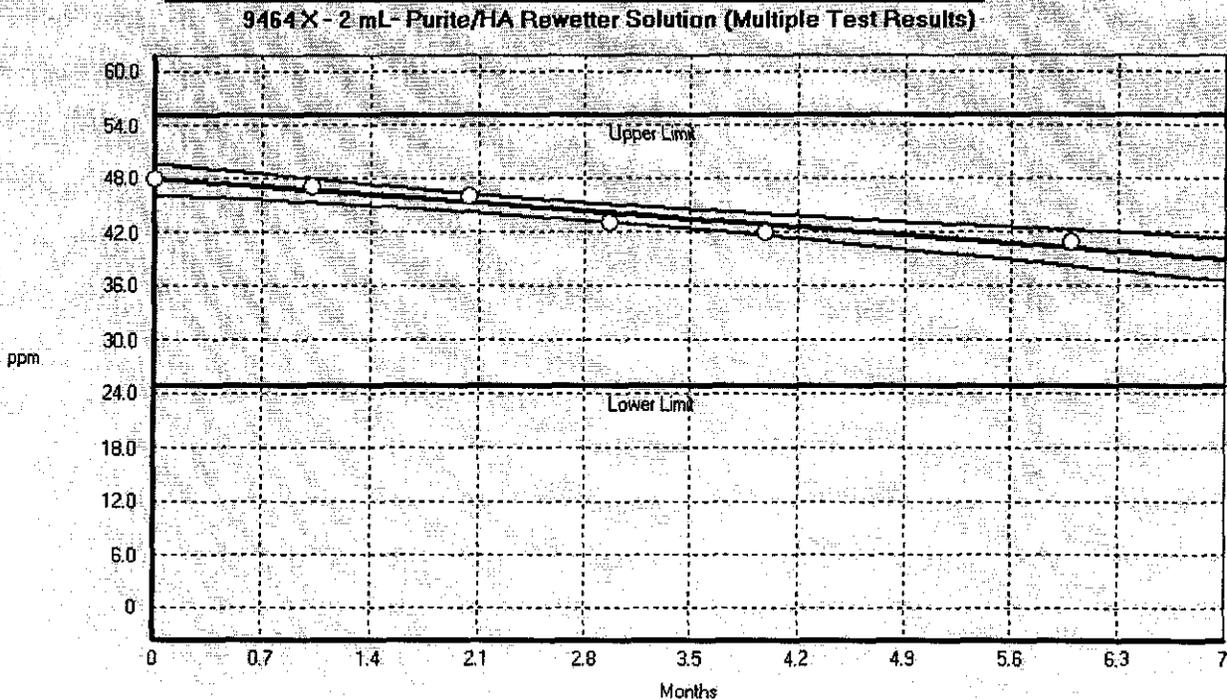


Figure 9: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 2 mL
Potential Chlorine Dioxide, 40°C/20%RH Lot: 02RD51B

(b)(4) Confidential and Proprietary Information

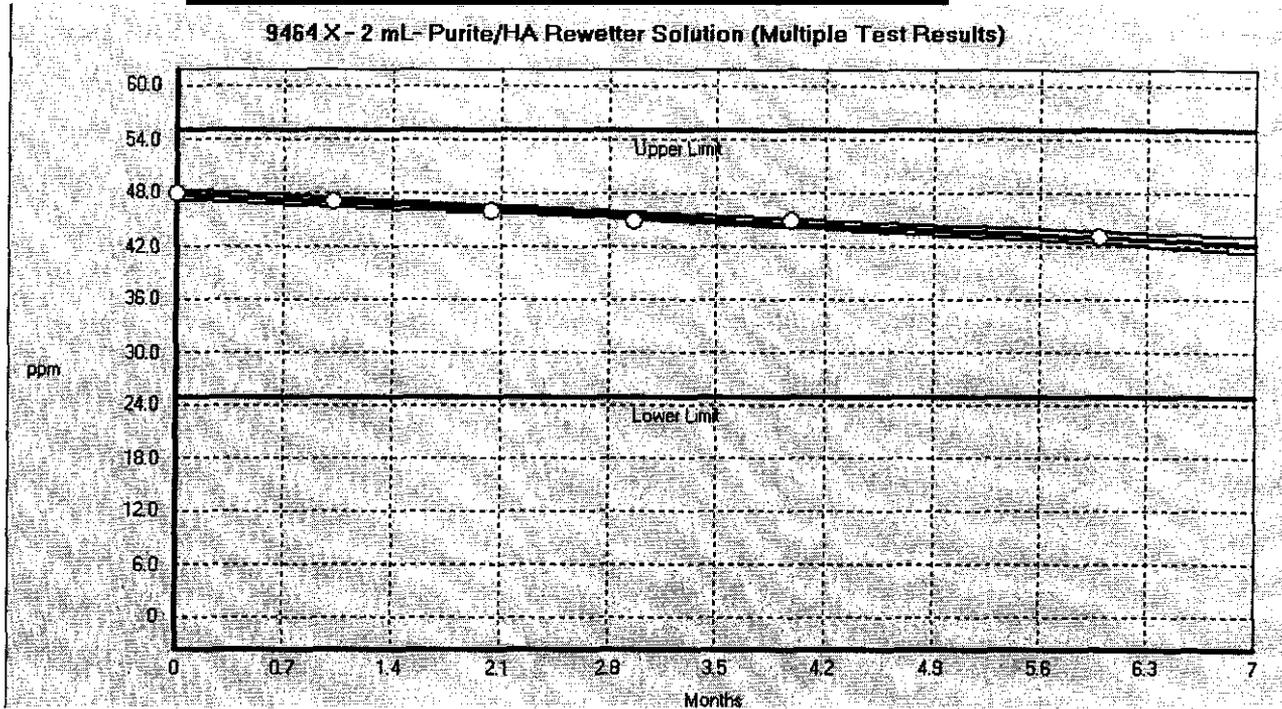
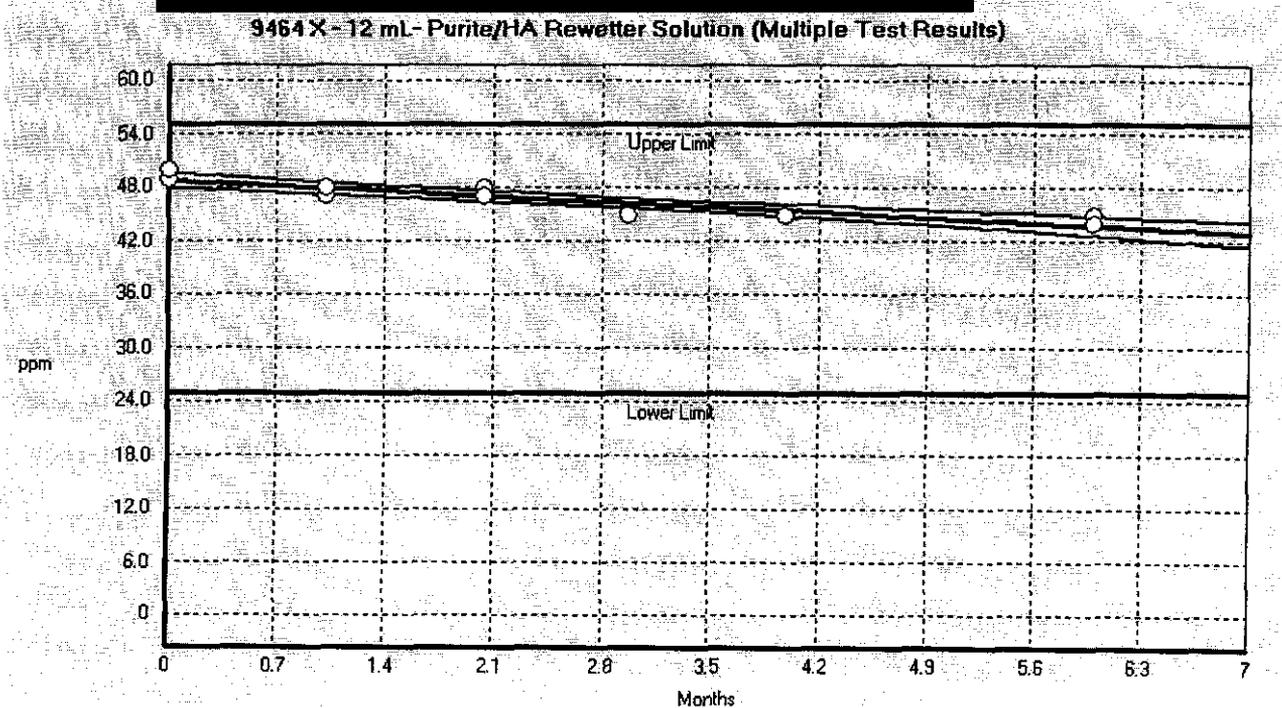


Figure 10: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 12 mL
Potential Chlorine Dioxide, 40°C/20%RH Lot: 02RD24A

(b)(4) Confidential and Proprietary Information



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Figure 11: Shelf Life Projection
*blink*TM CL Lubricant Eye Drops (9464X), 12 mL
Potential Chlorine Dioxide, 40°C/20%RH Lot: 02RD45A

(b)(4) Confidential and Proprietary Information

9464X - 12 mL- Purite/HA Rewetter Solution (Multiple Test Results)

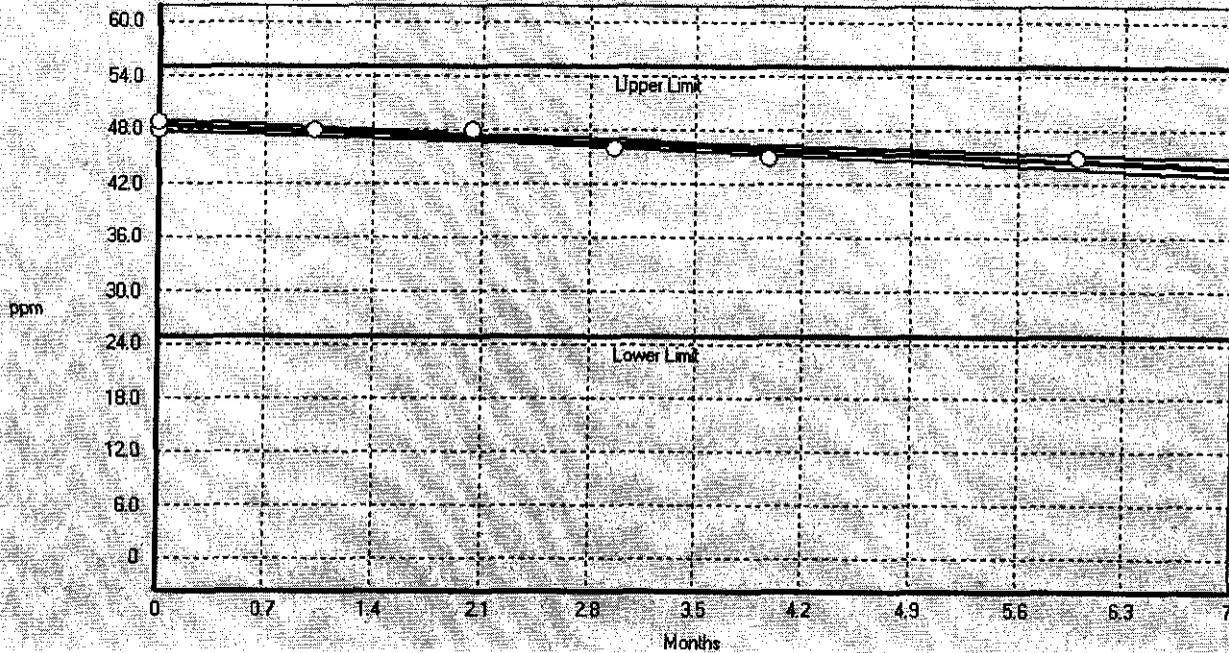


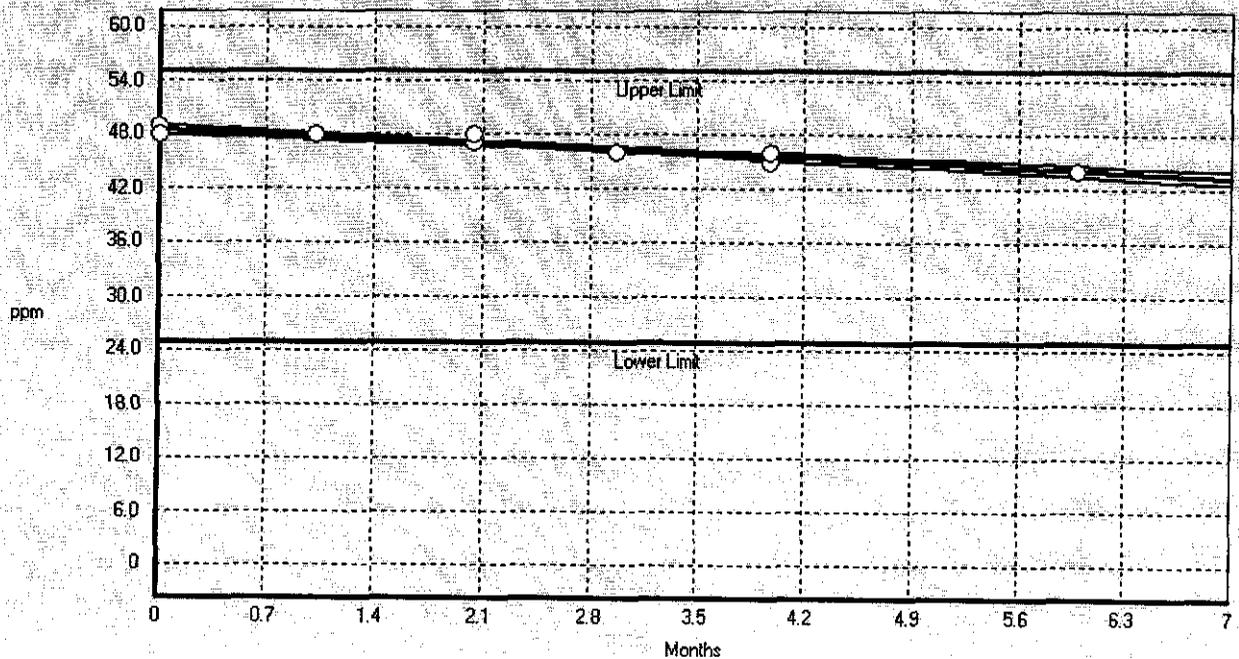
Figure 12: Shelf Life Projection

*blink*TM CL Lubricant Eye Drops (9464X), 12 mL

Potential Chlorine Dioxide, 40°C/20%RH Lot: 02RD51A

(b)(4) Confidential and Proprietary Information

9464X - 12 mL- Purite/HA Rewetter Solution (Multiple Test Results)



TOXICOLOGY

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NONCLINICAL REPORT SUMMARIES

Department: Toxicology
Study Type: Cytotoxicity
Title: Cytotoxicity Testing: Advanced Medical Optics Eye Care Solutions
Study Date: February 13, 2003
Study Number: (b)(4) Confidential and Proprietary Information

Study Summary: The purpose of this *in vitro* agar overlay method study was to determine the cytotoxic potential of *blink*TM CL Lubricant Eye Drops. Two formulations of *blink*TM CL Lubricant Eye Drops (9464X and 9467X) were evaluated. For comparison, Refresh Contacts Lubricating and Rewetting Drops (9329X) was also tested.

Each of the above solutions were saturated on filter discs immediately before applying on top of an agar layer covering a confluent monolayer of human fibroblast cells. Two one cm² filter discs, which represented about 1/10 of the surface area of the culture plate, were placed in direct contact with an agar layer overlaying a confluent monolayer of cells. A negative control was also employed in this procedure.

The results of the study showed no cell lysis for any of the three test solutions.

It can be concluded that *blink*TM CL Lubricant Eye Drops is non-cytotoxic and substantially equivalent to Refresh Contacts Lubricating and Rewetting Drops by this test method.

NONCLINICAL REPORT SUMMARIES

Department: Toxicology
Study Type: Acute Ocular Toxicity
Title: Contact Lens Rewetter: 1-Day Ocular Toxicity Study with a 3-Day Recovery Period in Rabbits
Study Dates: December 20, 2002
Study Number: (b)(4) Confidential and Proprietary Information
Study Summary:

The objective of this study was to determine the ocular effects in rabbits after one day of topical instillations of *blink*TM CL Lubricant Eye Drops. Two formulations were tested: 9464X and 9467X.

Two groups of female New Zealand White rabbits (4/group) received 8 topical instillations (~70 µL/drop/hour) of formulation no. 9464X or formulation no. 9467X into the left eye. The right eye was untreated and served as a control. Rabbits were observed for signs of ocular irritation during a 3-day recovery period.

No mortality or treatment-related effects were observed on clinical observations, gross ocular observations, or slit lamp biomicroscopy.

It can be concluded that *blink*TM CL Lubricant Eye Drops is non-irritating and well-tolerated in rabbit eyes following one day of multiple instillations.

Cytotoxicity

(b)(4) Confidential and
Proprietary Information

Quality Biology Laboratory Study No. (b)(4) Confidential and Proprietary Information

February 13, 2003

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CYTOTOXICITY TESTING

ADVANCED MEDICAL OPTICS EYE CARE SOLUTIONS

GLP STUDY REPORT

(b)(4) Confidential
and Proprietary

QUALITY BIOLOGY LABORATORY STUDY NO. B2905
MBC SUBMISSION NO. 02-010

***ALL DATA RESULTING FROM THIS STUDY
IS CONSIDERED THE PROPRIETARY PROPERTY
OF
ADVANCED MEDICAL OPTICS
AND
MAY NOT BE SHARED OR DISTRIBUTED
WITHOUT THE WRITTEN AUTHORIZATION OF ADVANCED MEDICAL
OPTICS.***

(b)(4) Confidential and Proprietary Information

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CYTOTOXICITY TESTING

ADVANCED MEDICAL OPTICS EYE CARE SOLUTIONS

PURPOSE

The purpose of this study was to evaluate the cytotoxicity of three eye care solutions.

All studies herein will be performed in compliance to the Good Laboratory Practice (GLP) guidelines (21 CFR Part 58).

CONTROL ARTICLES

The control articles were as outlined in the individual procedures and any modifications thereof are described in the Experimental Design.

TEST ARTICLE DESCRIPTION & EXPERIMENTAL DESIGN: B2905

Description:

Formula # 3 (9464X), Lot # 02RD24

(b)(4) Confidential and Proprietary Information

Formula # 6 (9467X), Lot # 02RD27

(b)(4) Confidential and Proprietary Information

Formula # 7 (9329X), Lot # 18833

(b)(4) Confidential and Proprietary Information

Manufacturing Process: All samples were prepared in accordance with Advanced Medical Optics' internal procedures with traceability to the manufacturing and sterilization processes. Maintaining and archiving the original data is the responsibility of Advanced Medical Optics.

Sterilization Process: All test article samples were sterilized according to documented procedures of Advanced Medical Optics.

Experimental Design:

Test articles B2905-01, B2905-02 and B2905-03 were individually evaluated by the Agar Overlay Method (b)(4) Confidential and Proprietary Information (Revision AB) with the following modification:

The surface area of the filter disc saturated with the test solution and the surface area of the negative control material to be tested were each approximately 10% of the surface of the test plate.

PREPARATION OF TEST ARTICLES

Test article preparation for the Agar Overlay procedure (QCOP L303) were as follows:

The test articles, B2905-01, B2905-02, and B2905-03 were saturated on filter discs immediately before applying on top of an agar layer covering a confluent monolayer of human fibroblast cells. Two-one cm² filter discs, which represented about 1/10 of the surface area of the culture plate, were placed in direct contact with an agar layer overlaying a confluent monolayer of cells. Approximately 2 cm² of the negative control material were placed in direct contact with an agar layer overlaying a confluent monolayer of cells.

RESULTS

The test articles, B2905-01, B2905-02, and B2905-03 were evaluated by the Agar Overlay procedure. This procedure utilized the test article itself and cellular exposure to those components, which might have diffused, from the sample and through an agar layer elicited no cell lysis.

In summary, there were no significant differences observed between the test articles and the negative control article in the test procedure. Therefore, the test articles, B2905-01, B2905-02, and B2905-03 were determined to be non-cytotoxic by this method.

TEST ARTICLE CHARACTERIZATION

Verification of the identity of the test articles B2905-01, B2905-02, and B2905-03 was the responsibility of Advanced Medical Optics.

CONTROL ARTICLE CHARACTERIZATION

The control articles used in the test methods designated herein were characterized and recorded in Biology Logbook 119A. All of the control articles employed for this procedure were considered to be stable at the time of usage.

CONTROL OF TEST SYSTEMS

The cell line to be used for the Agar Overlay procedure was a human fibroblast derived from infant foreskin tissue. These cells were obtained from (b)(4) Confidential and Proprietary Information under (b)(4) Confidential and Proprietary Information

ATCC No. CRL1634. This cell line is nourished with Complete Minimum Essential Medium (Eagles) containing Calf Serum with Iron as specified in QCOP L500, revision V.

STATISTICAL METHODS

No statistical methodology was employed for this study.

JUSTIFICATION

Parameters Justification

The use of these test parameters and test systems are justified based upon the stability of the materials, their general use, and the overall acceptance in the field of materials toxicology. The test methodology and test systems are recommended by United States Pharmacopeia, American Society for Testing and Materials, and International Standards Organization (ISO), or are generally accepted as preferred by leaders in this field.

Experimental Design Justification

The experimental design for test articles B2905-01, B2905-02, and B2905-03 has generally been accepted as useful in cytotoxicity testing of contact lens materials and solutions.

CONCLUSION

The test articles, B2905-01, B2905-02, and B2905-03, as defined in this GLP study report, were determined to be non-cytotoxic by the method outlined herein.

RECORDS TO BE MAINTAINED

The protocol, final report, OAI statement, and raw data will be stored in the (b)(4) Confidential and Proprietary Information Test article samples will be maintained in a similar manner.

TOXICITY CODE NO. <u>B2905-C1</u>	
MEDIUM ELUATE METHOD QCOP L305 Rev. _____	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Extraction Parameters Unit/Volume <input type="checkbox"/> _____ cm ² /mL <input type="checkbox"/> _____ gram/mL <input type="checkbox"/> Other _____ Actual Amount Used _____ Extraction Medium Log No. _____ Temperature/Time <input type="checkbox"/> 121°C/60 min <input type="checkbox"/> 70°C/24 hrs <input type="checkbox"/> 50°C/72hrs <input type="checkbox"/> 37°C/24 hrs <input type="checkbox"/> _____ Extraction Date/Time Started _____ Performed By _____ Completed _____ Performed By _____ Cell Line : HF _____ Passage No. _____ Incubation Date/Time Started _____ Performed By _____ Completed _____ Performed By _____	
CYTOTOXICITY SCORING	
Sample _____	<input type="checkbox"/> PASS <input type="checkbox"/> FAIL
Negative Control _____	Positive Control (Log No. _____)
Performed By / Date _____	
AGAR OVERLAY METHOD QCOP L303 Rev. (b)(4) <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
<input type="checkbox"/> SOLID <input checked="" type="checkbox"/> LIQUID <input type="checkbox"/> EXTRACT	
Extraction Parameters (for extract only) Unit/Volume <input type="checkbox"/> _____ cm ² /mL <input type="checkbox"/> _____ gram/mL <input type="checkbox"/> Other _____ Actual Amount Used _____ Extraction Medium/Lot No. <input type="checkbox"/> Normal Saline _____ <input type="checkbox"/> _____ Temperature/Time <input type="checkbox"/> 121°C/60 min <input type="checkbox"/> 70°C/24 hrs <input type="checkbox"/> 50°C/72hrs <input type="checkbox"/> 37°C/24 hrs <input type="checkbox"/> _____ Extraction Date/Time Started _____ Performed By _____ Completed _____ Performed By _____ Cell Line : HF <u>C8</u> Passage No. <u>17</u> <u>3x 1.5m² filter dishes were saturated with 10 drops of sample. Two dishes were applied once with agar overlay</u> Incubation Date/Time Started <u>11-26-02 / 1:30 pm</u> Performed By <u>[Signature]</u> Completed <u>11-27-02 / 2:00 pm</u> Performed By <u>[Signature]</u>	
CYTOTOXICITY SCORING	
Sample <u>1/0, 1/0, 1/0</u>	<input checked="" type="checkbox"/> PASS <input type="checkbox"/> FAIL
Negative Control (Log No. <u>B99-132</u>) <u>0/0, 0/0, 0/0</u>	Positive Control (Log No. <u>B98-C15</u>) <u>3/4, 3/4, 3/4</u>
Performed By / Date _____	
Approved By / Date _____	

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TOXICITY CODE NO. <u>B2905-02</u>	
MEDIUM ELUATE METHOD QCOP L305 Rev. _____	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Extraction Parameters Unit/Volume <input type="checkbox"/> _____ cm ² /mL <input type="checkbox"/> _____ gram/mL <input type="checkbox"/> Other _____ Actual Amount Used _____ Extraction Medium Log No. _____ Temperature/Time <input type="checkbox"/> 121°C/60 min <input type="checkbox"/> 70°C/24 hrs <input type="checkbox"/> 50°C/72hrs <input type="checkbox"/> 37°C/24 hrs <input type="checkbox"/> _____ Extraction Date/Time Started _____ Performed By _____ Completed _____ Performed By _____ Cell Line : <u>HF</u> Passage No. _____ Incubation Date/Time Started _____ Performed By _____ Completed _____ Performed By _____	
CYTOTOXICITY SCORING	
Sample _____	<input type="checkbox"/> PASS <input type="checkbox"/> FAIL
Negative Control _____	Positive Control (Log No. _____)
Performed By / Date _____	
AGAR OVERLAY METHOD QCOP L303 Rev. <u>(b)(4)</u> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
<input type="checkbox"/> SOLID <input checked="" type="checkbox"/> LIQUID <input type="checkbox"/> EXTRACT	
Extraction Parameters (for extract only) Unit/Volume <input type="checkbox"/> _____ cm ² /mL <input type="checkbox"/> _____ gram/mL <input type="checkbox"/> Other _____ Actual Amount Used _____ Extraction Medium/Lot No. <input type="checkbox"/> Normal Saline _____ <input type="checkbox"/> _____ Temperature/Time <input type="checkbox"/> 121°C/60 min <input type="checkbox"/> 70°C/24 hrs <input type="checkbox"/> 50°C/72hrs <input type="checkbox"/> 37°C/24 hrs <input type="checkbox"/> _____ Extraction Date/Time Started _____ Performed By _____ Completed _____ Performed By _____ Cell Line : <u>HF</u> <u>CS</u> Passage No. <u>17</u> <u>5x-10m² filter discs were saturated with 10 drops of sample. Swab discs were applied onto each agar plate.</u> Incubation Date/Time Started <u>11-26-02 / 1:30 PM</u> Performed By <u>Shirley</u> Completed <u>11-27-02 / 2:00 PM</u> Performed By <u>Shirley</u>	
CYTOTOXICITY SCORING	
Sample <u>1/6, 1/6, 1/6</u>	<input checked="" type="checkbox"/> PASS <input type="checkbox"/> FAIL
Negative Control (Log No. <u>B497-132</u>) <u>1/6, 1/6, 1/6</u>	Positive Control (Log No. <u>B98-015</u>) <u>2/4, 2/4, 2/4</u>
Performed By / Date _____	
Approved By / Date _____	

(b)(4) Confidential and Proprietary Information

TOXICITY CODE NO. B2905-03

MEDIUM ELUATE METHOD QCOP L305 Rev. _____ Yes No

Extraction Parameters
 Unit/Volume _____ cm²/mL _____ gram/mL Other _____
 Actual Amount Used _____

Extraction Medium Log No. _____

Temperature/Time 121°C/60 min 70°C/24 hrs 50°C/72hrs 37°C/24 hrs _____

Extraction Date/Time Started _____ Performed By _____
 Completed _____ Performed By _____

Cell Line : HF _____ Passage No. _____

Incubation Date/Time Started _____ Performed By _____
 Completed _____ Performed By _____

CYTOTOXICITY SCORING

Sample _____ PASS FAIL

Negative Control _____ Positive Control (Log No. _____)

Performed By / Date _____

AGAR OVERLAY METHOD QCOP L303 Rev. (b)(4) Yes No

SOLID LIQUID EXTRACT

Extraction Parameters (for extract only)
 Unit/Volume _____ cm²/mL _____ gram/mL Other _____
 Actual Amount Used _____

Extraction Medium/Lot No. Normal Saline _____ _____

Temperature/Time 121°C/60 min 70°C/24 hrs 50°C/72hrs 37°C/24 hrs _____

Extraction Date/Time Started _____ Performed By _____
 Completed _____ Performed By _____

Cell Line : HF CS Passage No. 17
5x5 cm² filter dishes were pre-washed with 10 drops of sample. Two dishes were applied into each agar plate.

Incubation Date/Time Started 11-26-02 / 1:30 PM Performed By [Signature]
 Completed 11-27-02 / 2:00 PM Performed By [Signature]

CYTOTOXICITY SCORING

Sample 1/0, 1/0, 1/0 PASS FAIL

Negative Control (Log No. B99-18A) 0/0, 0/0, 0/0 Positive Control (Log No. B99-015) 2/4, 2/4, 2/4

Performed By / Date _____

Approved By / Date _____



November 15, 2002

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RECEIVED
11-16-02

Please find enclosed three samples for GLP cytotoxicity testing. The samples are identified as follows:

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Each sample is to be tested by the Agar Overlay Method according to the (b)(4) approved protocol.

If you have any questions, please contact me by phone at 714-247-8320 or by email at james.cook@amo-inc.com.

Sincerely,

James Cook
Manager, Formulation Development
and Analytical Chemistry

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Formula # 3 (9464X)
Lot# 02RD24
11/15/2002
82905-01

Formula # 6 (9467)
Lot# 02RD27
11/15/2002
82905-02

Formula # 7 (9329)
Lot# 18833
11/15/2002
82905-03

CYTOTOXICITY TESTING

ADVANCED MEDICAL OPTICS EYE CARE SOLUTIONS

GLP PROTOCOL

EDWARDS QUALITY BIOLOGY LABORATORY STUDY NO. B2905
MBC SUBMISSION NO. 02-010

***ALL DATA RESULTING FROM THIS STUDY
IS CONSIDERED THE PROPRIETARY PROPERTY
OF
ADVANCED MEDICAL OPTICS
AND
MAY NOT BE SHARED OR DISTRIBUTED
WITHOUT THE WRITTEN AUTHORIZATION OF ADVANCED MEDICAL
OPTICS.***

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CYTOTOXICITY TESTING

ADVANCED MEDICAL OPTICS EYE CARE SOLUTIONS

PURPOSE

The purpose of this study is to evaluate the cytotoxicity of three eye care solutions.

All studies herein will be performed in compliance to the Good Laboratory Practice (GLP) guidelines (21 CFR Part 58).

CONTROL ARTICLES

The control articles will be as outlined in the individual procedures and any modifications thereof are described in the Experimental Design.

TEST ARTICLE DESCRIPTION & EXPERIMENTAL DESIGN: B2905

Description:

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Manufacturing Process: All samples will be prepared in accordance with Advanced Medical Optics' internal procedures with traceability to the manufacturing and sterilization processes. Maintaining and archiving the original data is the responsibility of Advanced Medical Optics.

Sterilization Process: All test article samples will be sterilized according to documented procedures of Advanced Medical Optics.

Experimental Design:

Test articles B2905-01, B2905-02 and B2905-3 will be individually evaluated by the Agar Overlay Method (b)(4) with the following modification:

The surface area of the filter disc saturated with the test solution and the surface area of the negative control material to be tested will each be approximately 10% of the surface of the test plate.

PREPARATION OF TEST ARTICLES

Test article preparation for the Agar Overlay procedure (QCOP L303) will be as follows:

The test articles, B2905-01, B2905-02, and B2905-03 will be saturated on filter discs immediately before applying on top of an agar layer covering a confluent monolayer of human fibroblast cells. The samples will be evaluated as described in the test procedure.

TEST ARTICLE CHARACTERIZATION

Verification of the identity of the test articles B2905-01, B2905-02, and B2905-03 will be the responsibility of Advanced Medical Optics.

CONTROL ARTICLE CHARACTERIZATION

The control articles used in the test methods designated herein will be characterized and recorded in Biology Logbook 119A. All of the control articles employed for these procedures is considered to be stable at the time of usage.

CONTROL OF TEST SYSTEMS

The cell line to be used for the Agar Overlay procedure is a human fibroblast derived from infant foreskin tissue. These cells were obtained from American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852-1776, under ATCC No. CRL1634. This cell line is nourished with Complete Minimum Essential Medium (Eagles) containing Calf Serum with Iron as specified in QCOP L500.

STATISTICAL METHODS

No statistical methodology will be employed for this study.

JUSTIFICATION

Parameters Justification

The use of these test parameters and test systems are justified based upon the stability of the materials, their general use, and the overall acceptance in the field of materials toxicology. The test methodology and test systems are recommended by United States Pharmacopeia, American Society for Testing and Materials, and

4 of 5

ADVANCED MEDICAL OPTICS CONFIDENTIAL DATA

(Not to be shared or distributed without the written authorization of Advanced Medical Optics)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

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International Standards Organization (ISO), or are generally accepted as preferred by leaders in this field.

Experimental Design Justification

The experimental design for test articles B2905-01, B2905-02, and B2905-03 has generally been accepted as useful in cytotoxicity testing of contact lens materials and solutions.

RECORDS TO BE MAINTAINED

The protocol, final report, OAI statement, and raw data will be stored in the (b)(4) Confidential and Proprietary Information Archives. Test article samples will be maintained in a similar manner.

Acute Ocular Toxicity

(b)(4) Confidential and Proprietary Information



December 20, 2002

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(b)(4) Confidential and Proprietary Information

SAFETY EVALUATION DEPARTMENT

FINAL REPORT

**CONTACT LENS REWETTER: 1-DAY OCULAR TOXICITY
STUDY WITH A 3-DAY RECOVERY PERIOD IN RABBITS**

Testing Facility:

(b)(4) Confidential and Proprietary
Information

Study Identification Number:

TX02106

Project Name:

AMO Transitional Service
Support

Sponsor:

Advanced Medical Optics
1700 St. Andrews Place
Santa Ana, CA 92799

Study Initiation Date:

11/14/2002

Treatment Date:

11/19/2002

Observation Period Dates:

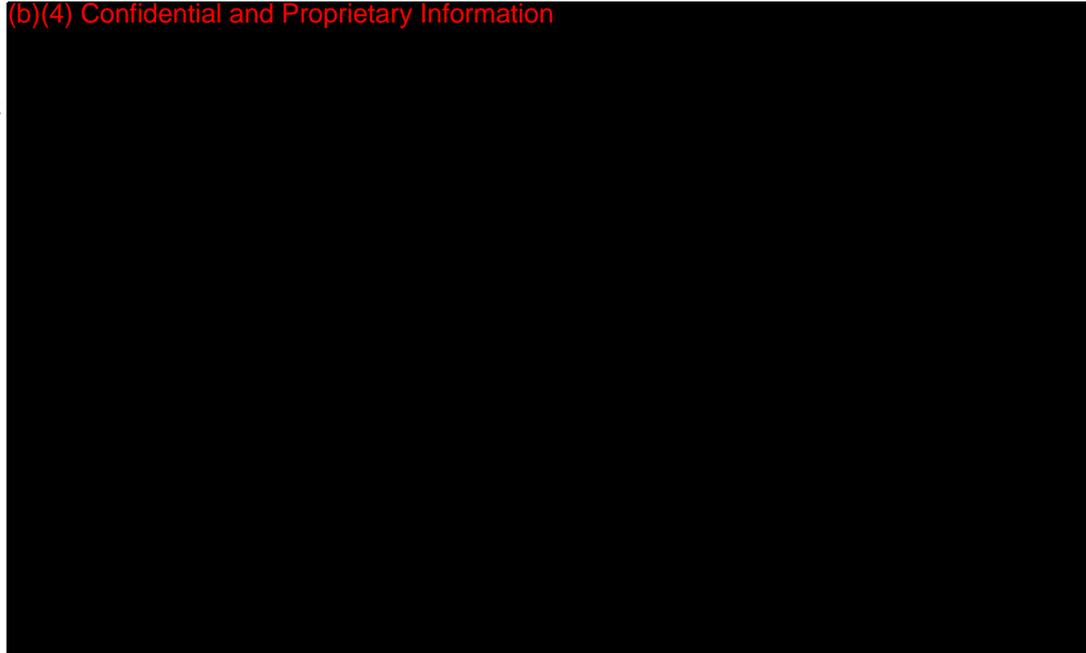
11/20/2002 – 11/22/2002

SIGNATURE PAGE

Toxicology Study No. TX02106 Final Report

Study Director:

Management:



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KEY PERSONNEL

Project Representative (b)(4) Confidential and Proprietary Information
Senior Scientist
Safety Evaluation – Toxicology

In Vivo Toxicology: (b)(4) Confidential and Proprietary Information
Director of In Vivo Toxicology
Safety Evaluation – Toxicology

Laboratory Animal (b)(4) Confidential and Proprietary Information
Science: Director of Lab Animal Science
Safety Evaluation - Laboratory Animal Science

STATEMENT OF COMPLIANCE

Toxicology Study No. TX02106 Final Report

This study was conducted in compliance with the Good Laboratory Practices as described in the Food and Drug Administration (FDA) Regulations Part 58 of Title 21 CFR, with the exception that test article analyses were characterized using a Good Manufacturing Practices compliant method. This final report accurately reflects all raw data obtained during the study. There were no significant deviations from Good Laboratory Practice Regulations, protocol or departmental standard operating procedures that could have affected the quality or integrity of the study.

(b)(4) Confidential and Proprietary Information

Study Director:



(b)(4) Confidential and Proprietary

Research Compliance Department
INSPECTION STATEMENT

Final Report

Study Number: TX02106

Study Title: Contact Lens Rewetter: 1-Day Ocular Toxicity Study With a 3-Day Recovery Period in Rabbits

<u>Phase Inspected</u>	<u>Date Inspected</u>	<u>Reported to Management and Study Director</u>	<u>Inspector</u>
Protocol Review	11/5/2002	11/6/2002	P. Van Schaack / D. Wadkins
Protocol Review - Follow-Up	11/14/2002	11/14/2002	P. Van Schaack / D. Wadkins
Dose Administration	11/19/2002	11/20/2002	P. Van Schaack / G. Barajas
Report Review	12/18/2002	12/19/2002	P. Van Schaack / G. Barajas

The above has been inspected in accordance with the applicable Standard Operating Procedures of Allergan's Research Compliance department, the Good Laboratory Practices Quality Assurance Requirements (21 Code of Federal Regulations, Part 58.35) and 21 CFR Part 11, Electronic Records; Electronic Signatures; Final Rule.

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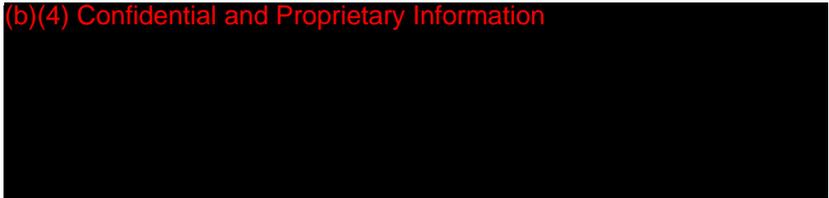


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Final Report

SUMMARY

The purpose of this study was to determine the ocular effects of topical instillation of two contact lens rewetter formulations (8 drops/day) for one day followed by a 3-day recovery period in New Zealand White (NZW) rabbits.

Two groups of female NZW rabbits (4/group) received 8 topical instillations (~70 μ L/drop/hour) into the left eye of rewetter formulation no. 3 (9464X) or no. 6 (9467X) for 1 day. The right eye was untreated and served as a control. Rabbits were observed for signs of ocular irritation during a 3-day recovery period.

The following parameters were evaluated: viability, clinical observations, gross ocular observations, and slit lamp biomicroscopy.

No mortality or treatment-related effects were observed on clinical observations, gross ocular observations, or slit lamp biomicroscopy.

In conclusion, contact lens rewetter formulation no. 3 (9464X) or no. 6 (9467X) was administered into the left eyes of New Zealand White rabbits 8 times for 1 day. Both formulations were well tolerated.

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(b)(4) Confidential and Proprietary Information

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1. INTRODUCTION

1.1 Background

Contact lens rewetter products are used during contact lens wear to provide ocular lubrication. Two new multi-dose contact lens rewetter formulations, containing Purite™ as a preservative, are being developed. Contact lens care products are classified as medical devices in the Premarket Notification (510(k)) Guidance Document. These formulations were tested for potential ocular irritation according to the ISO 10993-10 guideline. The sponsor of this study was Advanced Medical Optics, Inc. (AMO).

1.2 Objective

The purpose of this study was to determine the ocular effects of topical instillation of two contact lens rewetter formulations (8 drops/day) for one day followed by a 3-day recovery period in New Zealand White (NZW) rabbits.

1.3 Rationale for Species Selection and Route of Administration

The NZW rabbit was selected on the basis of accumulated historical data and experience at (b)(4) Confidential in ocular contact lens toxicity studies with this species. The selected route of administration was topical ocular instillation as this is the intended route of human administration.

1.4 Rationale for Dose Selection

Contact lens rewetters are labeled “instill 1 or 2 drops in the affected eye(s) as needed.” In the present study, one drop of the test article was instilled 8 times in a one-day period to evaluate an “as needed” dose regimen.

2. TEST ARTICLES

2.1 Contact Lens Rewetters

- Rewetter Formulation No. 3 (9464X), Lot No. 02RD24
- Rewetter Formulation No. 6 (9467X), Lot No. 02RD27

2.2 Source

Test articles were provided by the sponsor, AMO.

2.3 Storage Conditions

The test articles were stored in the Safety Evaluation Department between 15°C and 30°C (room temperature).

2.4 Receipt and Distribution Documentation

The source, receipt, distribution, storage, and disposition of the test articles were documented in the raw data. Numbers of containers used in the study were recorded.

2.5 Test Article Analysis

Test articles were analyzed by the sponsor prior to the start of the study. Documentation of test article identity, strength, purity, composition, and stability is included in the final report.

2.6 Retention Samples

Test article samples were not retained as the study duration was shorter than one month.

2.7 Handling Precautions

Protective garments were worn at all times when handling the test articles. Additionally, all laboratory personnel were required to comply with Allergan safety procedures outlined in the

(b) (4) Research & Development Performance Based Exposure Control Guidelines.

3. ANIMALS AND ANIMAL CARE

3.1 Test System Description

Eight female Specific Pathogen-Free New Zealand White [Hra: (NZW) SPF] rabbits (Charles River Laboratories, Canada), approximately 3 months old, and weighing 2.2 to 2.8 kg at study start were used for the study.

3.2 Quarantine Period

Upon arrival, rabbits were quarantined for a minimum of 7 days, and evaluated for general health by the Laboratory Animal Science (LAS) staff prior to their release.

3.3 Animal Husbandry

3.3.1 Housing, Diet, and Drinking Water

Rabbits were individually housed in stainless steel cages and were fed approximately 145g daily of Purina certified high fiber rabbit chow (Product code 5325). Drinking water purified by reverse osmosis and provided by an automatic watering system was offered *ad libitum*. Results of dietary analyses (provided by the manufacturer) and water analysis results are maintained by the (b) (4) Safety Evaluation Department.

3.3.2 Environmental Conditions

Rabbits were housed in environmentally-controlled rooms with time-controlled fluorescent lighting systems providing daily 12-hour light (0600 to 1800) and dark cycles (1800 to

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Proprietary Information**

Final Report

0600), except as required for study procedures (ophthalmic examinations). Room temperature was maintained between 62°F and 70°F, relative humidity was maintained between 42-76%, and airflow was maintained at 22 air changes per hour. Relative humidity was out of range on study days 1 and 4 (11/19 and 11/22) due to outside weather conditions. The high humidity was documented by LAS and maintenance was notified. Humidity returned to normal ranges within 2 hours. In the opinion of the Study Director, this protocol deviation had no impact on the study. These parameters were monitored by the Edstrom Watchdog[®] environmental monitoring system (v.40) and documented.

3.4 Animal Identification

Upon receipt, all rabbits were assigned a *permanent animal number*. Rabbits selected for the study were assigned *study animal numbers*. A metal ear tag and corresponding cage card individually identified rabbits.

4. EXPERIMENTAL DESIGN

4.1 Animal Selection, Exclusion, And Replacement

Rabbits selected for the study were in good health (no apparent evidence of morbidity) and had normal findings in screening ophthalmic examinations. Replacements were not allowed after the first instillation (day 1). No rabbits were replaced or excluded.

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Final Report

4.2 Study Animal Distribution

Table 4.2-1 Study Group Arrangement

Group	No. Animals & Sex	Study Animal Numbers	1 drop each hour for 8 hours (\pm 12 min.)	
			OS	OD
1	4F	150-153	Rewetter Formulation No. 3 (9464X)	untreated
2	4F	250-253	Rewetter Formulation No. 6 (9467X)	untreated

OS – Left eye, OD – Right eye

4.3 Ocular Instillation

One drop of test article was instilled 8 times per day at 1 hour (\pm 12 minutes) intervals into the left eye (OS). The right eye was not treated and served a control.

5. STUDY PROCEDURES

5.1 Viability Check

Rabbits were observed twice daily for mortality, moribundity, and general appearance. The clinical observation served as the AM viability observation.

5.2 Clinical Observations

Once pretest, and daily throughout the study, each rabbit was observed at cage side for treatment-related findings. All clinical findings were manually recorded.

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a.hhs.gov or call 301-796-8118.

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5.3 Body Weight

Individual body weights were obtained prior to initiation of dosing to record body weight range of rabbits.

5.4 Ocular Observations

5.4.1 Gross Ocular Observations

Both eyes of each rabbit were grossly examined for evidence of ocular irritation immediately before and after each topical instillation (day 1) and once daily during the recovery period (days 2-4). All findings were manually recorded onto raw data sheets. Numerical scores were recorded to reflect obvious ocular changes including conjunctival hyperemia, discharge, and swelling. Absence of abnormalities or inflammation was considered normal and recorded as "0".

5.4.2 Slit Lamp Biomicroscopy

Both eyes of each rabbit were examined with a slit lamp biomicroscope prior to initiation of treatment (screening examination - not more than 24 hours prior to initiation of treatment) and approximately 1 hour after the last instillation on day 1. All findings were manually recorded onto raw data sheets. The slit lamp evaluation included the examination of conjunctiva, iris (including pupillary reflex), and cornea (including fluorescein staining).

5.5 Animal Disposition

Rabbits were returned to the LAS rabbit colony at the end of the study period.

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6. ANALYSIS

6.1 Statistics

Descriptive statistics were not performed as there were no ocular findings.

6.2 Computer Software

6.2.1 Microsoft Excel

Microsoft Excel[®] (version 97 SR-2) was not used for data tabulation as there were no ocular findings.

7. RECORDS AND STORAGE

Upon conclusion of the study, all raw data, the original protocol, and the final study report were stored and maintained by (b) (4) Records Management Department. Facility records are retained in the (b) (4) Evaluation Department. A copy of the final study report was sent to the study sponsor and a copy is stored in the Safety Evaluation Department archives.

8. RESULTS

8.1 Viability

No mortality occurred in either group during the course of the study.

8.2 Clinical Observations

Individual clinical observation data are presented in Appendix III.

No treatment-related effects on clinical observations were noted during the course of the study.

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Final Report

8.3 Ocular Observations

8.3.1 Gross Ocular Observations

Individual gross ocular observation data is presented in Appendix IV.

No gross ocular irritation was noted in any rabbit during the course of the study.

8.3.2 Slit Lamp Biomicroscopy

Individual slit lamp data is presented in Appendix V.

Slit lamp examinations at the end of treatment revealed no abnormal findings.

9. CONCLUSION

In conclusion, contact lens rewetter formulation no. 3 (9464X) or no. 6 (9467X) was administered into the left eyes of New Zealand White rabbits 8 times for 1 day. Both formulations were well tolerated.

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APPENDIX I: STUDY PROTOCOL

(b)(4) Confidential and Proprietary Information

**SAFETY EVALUATION / TOXICOLOGY
GLP STUDY PROTOCOL**

**CONTACT LENS REWETTER: 1-DAY OCULAR TOXICITY
STUDY WITH A 3-DAY RECOVERY PERIOD IN RABBITS**

Study Identification Number:

TX02106

Project Name and Number:

**AMO Transitional
Service Support**

Testing Facility:

(b)(4) Confidential and Proprietary Information

Study Director:

Management:

**Sponsor's
Representative:**

Key Personnel:

Estimated Start Date:

Nov. 19, 2002

(b)(4) Confidential and Proprietary Information

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1 STUDY RATIONALE

1.1 Background

Contact lens rewetter products are used during contact lens wear to provide ocular lubrication. Two new multi-dose contact lens rewetter formulations, containing Purite™ as a preservative, are being developed. Contact lens care products are classified as medical devices in the Premarket Notification (510(k)) Guidance Document. These formulations will be tested for potential ocular irritation according to the ISO 10993-10 guideline. The sponsor of this study is Advanced Medical Optics, Inc. (AMO).

1.2 Objective

The purpose of this study is to determine the ocular effects of topical instillation of two contact lens rewetter formulations (8 drops/day) for one day followed by a 3-day recovery period in New Zealand White (NZW) rabbits.

1.3 Rationale for Species Selection and Route of Administration

The NZW rabbit is selected on the basis of accumulated historical data and experience at (b)(4) Confidential in ocular contact lens toxicity studies with this species. The selected route of administration is topical ocular instillation as this is the intended route of human administration.

1.4 Rationale for Dose Selection

Contact lens rewetters are labeled “instill 1 or 2 drops in the affected eye(s) as needed.” In the present study, one drop of the test article will be instilled 8 times in a one-day period to evaluate an “as needed” dose regimen.

2 TEST ARTICLES

2.1 Contact Lens Rewetters

- Rewetter Formulation No. 3, 9464X, Lot No. 02RD24
- Rewetter Formulation No. 6, 9467X, Lot No. 02RD27

2.2 Source

Test articles will be provided by the sponsor, AMO.

2.3 Storage Conditions

The test articles will be stored in the Safety Evaluation Department between 15°C and 30°C (room temperature).

2.4 Receipt and Distribution Documentation

The source, receipt, distribution, storage, and disposition of the test articles will be documented in the raw data. Numbers of containers used in the study will be recorded.

2.5 Test Article Analyses

Test articles will be analyzed by the sponsor prior to the start of the study. Documentation of test article identity, strength, purity, composition and stability will be included in the final report.

2.6 Retention Samples

Test article samples will not be retained as the study duration is shorter than one month.

2.7 Handling Precautions

Protective garments will be worn at all times when handling the test articles. Additionally, all laboratory personnel are required to comply with (b) (4) procedures outlined in

the (b)(4) Research & Development Performance Based Exposure Control Guidelines, the latest version of which is available on the AllerWeb

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3 ANIMALS AND ANIMAL CARE

3.1 Test System Description

Eight female Specific Pathogen-Free New Zealand White [Hra: (NZW) SPF] rabbits (Charles River Laboratories), approximately 3 months old, and weighing approximately 2.0 to 3.5 kg at study start will be used for the study.

3.2 Quarantine Period

Upon arrival, rabbits will be quarantined for a minimum of 7 days, and evaluated for general health by the Laboratory Animal Science (LAS) staff prior to their release.

3.3 Animal Husbandry

3.3.1 Housing, Diet, and Drinking Water

Rabbits will be individually housed in stainless steel cages and will be fed approximately 145 grams daily of Purina certified high fiber rabbit chow (Product code 5325). Drinking water purified by reverse osmosis and provided by an automatic watering system will be offered *ad libitum*. Results of dietary analyses (provided by the manufacturer) and water analysis results will be maintained by the Allergan Safety Evaluation Department.

3.3.2 Environmental Conditions

Rabbits will be housed in environmentally-controlled rooms with time-controlled fluorescent lighting systems providing daily 12-hour light (0600 to 1800) and dark cycles (1800 to 0600), except as required for study procedures (ophthalmic examinations). Room temperature will be maintained between 61°F and 72°F, relative humidity will be maintained between 30-70%, and airflow will be maintained between 10 and 35 air changes per hour.

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These parameters will be monitored by the Edstrom Watchdog® environmental monitoring system (v.40) and documented .

3.4 Animal Identification

Upon receipt, all rabbits will be assigned a *permanent animal number*. Rabbits selected for the study will be assigned *study animal numbers*. A metal ear tag and corresponding cage card will individually identify rabbits.

4 EXPERIMENTAL DESIGN

4.1 Animal Selection, Exclusion, And Replacement

Rabbits selected for the study will be in good health (no apparent evidence of morbidity) and will have normal findings in screening ophthalmic examinations. Replacements will not be allowed after the first day of treatment (day 1). All data from any rabbits replaced prior to day 1 will be maintained in the raw data, and will include all reasons for replacement. Data from rabbits excluded during the course of the study (due to mortality or morbidity) will be maintained in the raw data.

4.2 Study Animal Distribution

Table 4.2-1 Study Group Arrangement

Group	No. Animals & Sex	1 drop each hour for 8 hours (\pm 12 min.)	
		OS	OD
1	4F	Rewetter Formulation No. 3 (9464X)	untreated
2	4F	Rewetter Formulation No. 6 (9467X)	untreated

OS – Left eye, OD – Right eye

4.3 Ocular Instillation

One drop of test article will be instilled 8 times per day at 1 hour (± 12 minutes) intervals into the left eyes (OS). Right eyes will not be treated and will serve as controls.

5 STUDY PROCEDURES

5.1 Viability Check

Rabbits will be observed twice daily for mortality, moribundity, and general appearance. The clinical observation will serve as the AM viability observation.

5.2 Clinical Observations

Once pretest, and daily throughout the study, each rabbit will be observed at cage side for treatment-related findings. Rabbits that become ill may be treated, isolated, or euthanized at the discretion of the facility veterinarian and Study Director. All clinical findings will be manually recorded.

5.3 Body Weight

Individual body weights will be obtained prior to initiation of dosing to record body weight range of the rabbits.

5.4 Ocular Observations

5.4.1 Gross Ocular Observations

Both eyes of each rabbit will be grossly examined for evidence of ocular irritation immediately before and after each topical instillation (day 1) and once daily during the recovery period (days 2-4). All findings will be manually recorded onto raw data sheets. Numerical scores will be recorded to reflect obvious ocular changes including conjunctival hyperemia, discharge, and swelling. Absence of abnormalities or inflammation will be considered normal and recorded as "0". Any ocular abnormalities of the cornea, iris, or anterior chamber other than scored observations of inflammation will be confirmed and

defined by slit lamp biomicroscopy. Additional gross ocular examinations may be performed to evaluate any abnormal findings.

5.4.2 Slit Lamp Biomicroscopy

Both eyes of each rabbit will be examined with a slit lamp biomicroscope prior to initiation of treatment (screening examination - not more than 24 hours prior to initiation of treatment) and approximately 1 hour after the last instillation on day 1. Additional examinations may be performed to further evaluate any findings. All findings will be manually recorded onto raw data sheets. The slit lamp evaluation includes, but may not be limited to the examination of conjunctiva, iris (including pupillary reflex) and cornea (including fluorescein staining). Slit lamp examination may also be performed during the recovery period to characterize any abnormal findings.

5.5 Pathology

Any rabbit that dies during the study will undergo a necropsy to identify any pathological changes. Eyes and any gross lesions will be collected for possible future evaluations. All other tissues will be discarded. Histopathological evaluation may be performed at the discretion of the Study Director and Study Pathologist.

5.6 Animal Disposition

Rabbits surviving to the end of the study period will be returned to the LAS rabbit colony.

6 ANALYSIS

6.1 Statistics

Descriptive statistics may be performed on ocular findings. Evaluations may include means, standard deviations, sample sizes and percent changes.

6.2 Computer Software

6.2.1 Microsoft Excel

Microsoft Excel® (version 97 SR-2) may be used for data tabulation of ocular findings.

7 RECORDS AND STORAGE

Upon conclusion of the study, all raw data, the original protocol, and the final study report will be stored and maintained by (b) (4) R&D Records Management Department. Facility records will be retained in the (b) (4) Evaluation Department. A copy of the final study report will be stored in the Safety Evaluation Department archives.

8 REPORT

After completion of the study, a comprehensive report containing the results of all parameters investigated and an interpretive summary of the study results will be provided to the sponsor, AMO.

9 AMENDMENTS

Alterations, additions, or modifications of this protocol may be made as the study progresses. The changes to the protocol will be documented and justified in protocol amendments, and approved by the Sponsor, Study Director and toxicology management.

10 REGULATORY REFERENCES AND ACCREDITATION

10.1 Good Laboratory Practices

This study will be conducted in compliance with policies and procedures set forth in the Good Laboratory Practice (GLP) regulations (21 CFR Part 58).

10.2 Regulatory Guidance

This study will be conducted in compliance with policies and procedures set forth in the ISO 10993-10:1995 (E) standard for biological evaluation of medical devices.

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TX02106 Study Protocol

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10.3 Animal Welfare Act Compliance

This study will comply with all requirements of the United States Department of Agriculture (USDA) and all regulations issued by the USDA implementing the Animal Welfare Act, 9 CFR, Parts 1, 2 and 3. The animal procedures that will be used have been approved by the (b) (4) Animal Care and Use Committee (AACUC) and are described in approved AACUC protocols (AACUC Protocol Number 370) located in the Allergan Laboratory Animal Sciences (LAS) Department.

10.4 Animal Facility Accreditation

(b) (4) is fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

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(b) (4) Study Number TX02106

PROTOCOL AMENDMENT NUMBER 1

Study Title:

CONTACT LENS REWETTER: 1-DAY OCULAR TOXICITY STUDY WITH A 3-DAY RECOVERY PERIOD IN RABBITS

Change From:

4.2 STUDY ANIMAL DISTRIBUTION

Table 4.2-1 Study Group Arrangement

Group	No. Animals & Sex	1 drop each hour for 8 hours (± 12 min.)	
		OS	OD
1	4F	Rewetter Formulation No. 3 (9464X)	untreated
2	4F	Rewetter Formulation No. 6 (9467X)	untreated

OS – Left eye, OD – Right eye

Change To:

4.2 STUDY ANIMAL DISTRIBUTION

Table 4.2-1 Study Group Arrangement

Group	No. Animals & Sex	Study Animal Numbers	1 drop each hour for 8 hours (± 12 min.)	
			OS	OD
1	4F	150-153	Rewetter Formulation No. 3 (9464X)	untreated
2	4F	250-253	Rewetter Formulation No. 6 (9467X)	untreated

OS – Left eye, OD – Right eye

Reason for Change:

Addition of study animal number information.

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Approved By:
Study Director:

Management:

APPENDIX II: TEST ARTICLE INFORMATION



Contact Lens Care Product, Research & Development
 1700 E. St. Andrew Place, Santa Ana, CA 92705
 Phone: 714/247-8200 Fax: 714/247-8673

Certificate of Analysis

Sample Description: Purite/HA Rewetter (9467X), 12 mL fill in 15 mL Bottle
 Contract Manufacturer Name: (b) (4)
 Contract Manufacturer Lot #: 02RD27

AMO sample #: 02-009

Test	Specifications	Result	Reference
Physical Appearance	(b)(4) Confidential and Proprietary Information	Clear, Colorless (n=3)	659/57-58
pH	(b)(4) Confidential and Proprietary Information	7.2, 7.2, 7.2 Mean = 7.2	670/23-24
Potential Chlorine Dioxide (PPM)	(b)(4) Confidential and Proprietary Information	48, 48, 48 Mean = 48	670/22-23
Sodium Hyaluronate Concentration (%w/v)	(b)(4) Confidential and Proprietary Information	0.075, 0.074, 0.075 Mean = 0.074	659/52-55
Osmolality (mOsm/kg)	(b)(4) Confidential and Proprietary Information	278, 278, 277 Mean = 278	670/24-25
Viscosity (cps)	(b)(4) Confidential and Proprietary Information	4.7, 4.7, 4.7 Mean = 4.7	652/18
Visible Light Absorbance (au)	(b)(4) Confidential and Proprietary Information	0.00, 0.00, 0.00 Mean = 0.00	659/56

Meets Specifications Does Not Meet Specifications

Approved by:

(b)(4) Confidential and Proprietary Information

Date

Title: Sterility Testing by Membrane Filtration

SOP QA-26 Rev # 5

(Attachment I)
STERILITY TEST REPORT

Testing Follows USP Methods When Applicable

TEST ARTICLE SUBMITTED: 0.075% Sodium Hyaluronate 0.075%HPMC (12g) Formula 6

Lot No: 02RD27

TEST START DATE: 10/24/02

TEST TERMINATION DATE: 11/7/02

PROC/TEST METHOD USED
Membrane Filtration

STERILITY TEST RESULTS

<u>NO. ARTICLES TESTED</u>	<u>ARTICLES TESTED</u>	<u>MEDIA VOLUME(ml)</u>	
		<u>SCDB</u>	<u>FT</u>
<u>1</u>	<u>½ F</u>	<u>100</u>	
<u>1</u>	<u>½ F</u>		<u>100</u>
<u>NA</u>	<u>½ F Neg Control</u>	<u>100</u>	
<u>NA</u>	<u>½ F Neg Control</u>		<u>100</u>

TESTED ARTICLE AS SUBMITTED FOUND TO BE: Sterile

SCDB Media Lot: 02-1016-02

FTM Media Lot: 02-1016-01

Fluid D Lot: 02-0913-01

Open Control no growth

SCDB= Soybean Casein Digest Broth

FT= Fluid Thioglycollate

(b)(4) Confidential and Proprietary Information

Microbiologist: _____

Approved: _____

COMMENTS: Raw data in Sterility Test Log Book No. 2 QC-40 pages 90-97.

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Contact Lens Care Product, Research & Development
 1700 E. St. Andrew Place, Santa Ana, CA 92705
 Phone: 714/247-8200 Fax: 714/247-8673

Certificate of Analysis

Sample Description: Purite/HA Rewetter (9464X), 12 mL fill in 15 mL Bottle
 Contract Manufacturer Name: (b) (4)
 Contract Manufacturer Lot #: 02RD24

AMO sample #: 02-004

Test	Specifications	Result	Reference
Physical Appearance	(b)(4) Confidential and Proprietary Information	Clear, Colorless (n=3)	659/57-58
pH	(b)(4) Confidential and Proprietary Information	7.2, 7.2, 7.2 Mean = 7.2	670/20-21
Potential Chlorine Dioxide (PPM)	(b)(4) Confidential and Proprietary Information	49, 49, 50 Mean = 49	670/19-25
Sodium Hyaluronate Concentration (%w/v)	(b)(4) Confidential and Proprietary Information	0.146, 0.150, 0.151 Mean = 0.149	659/42-44
Osmolality (mOsm/kg)	(b)(4) Confidential and Proprietary Information	288, 276, 288 Mean = 284	670/20-21, 25
Viscosity (cps)	(b)(4) Confidential and Proprietary Information	6.6, 6.6, 6.6 Mean = 6.6	652/18
Visible Light Absorbance (au)	(b)(4) Confidential and Proprietary Information	0.00, 0.00, 0.00 Mean = 0.00	659/45

Meets Specifications Does Not Meet Specifications

Approved by

(b)(4) Confidential and Proprietary Information

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Title: Sterility Testing by Membrane Filtration

SOP QA-26 Rev # 5

(Attachment I)

STERILITY TEST REPORT

Testing Follows USP Methods When Applicable

TEST ARTICLE SUBMITTED: 0.15% Sodium Hyaluronate Formula 3 (12g)

Lot No: 02RD24

TEST START DATE: 10/24/02

TEST TERMINATION DATE: 11/7/02

PROC/TEST METHOD USED: Membrane Filtration

STERILITY TEST RESULTS

NO. ARTICLES TESTED	ARTICLES TESTED	MEDIA VOLUME(ml)	
		SCDB	FT
1	1/2 F	100	
1	1/2 F		100
NA	1/2 F Neg Control	100	
NA	1/2 F Neg Control		100

TESTED ARTICLE AS SUBMITTED FOUND TO BE: Sterile

SCDB Media Lot: 02-1016-02

FTM Media Lot: 02-1016-01

Fluid D Lot: 02-0913-01

Open Control: no growth

SCDB= Soybean Casein Digest Broth

FT= Fluid Thioglycollate

Microbiologist: (b)(4) Confidential and Proprietary Information
Approved: (b)(4) Confidential and Proprietary Information

COMMENTS: Raw data in Sterility Test Log Book No. 2 QC-40 pages 90-97.

ADVANCED MEDICAL OPTICS

**RESEARCH AND DEVELOPMENT
ANALYTICAL CHEMISTRY**

TECHNICAL REPORT

TR No.: 2211

**ONE-MONTH STABILITY DATA ON REWETTER FORMULATIONS
9464X AND 9467X**

ISSUED: DATE OF LAST SIGNATURE

Author:

Reviewed by

Approved by

(b)(4) Confidential and Proprietary Information



(b)(4) Confidential and Proprietary Information

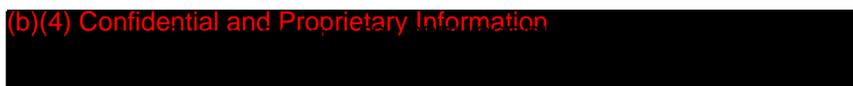


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4.0	CONCLUSIONS	4
5.0	REFERENCES	4

1.0 INTRODUCTION

This document reports the results of storage stability testing on two contact lens rewetter formulations, formulation no. 3 (9464X) and formulation no. 6 (9467X), following one-month storage at controlled room temperature. The testing was conducted to verify the stability of study samples provided to (b) (4) Evaluation Department for a 1-day Ocular Toxicity Test (study no. TX02106).

2.0 METHOD

Samples of formulation no. 3 (9464X, lot # 02RD24) and formulation no. 6 (9467X, lot # 02RD27) contained in 15-mL teal LDPE bottles were tested following storage for one month at controlled room temperature. All chemistry parameters conducted for release were repeated at this 1-month interval. The test methods used for each parameter are referenced in Tables 1 and 2.

3.0 RESULTS

The results from the study are listed in Tables 1 and 2. The release (0-time) data are included for comparison.

Table 1. 1-Month Stability Results for Contact Lens Rewetter Formula No. 3 (9464X)

Test Parameter	Specification (b)(4) Confidential and Proprietary Information	Results		Test Method
		0-Time	1-month	
Physical Appearance	(b)(4) Confidential and Proprietary Information	Clear, Colorless (n=3)	Clear, Colorless (n=3)	AC-S-002A
pH	(b)(4) Confidential and Proprietary Information	7.2, 7.2, 7.2 Mean = 7.2	7.1, 7.2, 7.2 Mean = 7.2	USP
Potential Chlorine Dioxide (PPM)	(b)(4) Confidential and Proprietary Information	49, 49, 50 Mean = 49	49, 48, 49 Mean = 49	AC-S-006A
Sodium Hyaluronate Concentration (%w/v)	(b)(4) Confidential and Proprietary Information	0.15, 0.15, 0.15 Mean = 0.15	0.16, 0.15, 0.15 Mean = 0.15	AC-S-007A
Osmolality (mOsm/kg)	(b)(4) Confidential and Proprietary Information	288, 276, 288 Mean = 284	283, 284, 284 Mean = 284	USP
Viscosity (cps)	(b)(4) Confidential and Proprietary Information	6.6, 6.6, 6.6 Mean = 6.6	6.5 Pool of 2 bottles	AC-S-003A
Visible Light Absorbance (au)	(b)(4) Confidential and Proprietary Information	0.00, 0.00, 0.00 Mean = 0.00	0.00, 0.00, 0.00 Mean = 0.00	AC-S-005A

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Table 2. 1-Month Stability Results for Contact Lens Rewetter Formula No. 6 (9467X)

Test Parameter	Specification	Results		Test Method
		0-Time	1-month	
Physical Appearance	(b)(4) Confidential and Proprietary Information	Clear, Colorless (n=3)	Clear, Colorless (n=3)	AC-S-002A
pH		7.2, 7.2, 7.2 Mean = 7.2	7.2, 7.1, 7.2 Mean = 7.2	USP
Potential Chlorine Dioxide (PPM)		48, 48, 48 Mean = 48	48, 48, 48 Mean = 48	AC-S-006A
Sodium Hyaluronate Concentration (%w/v)		0.075, 0.074, 0.075 Mean = 0.075	0.070, 0.072, 0.073 Mean = 0.072	AC-S-007A
Osmolality (mOsm/kg)		278, 278, 277 Mean = 284	282, 279, 280 Mean = 280	USP
Viscosity (cps)		4.7, 4.7, 4.7 Mean = 4.7	4.6 (pool of 2 bottles)	AC-S-003A
Visible Light Absorbance (au)		0.00, 0.00, 0.00 Mean = 0.00	0.00, 0.00, 0.00 Mean = 0.00	AC-S-005A

4.0 CONCLUSIONS

The 1-month stability results from both formulation no. 3 (9464X) and formulation no. 6 (9467X) showed no significant difference from 0-time in any of the parameters tested. The results establish formulation no. 3 (9464X) and formulation no. 6 (9467X) to be stable for at least 1 month (30 days) when stored at controlled room temperature. The results verify that test samples of these formulations provided to (b)(4) Evaluation Department for a 1-day Ocular Toxicity Test (study no. TX02106) were stable throughout the duration of the study.

5.0 REFERENCES

1. AMO Notebook No. 659, pgs. 76-78
2. AMO Notebook No. 652, pg. 24
3. AMO Notebook No. 670, pgs. 40-42
4. GLP Study Protocol, Study Identification Number: TX02106 "Contact Lens Rewetter: 1-Day Ocular Toxicity Study with a 3-Day Recovery Period in Rabbits"

APPENDIX III: CLINICAL OBSERVATIONS

(b)(4) Confidential and Proprietary Information

Safety Evaluation – Toxicology
Study No.: TX02106

Appendix III: Clinical Observations

Clinical Observations - Days 1-4

Permanent Animal Number	Study Animal Number	Day 1	Day 2	Day 3	Day 4
2094	150	Normal	Normal	Normal	Normal
2095	151	Normal	Normal	Normal	Normal
2096	152	Normal	Normal	Normal	Normal
2097	153	Normal	Normal	Normal	Normal
2098	250	Normal	Normal	Normal	Normal
2099	251	Normal	Normal	Normal	Normal
2100	252	Normal	Normal	Normal	Normal
2101	253	Normal	Normal	Normal	Normal

(b)(4) Confidential and Proprietary Information

APPENDIX IV: GROSS OCULAR OBSERVATIONS

(b)(4)
Confidential
and
Proprietary
Information

Safety Evaluation - Toxicology
Study No.: TX02106

Appendix IV: Gross Ocular Observations

Gross Ocular Observations - Day 1		Pre 1st Dose			Post 1st Dose			Pre 2nd Dose			Post 2nd Dose		
Group No.	Test/Control Articles	Study Animal No.	Eye*	H	D	S	H	D	S	H	D	S	
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0	0	0	0	0	0	0	

* Right eye was untreated. No reactions were observed in the right eye.
 H = Hyperemia [+1 mild, +2 moderate, +3 severe], S = Swelling [+1 minimal, +2 mild, +3 moderate, +4 severe],
 D = Discharge [+1 mild, +2 moderate, +3 severe]
 0 = Indicates no hyperemia, swelling or discharge

(b)
(4)
Confidential and Proprietary Information

Safety Evaluation - Toxicology
Study No.: TX02106

Appendix IV: Gross Ocular Observations

Gross Ocular Observations - Day 1		Pre 3rd Dose			Post 3rd Dose			Pre 4th Dose			Post 4th Dose		
Group No.	Test/Control Articles	Study Animal No.	Eye*	H	D	S	H	D	S	H	D	S	
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0	0	0	0	0	0	0	

* Right eye was untreated. No reactions were observed in the right eye.
H = Hyperemia [-1 mild, +2 moderate, +3 severe], S = Swelling [+1 minimal, +2 mild, +3 moderate, +4 severe],
D = Discharge [+1 mild, +2 moderate, +3 severe]
0 = Indicates no hyperemia, swelling or discharge

(b)
(4)
Confidential and Proprietary Information

Safety Evaluation - Toxicology
Study No.: TX02106

Appendix IV: Gross Ocular Observations

Gross Ocular Observations - Day 1		Pre 5th Dose			Post 5th Dose			Pre 6th Dose			Post 6th Dose		
Group No.	Test/Control Articles	Study Animal No.	Eye*	H	D	S	H	D	S	H	D	S	
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0	0	0	0	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0	0	0	0	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0	0	0	0	0	0	0	

* Right eye was untreated. No reactions were observed in the right eye.
 H = Hyperemia [+1 mild, +2 moderate, +3 severe], S = Swelling [+1 minimal, +2 mild, +3 moderate, +4 severe],
 D = Discharge [+1 mild, +2 moderate, +3 severe]
 0 = Indicates no hyperemia, swelling or discharge

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Safety Evaluation - Toxicology
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Appendix IV: Gross Ocular Observations

Gross Ocular Observations - Day 1		Pre 7th Dose			Post 7th Dose			Pre 8th Dose			Post 8th Dose				
Group No.	Test/Control Articles	Study Animal No.	Eye*	H	D	S	H	D	S	H	D	S	H	D	S
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0	0	0	0	0	0	0	0	0	0

* Right eye was untreated. No reactions were observed in the right eye.
 H = Hyperemia [+1 mild, +2 moderate, +3 severe], S = Swelling [+1 minimal, +2 mild, +3 moderate, +4 severe],
 D = Discharge [+1 mild, +2 moderate, +3 severe]
 0 = Indicates no hyperemia, swelling or discharge

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Safety Evaluation - Toxicology
Study No.: TX02106

Appendix IV: Gross Ocular Observations

Day 2						
Group No.	Test/Control Articles	Study Animal No.	Eye*	H	S	D
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0

* Right eye was untreated. No reactions were observed in the right eye.
H = Hyperemia [+1 mild, +2 moderate, +3 severe]. S = Swelling [+1 minimal, +2 mild, +3 moderate, +4 severe].
D = Discharge [+1 mild, +2 moderate, +3 severe]
0 = Indicates no hyperemia, swelling or discharge

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Safety Evaluation - Toxicology
Study No.: TX02106

Appendix IV: Gross Ocular Observations

Day 3							
Group No.	Test/Control Articles	Study Animal No.	Eye*	H	S	D	
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0	
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0	
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0	

* Right eye was untreated. No reactions were observed in the right eye.
 H = Hyperemia [+1 mild, +2 moderate, +3 severe], S = Swelling [+1 minimal, +2 mild, +3 moderate, +4 severe],
 D = Discharge [+1 mild, +2 moderate, +3 severe]
 0 = Indicates no hyperemia, swelling or discharge

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Safety Evaluation - Toxicology
Study No.: TX02106

Appendix IV: Gross Ocular Observations

Day 4						
Group No.	Test/Control Articles	Study Animal No.	Eye*	H	S	D
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0

* Right eye was untreated. No reactions were observed in the right eye.
 H = Hyperemia [+1 mild, +2 moderate, +3 severe], S = Swelling [+1 minimal, +2 mild, +3 moderate, +4 severe],
 D = Discharge [+1 mild, +2 moderate, +3 severe]
 0 = Indicates no hyperemia, swelling or discharge

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Safety Evaluation - Toxicology
Study No.: TX02106

Appendix IV: Gross Ocular Observations

Scale for Ocular Observation Scoring

Hyperemia (H)

Normal (0) = Normal. May appear blanched to reddish pink without perilimbal injection (except at 12 and 6 o'clock positions) with vessels of the palpebral and bulbar conjunctiva easily observed.

- +1 = **Mild:** A flushed, reddish color predominantly confined to the palpebral conjunctiva with some perilimbal injection but primarily confined to the lower and upper parts of the eye from the 4 and 7 o'clock and the 11 and 1 o'clock positions.
- +2 = **Moderate:** bright crimson red color of the palpebral conjunctiva with accompanying perilimbal injection covering at least 75% of the circumference of the perilimbal region. Individual vessels are not easily discernable.
- +3 = **Severe:** dark, beefy red color with congestion of both the bulbar and the palpebral conjunctiva along with pronounced perilimbal injection. Petechia may be present on the nictitating membrane and/or the upper palpebral conjunctiva.

Chemosis / Swelling (S)

Normal (0) = No swelling of the conjunctival tissue. No score required.

- +1 = **Minimal:** swelling above normal without eversion of the lids (can be easily ascertained by noting that the upper and lower eyelids are positioned as in the normal eye); swelling generally starts in the lower cul-de-sac near the inner canthus.
- +2 = **Mild:** swelling with misalignment of the normal approximation of the lower and upper eyelids; primarily confined to the upper eyelid so that in the initial stages the misapproximation of the eyelids begins by partial eversion of the upper eyelid. In this stage, swelling is confined generally to the upper eyelid, although it exists in the lower cul-de-sac.
- +3 = **Moderate:** swelling definite with partial eversion of the upper and lower eyelids essentially equivalent. This can be easily ascertained by looking at the animal head-on and noticing the positioning of the eyelids; if the eye margins do not meet, eversion has occurred. (Eyelids appear half-closed.)
- +4 = **Severe:** if eversion of the upper eyelid is pronounced with less pronounced eversion of the lower eyelid, and it is difficult to retract the lids and observe the perilimbal region (eyelids appear more than half-closed), add the comment "Extreme" to the numerical score.

Discharge (D)

Normal (0) = No discharge.

- +1 = **Mild:** discharge above normal and present on the inner portion of the eye but not on the lids or hairs of the eyelids. One can ignore the small amount that is in the inner and outer canthus if it has not been removed prior to starting the study.
- +2 = **Moderate:** discharge is abundant, easily observed, and has collected on the lids and around the hairs of the eyelids.
- +3 = **Severe:** discharge has been flowing over the eyelids so as to wet the hairs substantially on the skin around the eye.

APPENDIX V: SLIT LAMP BIOMICROSCOPY

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Study No.: TX02106

Appendix V: Slit Lamp Findings

Slit Lamp Findings – Pre-Study (Day 0)

Group No.	Test/Control Articles	Study Animal No.	Eye*	Conjunctiva			Flare	Iris	Cornea		Pannus	Fluorescein	
				C	S	D			Cloudy	Area		Intensity	Area
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0	0	0	0	0	0	0	0

- * Right eye was untreated. No findings were observed in the right eye of any animal.
- Pupillary reflex was normal for all rabbits.

Key:

Slit lamp biomicroscopy includes examination of the conjunctiva (congestion, swelling, discharge), anterior chamber (flare and iritis), cornea (opacity and area of involvement, pannus, and fluorescein staining (intensity and area)).

Normal (0) = Indicates no congestion, swelling, discharge, flare, iritis, corneal cloudiness, pannus, or fluorescein staining
Cloudy = Corneal opacity

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Appendix V: Slit Lamp Findings

Slit Lamp Findings Following Last Instillation - Day 1

Group No.	Test/Control Articles	Study Animal No.	Eye*	Conjunctiva			Flare	Iris	Cornea		Pannus	Fluorescein	
				C	S	D			Cloudy	Area		Intensity	Area
1	Rewetter Formulation No. 3 (9464X)	150	Left	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	151	Left	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	152	Left	0	0	0	0	0	0	0	0	0	0
1	Rewetter Formulation No. 3 (9464X)	153	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	250	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	251	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	252	Left	0	0	0	0	0	0	0	0	0	0
2	Rewetter Formulation No. 6 (9467X)	253	Left	0	0	0	0	0	0	0	0	0	0

- * Right eye was untreated. No findings were observed in the right eye of any animal.
- Pupillary reflex was normal for all rabbits.

Key:

Slit lamp biomicroscopy includes examination of the conjunctiva (congestion, swelling, discharge), anterior chamber (flare and iritis), cornea (opacity and area of involvement, pannus, and fluorescein staining (intensity and area)).

Normal (0) = Indicates no congestion, swelling, discharge, flare, iritis, corneal cloudiness, pannus, or fluorescein staining
Cloudy = Corneal opacity

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Appendix V: Slit Lamp Findings Slit Lamp Scoring

RECORDING OBSERVATIONS

All parameters normal = No slit lamp findings

Other parameters normal = No slit lamp findings except for those indicated

CONJUNCTIVAL CONGESTION:

Normal = Normal in appearance *for the species*. May appear blanched to reddish pink without perilimbal injection (except at 12 and 6 o'clock positions) with vessels of the palpebral and bulbar conjunctiva defined and easily observed.

+1 = **Mild**. A flushed, reddish color predominantly confined to the palpebral conjunctiva with some perilimbal injection, primarily located but not confined to the upper and lower regions of the eye.

+2 = **Moderate**. The palpebral conjunctiva appears bright red with accompanying perilimbal injection covering at least 75% of the circumference of the perilimbal region.

+3 = **Severe**. Both the bulbar and palpebral conjunctiva exhibit a dark, beefy-red color with pronounced perilimbal injection. Petechia on the conjunctiva may be present. The petechia generally predominate along the nictitating membrane and/or the upper palpebral conjunctiva.

CONJUNCTIVAL SWELLING

Normal = Normal. No swelling of the conjunctival tissue is observed.

+1 = **Minimal**. Swelling above normal but without eversion of the lids. Swelling generally begins in the lower cul-de-sac near the inner canthus.

+2 = **Mild**. Swelling with misalignment of the normal approximation of the lower and upper eyelids. In this stage, swelling is confined generally to the upper eyelid, with some swelling observed in the lower cul-de-sac.

+3 = **Moderate**. Swelling is definite, with partial eversion of the upper and lower eyelids essentially equivalent. Eversion of the eyelids may be determined by looking at the animal head-on and observing the positioning of the eyelids.

+4 = **Severe**. Eversion of the upper eyelid is pronounced with less pronounced eversion of the lower eyelid. At this level, it is difficult to retract the lids and observe the perilimbal region.

CONJUNCTIVAL DISCHARGE

Normal = Normal. May include a small amount of clear, mucoid material that is normally found in the medial canthus of a substantial number of animal eyes.

+1 = **Mild**. Discharge is above normal and present on the inner portion of the eye but not on the lids or hairs of the eyelids.

+2 = **Moderate**. Discharge is abundant, easily observed, and has collected on the lids and around the hairs of the eyelids.

+3 = **Severe**. Discharge has been flowing over the eyelids so as to substantially wet the hairs on the skin around the eye.

AQUEOUS FLARE

Normal = Absence of visible light beam in the anterior chamber (no Tyndall effect).

+1 = **Mild**. The Tyndall effect is barely discernible. The intensity of the light beam in the anterior chamber is less than the intensity of the slit beam as it passes through the lens.

+2 = **Moderate**. The Tyndall beam in the anterior chamber is easily discernible and is equal in intensity to the slit beam as it passes through the lens.

+3 = **Severe**. The Tyndall beam in the anterior chamber is easily discernible; its intensity is greater than the intensity of the slit lamp beam as it passes through the lens.

IRIS

Normal = Normal iris without any hyperemia of the iris vessels. Note: in rabbits, around the 12 to 1 o'clock position and the 6 to 7 o'clock position near the pupillary border, there may be a small area (approximately 1-3 mm in diameter) in which both the secondary and tertiary vessels may be slightly hyperemic. This is normal.

+1 = **Minimal**. Minimal injection of secondary and tertiary vessels observed. Generally, it is uniform, but may be of greater intensity at the 12 to 1 o'clock or 6 o'clock position. If it is confined to this area, the tertiary vessels must be substantially hyperemic.

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Appendix V: Slit Lamp Findings Slit Lamp Scoring

- +2 = **Mild** injection of tertiary vessels and minimal to moderate injection of the secondary vessels observed.
- +3 = **Moderate** injection of the secondary and tertiary vessels with slight swelling of the iris stroma (this gives the iris surface a slightly rugose appearance, which is usually most predominant near the 3 and 9 o'clock positions).
- +4 = **Severe**. Marked injection of the secondary and tertiary vessels with definite swelling of the iris stroma. The iris appears rugose and may be accompanied by hemorrhage in the anterior chamber.

CORNEAL CLOUDINESS SEVERITY

- Normal** = Normal. Appears with the slit lamp as having a bright gray line on the epithelial surface and a bright gray line on the endothelial surface with a uniform marble-like gray appearance of the stroma.
- +1 = **Minimal**. Some loss of transparency. Only the epithelium and/or the anterior half of the stroma is involved as observed with an optical section of the slit lamp. With diffuse illumination, the underlying structures are clearly visible, although some cloudiness may be readily apparent.
- +2 = **Mild**. Some loss of transparency. The cloudiness extends past the anterior half of the stroma. The affected stroma has lost its marble-like appearance and is homogeneously white. With diffuse illumination, underlying structures are visible, although there may be some loss of detail.
- +3 = **Moderate**. Involvement of the entire thickness of the stroma. With optical section, the endothelial surface is still visible. However, with diffuse illumination, the underlying structures are just barely visible (to the extent that the observer is still able to grade flare, iritis, observe for pupillary response, and note lenticular changes).
- +4 = **Severe**. Involvement of the entire thickness of the stroma. With optical section, the endothelium is not clearly visualized. With diffuse illumination, the underlying structures cannot be seen so that the evaluation of aqueous flare, iritis, pupillary response, and lenticular changes is not possible.

OCULAR SURFACE MEASUREMENT

- Normal** = No area of cloudiness
- +1 = Less than one fourth the corneal area
- +2 = One fourth to less than one half the corneal area
- +3 = One half to less than three fourths the corneal area
- +4 = Three fourths or greater of the corneal area

PANNUS

- Normal** = No pannus.
- +1 = Vasculization is present but vessels have not invaded the entire corneal circumference. Where localized vessel invasion has occurred, the vessels have not penetrated beyond 2 mm.
- +2 = Vessel invasion is greater than 2 mm in one or more areas, or involves the entire corneal circumference.

FLUORESCIN STAINING

- Normal** = Normal. This may include a small number of faint focal or hazy areas of fluorescein staining which may be present in normal eyes.
- +1 = **Slight** fluorescein staining. With diffuse illumination, the underlying structures are easily visible. (The outline of the pupillary margin can be seen as if there were no fluorescein staining).
- +2 = **Mild** fluorescein staining. With diffuse illumination, the underlying structures are visible, although there is some loss of detail.
- +3 = **Marked** fluorescein staining. With diffuse illumination, underlying structures are barely visible but not completely obscured.
- +4 = **Severe** fluorescein staining. With diffuse illumination, underlying structures cannot be observed.

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**APPENDIX VI: TABULAR SUMMARY
FOR ICH COMMON TECHNICAL DOCUMENT**

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Safety Evaluation - Toxicology
Study No. TX02106

Appendix VI: Tabular Summary for ICH CTD

2.6.7.6 Repeat-Dose Toxicity

Non-Pivotal Studies

Test Article: Rewetter Formulation No. 3 (9464X)
Rewetter Formulation No. 6 (9467X)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses	Gender and No. per Group	NOAEL ^a (mg/kg)	Noteworthy Findings	Study Number
Rabbit/ NZW	Ocular topical	1 day (with 3 day recovery)	1 drop (~70µL) OS 8X/day	4F	N/A	--	TX02106

NZW - New Zealand White

a - No Observed Adverse-Effect level

-- - No noteworthy findings

OS - left eye

CLINICAL

Document Type	Reference Number	Date	Page
Clinical Report Summary	N/A	N/A	1 250
Certification: Financial Interests and Arrangements of Clinical Investigators	Form FDA 3454	June 18, 2003	1 252
Clinical Assessment of Safety and Acceptability	HARW-102-9464	June 9, 2003	1 254

CLINICAL REPORT SUMMARY

Department: Clinical Research and Development
Study Type: Clinical Assessment of Safety and Acceptability in Hydrogel Lenses
Title: A Prospective, Multi-center, Randomized, Double-masked, Parallel-group Comparative Evaluation of the Safety and Acceptability of Three New Contact Lens Rewetter Solutions versus REFRESH CONTACTS™ Contact Lens Comfort Drops When Used with Hydrogel Contact Lenses

Study Date: June 9, 2003
Study Number: HARW-102-9464
Study Summary: AMO conducted a one-month clinical study to assess the safety and acceptability of three new formulations of *blink*™ CL Lubricant Eye Drops (b) (4) compared with REFRESH CONTACTS Contact Lens Comfort Drops (aka REFRESH@ CONTACTS™ Lubricating and Rewetting Solution, K992028, Oct. 7, 1999) as a control.

A total of 95 subjects were enrolled at four investigational sites in the U.S. Ninety subjects completed the study as planned. Subjects were evenly divided between the FDA Group 1 and Group 4 hydrogel lens materials. The subjects were randomized to use one of the three formulations of *blink*™ CL Lubricant Eye Drops or the REFRESH CONTACTS product as a control. All subjects were to use their drops at least three times per day in both eyes for one month in order to maximize exposure to the product.

Results of the study indicate that there were no statistically significant among-group differences for the three formulations of *blink*™ CL Lubricant Eye Drops and the control at any scheduled visit as measured by change from baseline in mean overall lens wearing comfort scores, mean end-of-day comfort scores, duration of comfort effect, mean rating of the cushioning effect, or for any symptoms of discomfort.

At study exit for rating of both overall comfort and ability to wear the lenses longer and more comfortably, pairwise analyses indicated that *blink*™ CL Lubricant Eye Drops (9464X) was not significantly different from the REFRESH CONTACTS group.

For rating of overall effect of the drops on vision quality, *blink*™ CL Lubricant Eye Drops (9464X) was not significantly different from REFRESH CONTACTS.

No significant among-group differences were noted for visual acuity, slit lamp examination findings, or adverse events.

CLINICAL REPORT SUMMARY, *continued*

In terms of overall product acceptability when compared to the commercial pre-study contact lens rewetter drops used with regard to lens wearing comfort, there was no statistically significant among-group difference. When subjects were asked at the end of the study if they would continue to use the test product if it was commercially available, pairwise comparison indicated that *blink*TM CL Lubricant Eye Drops (9464X) was rated as not significantly different from REFRESH CONTACTS.

Based on this study, all three formulations of *blink*TM CL Lubricant Eye Drops are safe, effective and acceptable lubricants/rewetters for use with hydrogel contact lenses. In general, *blink*TM CL Lubricant Eye Drops, formulation no. 9464X, performed better than the other two investigational formulations and AMO has elected to commercialize it over the other two formulations.

FDA Form 3454, Certification: Financial Interests and Arrangements of Clinical Investigators, follows this summary.

**Certification:
Financial Interests and Arrangements
of Clinical Investigators**

Form FDA 3454

June 18, 2003

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of

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- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Lynn Alan Lasswell, O.D.	TITLE Manager, Clinical Research, Eye Care
FIRM/ORGANIZATION Advanced Medical Optics, Inc.	
SIGNATURE 	DATE 18 JUNE 2003

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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Clinical Assessment of Safety and Acceptability

HARW-102-9464

June 9, 2003

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AMO, Inc.

CONFIDENTIAL

FINAL REPORT

BLINK™ BRAND CONTACT LENS REWETTER SOLUTION

CLINICAL TRIAL

STUDY NUMBER

HARW-102-9464

CONFIDENTIAL

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AMO, Inc.

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ABSTRACT

The safety and acceptability of three new formulations of an investigational contact lens rewetter (blink™ brand Contact Lens Rewetter Solution) containing hyaluronic acid were evaluated versus the currently marketed formulation of REFRESH CONTACTS™ Contact Lens Comfort Drops (b) (4) when used with daily wear hydrogel contact lenses.

Eligible subjects were adapted to the contact lens material to be worn during the study for at least one month prior to entry into the study and had successfully used a commercially marketed multi-purpose solution or peroxide-based care solution for at least one month prior to study entry. Virtually all subjects wore standard hydrogel contact lenses made of either FDA Group 1 or Group 4 materials (one subject wore lenses of an approved Group 1 silicone-hydrogel material, lotrafilcon A). Subjects were evenly divided between the FDA Group 1 and Group 4 materials. Subjects were randomized to use one of the three investigational rewetters or the REFRESH control. All subjects were to use the assigned rewetter solution at least three times per day in both eyes for one month in order to maximize exposure to the product. Subjects wore the same lenses during the study that they were wearing at the time of enrollment, unless their lenses were already due for replacement, in which case the subject received new lenses prior to starting the study.

A total of 95 subjects were enrolled at four investigational sites in the U.S. between February 14, 2003, and April 3, 2003, and 90 completed the study as planned. Slightly more than two-thirds (64/94, 68.1%) of the subjects were female. The mean age for all enrolled subjects was 38.3 years, with a range of 18.0 to 71.0 years. This report summarizes the clinical results (visual acuity, slit lamp findings, and complications) and subjective lens wearing comfort/symptoms questionnaire responses through the one-month final study exam.

Results of the study indicate that there were no statistically significant among-group differences for the three investigational rewetters and the REFRESH control at any scheduled visit as measured by change from baseline in mean overall lens wearing comfort scores, mean end-of-day comfort scores, duration of comfort effect, mean rating of the cushioning effect, or for any symptoms of discomfort. A significant among-group difference

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was found for the rating of comfort just after using the drops versus before using the drops at Day 30 and for the study exit questions for rating of overall comfort and rating of wearing lenses longer and more comfortably. Pairwise comparison analyses indicated that for comfort just after drop instillation, REFRESH was significantly better than all three investigational rewetters. At study exit for rating of both overall comfort and ability to wear the lenses longer and more comfortably, (b)(4) Confidential and Proprietary Information

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but was not significantly different

from the 9464X group. For quality of vision, no significant among-group differences were found for overall quality of vision or end-of-day vision at any study visit, however, a significant among-group difference was noted at Day 30 for rating of improvement in vision following use of the drops and for the rating of the overall effect of the drops at study exit. For improvement in vision quality following use of the drops, pairwise analyses revealed that REFRESH was significantly better than (b) (4), but not significantly better than (b) (4). For rating of the overall effect of the drops on vision quality, REFRESH was significantly better than 9467X, but not significantly different from (b) (4). No significant among-group differences were noted for visual acuity, slit lamp examination findings, or adverse events.

In terms of overall product acceptability when compared to the commercial pre-study contact lens rewetter drops used with regard to lens wearing comfort, there was no statistically significant among-group difference. When subjects were asked at the end of the study if they would continue to use the test product if it was commercially available, a significant among-group difference was found. (b)(4) Confidential and Proprietary Information

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(b) (4)

Based on this study, there were few statistically significant among-group or pairwise differences for the four tested rewetter solutions. In general, REFRESH tended to perform somewhat better for several performance measures, but was often matched or followed closely by formulation 9464X. The two remaining formulations performed somewhat less well, (b) (4) generally having the lowest performance. Overall, all four test solutions were shown to be safe and effective as rewetting solutions for hydrogel contact lenses.

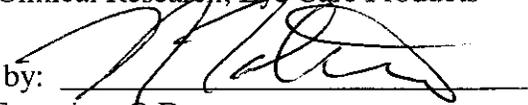
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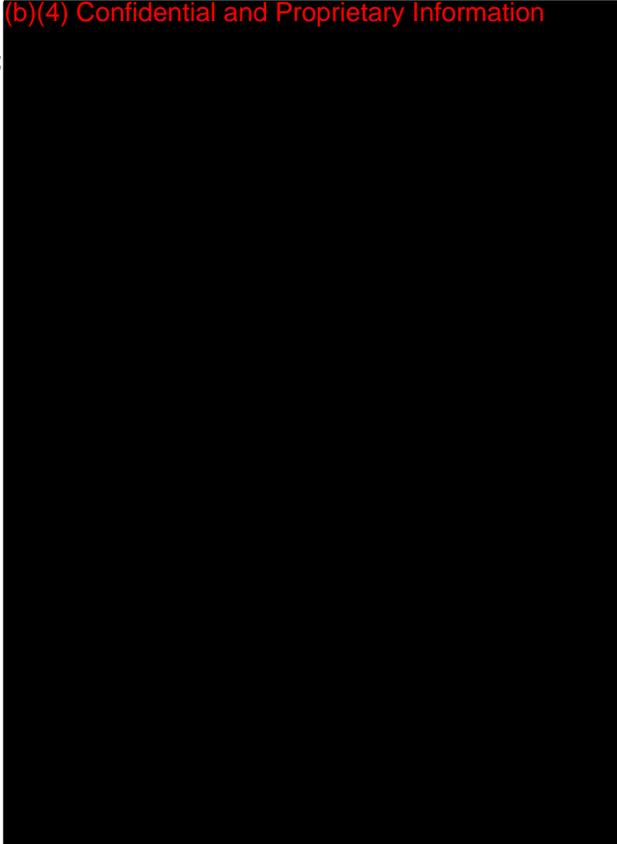
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1.0 PERSONNEL AND FACILITIES

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2.0 BACKGROUND

Wearers of contact lenses, of both soft hydrogel and rigid gas-permeable materials, often experience lens-associated contact lens dryness sometime during the daily lens wearing period. This can stem from a variety of causes, but is most often related to a disruption of the normal tear film structure and integrity caused by the presence of the contact lens on the eye. When the tear film is thus disturbed, loss of functional properties of the normal tear film can ensue, including a sensation of dryness caused by disruption of the anterior lipid layer and loss of the underlying aqueous layer which can lead to dehydration of the contact lens and cornea. To counteract this problem, contact lens wearers often resort to use of over-the-counter contact lens rewetting solutions to provide symptomatic relief of contact lens-related dry eye discomfort. There are available on the market numerous products in this category, and, for the most part, contact lens wearers tend to select a brand based on personal preference, although their eye care practitioner may recommend a particular brand or brands for a patient to start with initially. If a recommended product does not provide satisfactory relief, then patients will often engage in a process of self-directed trial-and-error to identify a product which does seem to provide the desired properties that make the contact lenses more tolerable for a longer period of time.

Advanced Medical Optics has developed several new investigational contact lens rewetter formulations based on the incorporation of a compound that occurs naturally in human ocular tissues called hyaluronic acid (or sodium hyaluronate). This compound can be formulated in a range of molecular weights through repeating sub-units, and has been used worldwide for over 30 years in various molecular weights/formulations as a viscoelastic protective agent in cataract surgery. It has also more recently been included in some over-the-counter contact lens rewetting solutions in both Europe and the United States.

The three blink™ brand contact lens rewetter solutions (formulations (b) (4), and (b) (4)) that are the subject of this report were evaluated in a prospective, multi-center clinical trial. All three products contain hyaluronic acid (sodium hyaluronate) as the principal demulcent/viscosity agent, (b)(4) Confidential and Proprietary Information

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sodium hyaluronate used in all three investigational formulations in this study has a molecular weight of 810,000 daltons. The three investigational products were all preserved with the Purite® system (stabilized oxychloro complex) and were formulated in a sodium borate/boric acid buffer base, with sodium chloride, potassium chloride, calcium chloride and magnesium chloride as tonicity agents. These ingredients are quite similar to those contained in the control product. (Refer to Section 5.2, Study Products, for a table containing more details on the product formulations and physical properties.)

These three test products represent the first hyaluronic-acid containing rewetter solutions that have been clinically investigated by AMO. However, as noted above, there are already some marketed hyaluronic acid-containing contact lens rewetters that have been developed by other companies.

3.0 STUDY OBJECTIVE

The purpose of this study was to compare the clinical safety and acceptability of three new formulations of a contact lens rewetter solution to that of currently marketed REFRESH CONTACTS™ Contact Lens Rewetter Drops (Allergan, Inc., Irvine, CA, and hereinafter referred to as "REFRESH") when used with hydrogel contact lenses.

The primary study endpoint was the change from baseline in the mean end-of-day lens wearing comfort as assessed by the study subjects at each study visit and overall at the end of the study. The null hypothesis was that there was no difference between the investigational solutions and the REFRESH CONTACTS Contact Lens Comfort Drops. Secondary acceptability variables included overall lens wearing comfort scores, symptoms of discomfort, subjective vision quality, product usage rates, lens wearing time, tear break-up time, and subjective product acceptability. Safety variables evaluated were changes in best contact lens-corrected visual acuity, slit lamp findings, complications and adverse events.

4.0 STUDY DESIGN

This study was a prospective, multi-center, randomized, double-masked, parallel-group comparative evaluation of the safety and acceptability of three formulations of blink™ brand

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contact lens rewetting drops versus REFRESH CONTACTS Contact Lens Comfort Drops when used with hydrogel contact lenses.

5.0 MATERIALS AND METHODS

5.1 STUDY POPULATION

Approximately 96 subjects from 4 investigational sites in the U.S. (approximately 24 subjects at each site) were to be enrolled. Subjects for this study were to be chosen from the normal hydrogel contact lens-wearing patient populations at each of the investigational sites according to the following inclusion and exclusion criteria.

5.1.1 SUBJECT INCLUSION CRITERIA:

- At least 18 years of age
- Subject must understand his or her rights as a research subject and give written informed consent.
- Be likely to complete the entire course of the study and to comply with appropriate instructions
- Have normal eyes (with the exception of unaided visual acuity) defined as:
 - No evidence of active lid abnormality or infection
 - No active conjunctival abnormality or infection
 - A clear cornea with no active slit lamp findings (edema, staining, scars, vascularization, abnormal opacities, etc.) graded 2 or greater (on a scale of 0 – 4, in which 0 = none, 1 = trace, 2 = mild, 3 = moderate, and 4 = severe)
 - No iritis
 - No other active ocular disease (by history and slit lamp examination without pupil dilation)
 - No aphakia or pseudophakia
- Have successfully worn hydrogel contact lenses of the same material (FDA Group 1 or Group 4) to be worn during the study on a daily-wear basis for at least one month immediately prior to entry into this study. Successfully means that the subject and the investigator are satisfied with subject's ocular health, comfort, and visual acuity. Subjects must be wearing their lenses on a daily wear basis for a minimum of 8 hours per day. Each subject must be wearing lens of the same material in both eyes.
- Have successfully used a multi-purpose contact lens solution (e.g., COMPLETE®, OPTI-FREE or ReNu) or a peroxide-based contact lens care solution (e.g., UltraCare®, AOSep) on a daily basis for at least one month immediately prior to entry into this study. Successfully means that the subject

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and the investigator are satisfied with the subject's ocular health, comfort, and visual acuity.

- Have need of a contact lens rewetter solution due to an established history of ocular dryness or irritation at some point during their daily contact lens wear period.
- Have a lens wearing comfort score of ≥ 5 in their present lenses in each eye at the time of entry into this study. Lens comfort is graded on a scale of 0-10, in which 0 = the lens cannot be tolerated and 10 = the lens cannot be felt.
- Have an overall subjective vision quality score of ≥ 5 in their current lenses in each eye at the time of entry into the study. Overall subjective vision quality is graded on a scale of 0-10, in which 0 = overall vision quality is poor and 10 = overall vision quality is excellent.
- Be in need of binocular contact lens correction (i.e., no monovision fits)
- Have distance visual acuity correctable with study lenses to 20/30 or better Snellen acuity in each eye
- Be wearing their contact lenses on a daily wear schedule of at least eight hours a day, seven days a week
- Be in good general health

5.1.2 SUBJECT EXCLUSION CRITERIA:

Subjects were not eligible to participate in the study if they met any of the following criteria:

- Wear lenses on an extended wear basis (i.e., overnight wear for 7 days or more) that are replaced on a schedule more frequently than once every month
- Wear daily disposable lenses
- Have a confirmed diagnosis of Sjogren's syndrome or other condition that results in a chronic and/or pathologic dry eye condition
- Require concurrent ocular medication or have used ocular medication within 24 hours prior to entry into the study
- Have a known sensitivity to the study products or to any ingredient(s) of those products
- Are currently enrolled in any other clinical study or have participated in such a study within 14 days of entry into this study
- Are pregnant, or anticipate becoming pregnant during the course of the study
- Have a condition or are in a situation that, in the investigator's opinion, may put them at significant risk, may confound the study results, or may interfere significantly with their participation in the study

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5.1.3 WITHDRAWAL CRITERIA

Subjects were to be withdrawn from the study if they experienced a clinically significant, study-related adverse event that either did not resolve upon discontinuation of lens wear or recurred during a re-challenge with the investigational product.

5.2 STUDY PRODUCTS

Three formulation variants of the hyaluronic acid-containing rewetter solutions were used in this study, along with the REFRESH CONTACTS Contact Lens Comfort Drops control product. A comparison of the key components and properties of the two formulations is presented below in Table A.

Table A
STUDY TREATMENTS/FORMULATIONS

SOLUTION	9463X	9464X	9467X	REFRESH CONTACTS
Ingredient	% (w/v)	% (w/v)	% (w/v)	% (w/v)
Sodium hyaluronate (0.81 million daltons M.W.)	0.1	0.15	0.075	N/A
Hydroxypropyl methylcellulose (F4M)	---	---	0.075	N/A
Sodium carboxy-methylcellulose (low viscosity)	---	---	---	0.5
Purite (preservative)	0.005	0.005	0.005	0.005
Viscosity (cps)	4.0	6.6	4.7	2 - 5
Osmolality	270	270	270	280
pH	7.2	7.2	7.2	7.0-7.4

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The investigational products were supplied to the study patients in masked 12-ml opaque plastic dropper-tip bottles. The REFRESH control product was provided in a similar masked 12-ml bottle. All units were provided with appropriate investigational labeling.

5.3 EXPERIMENTAL PLAN

Consenting subjects were assigned to use one of the four rewetter solutions according to the randomization schedule provided by the Sponsor. The randomization schedule was arranged in blocks to ensure that equal numbers of subjects at each site would be assigned to each of the four treatment arms during enrollment. Subjects were to use the assigned rewetter solution at least three times per day for the duration of the one-month study to maximize exposure to the study product. Each subject was instructed not to discuss the study product assigned with the investigator or any other site personnel performing study evaluations, as all persons collecting data were to be masked as to the study product assigned by randomization. Each study site designated a person to act as an unmasked advisor to provide product to subjects, to review subject instructions, and to act as a resource for product-related questions that may have arisen during the study.

No other ocular lubricants or lens rewetters were to be used during the course of the study, nor were any other product substitutions, additions, or changes to the study product regimen to be made.

Subjects continued to wear their current pre-study lenses for the study unless they were on a frequent replacement schedule and their study lenses were due to be replaced anyway at the time of study enrollment. Otherwise, subjects did not receive new study lenses at the beginning of the study as part of the study design.

Study products were to be stored at controlled room temperature. Frequency of use of the study products and compliance to the study regimen were monitored at each study visit. Investigators were provided separately with the warnings, precautions, contraindications, and potential adverse reactions associated with the use of the investigational study products.

Evaluations at each site were to be performed by the same evaluator throughout the study. If this was not possible, then the evaluators involved were to examine the subject together and

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discuss their findings for at least one visit prior to a change in evaluators in order to agree on assessment grading, etc.

The schedule of study visits and procedures is provided in Appendix A.

5.4 DATA ANALYSIS

5.4.1 ANALYSIS POPULATIONS

Two types of populations were used in the analyses: modified intent-to-treat (ITT) and per-protocol (PP) populations. Safety data were analyzed using the modified intent-to-treat population, defined as all randomized patients who used a study product at least once. Thus, safety analyses were performed on an as-treated basis. End-of-day comfort and comfort immediately post-drop instillation were analyzed using the per-protocol population, defined as all subjects who met all inclusion/exclusion criteria and had no major protocol violations during the study. For other acceptability variables (other lens comfort questions, vision quality, symptoms of discomfort) the intent-to-treat population was used. Non-safety data such as demographics and baseline characteristics were analyzed using the ITT population.

For the primary acceptability variable, end-of-day lens wearing comfort score, the analysis of the mean change from baseline in scores based on the per-protocol population was considered as the primary analysis. Patients/visits exclusions were determined prior to the lock of the database for the per-protocol population.

5.4.2 COLLECTION AND DERIVATION OF PRIMARY ACCEPTABILITY ASSESSMENTS

The end-of-day lens wearing comfort score is the key variable to evaluate acceptability. Data were collected for each eye on an 11-point scale of 0 to 10 (0 = lens cannot be tolerated; 10 = lens cannot be felt) at Days 0, 7, and 30. For the purpose of analysis, the scores for the right and left eyes were averaged.

5.4.3 HYPOTHESES AND METHODS OF ANALYSIS

5.4.3.1 Primary Acceptability Analyses

The null hypothesis is that there is no difference among groups in the mean change from baseline for end-of-day lens wearing comfort. The alternative hypothesis is that at least one of the three investigational rewetter formulations is different from the REFRESH control group. Mean change in baseline lens wearing comfort was analyzed using two-way analysis of variance with fixed effects for group and site. In addition, appropriate selections were made for reviewing two-group comparisons (e.g., Dunnett's procedure; contrasts from the ANOVA model). Two-sided 95% Confidence Intervals (CI) for between-regimen differences in mean score change were also generated based on the ANOVA model.

5.4.3.2 Secondary Acceptability Analyses

Additional acceptability variables evaluated during the study were additional questions on lens comfort (such as cushioning effect and comfort at study exit), overall subjective vision quality, symptoms of discomfort, and subjective product acceptability. Comparisons among groups for questions rated on the 0-10 scale were analyzed using analysis of variance. Among-group comparisons for ordinal data were performed using the Kruskal-Wallis test. The chi-square test or Fisher's exact test for small samples was used for comparing groups for categorical data.

5.4.3.3 Safety Analyses

For the safety analyses, slit lamp findings and study lens-corrected visual acuity, the frequency and proportion were reported and statistical significance was determined using the Kruskal-Wallis test.

For visual acuity, a cross-tabulation of baseline vs. final reported lens-corrected visual acuity was provided for all subjects (intent-to-treat). This tabulation was based on all eyes. Another tabulation was also provided for those subjects who experienced a clinically significant decrease in best lens-corrected visual acuity (a decrease of 2 lines or more). This tabulation was based on subjects.

6.0 RESULTS

6.1 STUDY POPULATION

Between February 14, 2003, and April 3, 2003, a total of 95 subjects were enrolled at four investigational sites in the U.S. The disposition of study subjects is provided in Tables 1 and 2. One subject (#1108) who had been enrolled decided afterwards not to participate and never used the assigned study product, which was returned to the investigator intact, and this subject has no study data beyond baseline. Thus, a total of 94 subjects were in the ITT population, while the per-protocol population (N = 91) was lower due to loss to follow-up, protocol violations, etc. Those subjects who were discontinued (N = 4) from the study are presented in Listings 1.1 through 1.4 with the reasons for their discontinuation. Before the data analyses, it was decided that subjects who deviated from the study protocol or were discontinued due to reasons not related to discomfort would be excluded from the per-protocol determination. It was also decided that any visit outside of the visit windows would become an interim visit, and, therefore, be excluded from the per-protocol analyses. Therefore, completion of the study was not the sole criterion for the per-protocol determination. Those subjects or visits excluded from the per-protocol analyses are presented in Listings 2.1 through 2.4 with the reasons for their exclusion. Listing 2.2 shows that one subject (#1109) was excluded from the per-protocol analysis for the Day 7 visit only because that visit was out of the visit window, but the subject was otherwise included in the per-protocol analysis.

Of the four discontinued subjects, there was one in each of the four treatment groups. (b)(4) Confidential and Proprietary Information

(b)(4) Confidential and Proprietary Information

subject (#3427) in the 9464X group was discontinued for discomfort and slit lamp findings that were deemed not regimen-related. The subject (#1409) (b)(4) Confidential and Proprietary Information

(b)(4) Confidential and Proprietary Information

The remaining subject (#1410) in the REFRESH group was discontinued due to discomfort and reduced visual acuity, which were deemed to be regimen-related.

Demographic data for all 94 intent-to-treat subjects are summarized in Table 3. There were no notable differences between the four treatment groups with regard to the demographics of

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age, sex, race, or iris color. The same is true for the distribution of pre-study lens rewetter usage, pre-study care regimen usage, and FDA lens material group (Table 4). For the overall sample population, slightly more than two-thirds of the subjects were female (64/94, 68.1%). The mean age for all enrolled subjects was 38.3 years, with a range of 18.0 to 71.0 years (Table 3). Regarding the brands of pre-study rewetters used, 19.1% (18/94) of subjects had used OPTI-FREE EXPRESS brand previously, 16.0% (15/94) had used ReNu Multi-Plus brand, 14.9% (14/94) had used REFRESH brand, 10.6% (10/94) had used COMPLETE brand, and 5.3% (5/94) had used Clerz Plus brand. However, the largest percentage was for the category of "other" brands (34.0%, 32/94), indicating the wide diversity of rewetter drops being used in the general marketplace.

Pre-study lens care system usage generally reflected the contact lens care system marketplace in the U.S., with OPTI-FREE EXPRESS having the highest usage rate (44.7%, 42/94), followed by ReNu Multi-Plus (27.7%, 26/94), and COMPLETE® Multi-Purpose Solution (18.1%, 17/94). Usage of peroxide or other care solutions was low (9/94, 9.6%).

The distribution of FDA lens material types by subject was exactly even at 50.0% (47/94) for Group 1 materials and 50.0% (47/94) for Group 4 materials (Table 4). One subject (#3135) wore Group 1 lenses made of a silicone hydrogel material (lotrafilcon A). This subject was in the 9464X group. Otherwise, all lenses used in the study were standard hydrogel materials.

6.2 PROTOCOL DEVIATIONS

There were a total of three subjects who were excluded from the per-protocol analysis because of protocol deviations. As noted above, one subject (#1109) was excluded only for the Day 7 analyses, but was otherwise included. (b)(4) Confidential and Proprietary Information

(b) (4) and one was in the REFRESH group. In the (b) (4), the first subject (#1110) did not wear her contact lenses as scheduled for any of the follow-up visits. The other subject (#1409) was discontinued from the study for missed visits after the baseline visit. The one subject in the REFRESH group (#1103) was excluded because the Day 30 visit was considerably outside the visit window (54 days).

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6.3 ACCEPTABILITY

6.3.1 LENS WEARING COMFORT SCORES

Subjects were asked at each study visit to rate their lens wear comfort for each eye while wearing their contact lenses, using an 11-point scale from 0 to 10, where 0 meant that the lens could not be tolerated and 10 indicated that the lens could not be felt. The primary acceptability variable established for this study was the mean change from baseline in end-of-day lens wearing comfort score. The average of the scores for the two eyes at baseline and at the follow-up visits was used for the analysis.

Table 5.1 presents the raw mean baseline lens comfort scores and subsequent mean scores at each scheduled visit in the per-protocol population. Table 5.2 presents the results for the change from baseline in mean end-of-day comfort scores at each scheduled visit, along with the pairwise comparison of each of the three test rewetter solutions versus the REFRESH control. It can be seen that there were no statistically significant differences in change from baseline for any of these pairwise comparisons at baseline or at the two scheduled follow-up visits. Since the study subjects were already experiencing some lens-related dryness when they entered the study, the mean lens comfort baseline values for all four groups are not that high, in the range of 7.2 to 7.8 on the 0-10 scale. From the changes in the mean score values, it can be seen that for all groups except the (b) (4) mean scores increased somewhat compared to baseline at both the Day 7 and Day 30 visits. The 9467X group evidenced a mean decrease of -0.1 units at Day 7 and -0.7 units at Day 30. However, even though the difference between (b) (4) REFRESH groups was larger than that of the other two test formulations versus REFRESH, this difference was not statistically significant at either follow-up timepoint.

Presented in Table 5.3 are the results for the pairwise comparison of just the three test rewetter solutions against each other.

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Subjects were also asked to rate the comfort of their lenses immediately after instilling the rewetter drops in their eyes compared to just before they instilled the drops. Table 6.1 presents the results for this assessment based on the raw mean scores at each visit. Generally speaking, there was not much change in the mean scores from baseline through the Day 7 and Day 30 visits for any of the four products. Table 6.2 presents the results for these same data when analyzed in pairwise comparisons of the three test products to the REFRESH control. For this analysis, there were no statistically significant differences for any of the pairings at any visit.

Table 6.3 presents a separate pairwise comparison analysis of the three test rewetter solutions against each other. For all three comparisons, there were no statistically significant differences at any visit, although the comparison of formulations (b)(4) Confidential and Proprietary Information 30 did approach significance ($p = 0.0884$), with the 9464X group having a higher mean score by 1.1 units.

Subjects were asked at each follow-up visit to rate the cushioning effect of the drops immediately after drop instillation. Table 7 indicates that at both the Day 7 and Day 30 visits there were no statistically significant among-group differences for the four rewetter solutions with regard to the cushioning effect after the drops were instilled.

Table 8 presents somewhat similar information regarding the effect of the drops on lens comfort just after instilling the drops compared to the comfort level just before the drops were used. There was not a statistically significant among-group difference at Day 7 (although it approached significance, $p = 0.0841$), but there was at Day 30 ($p = 0.0079$). The REFRESH group had a significantly higher rating of comfort compared to the (b)(4) Confidential and Proprietary Information

(b)(4) Confidential and Proprietary Information ($p = 0.0317$), and (b)(4) Confidential and Proprietary Information ($p = 0.0012$). At this visit, the

REFRESH group had the highest percentage of "much better" responses (57.1%, 12/21)

(b)(4) Confidential and Proprietary Information

Subjects were also asked at the follow-up visits to estimate how long the comfort effect of the drops persisted after drop instillation. Categories of time intervals were provided for the subjects to select from. Table 9 presents the results for this analysis. It can be seen that at

both Day 7 and Day 30 there was no statistically significant among-group difference for this parameter. For all four groups, a fairly high percentage of subjects said that the drops lasted more than 2 hours or from 1 to 2 hours, indicating a good level of residual effect. There was also a notable percentage of subjects in each group who indicated that they did not feel the need for additional drops after one instillation. However, because the study protocol called for use of the drops at least three times per day, it is difficult to assess how this might have impacted overall drop usage if the three-times-per-day minimum had not been stipulated.

At enrollment, subjects were instructed to use the drops a minimum of three times per day, but were told that they could use the drops more often if they felt the need to do so to enhance or maintain their lens wearing comfort. Subjects were asked to keep track of the number of times, on average, that they used the assigned study drops each day. Table 10 presents the results for this parameter. For both the Day 7 and Day 30 visits, there were no statistically significant among-group differences. At Day 30, the highest reported mean usage was 3.87 times per day for the (b) (4) and the lowest reported mean usage was 3.14 times per day for the 9464X group. Lower reported usage is presumed to indicate that the subjects felt less need to use the drops during the lens wearing period because of greater overall lens comfort following drop instillation.

6.3.2 OCULAR SYMPTOMS OF DISCOMFORT

At each study visit, subjects were asked if they were experiencing symptoms of discomfort, which may have included, but were not limited to, burning and stinging, blurry vision, dry eye feeling, unusual eye secretions, excessive tearing, itching, increased lens awareness, redness, light sensitivity, or other symptoms.

Tables 11.1 through 11.10 present the results for all ten categories of discomfort findings by treatment group and by visit. For each of the ten categories, there were no occurrences of a statistically significant among-group difference at any visit timepoint. In general, the distribution of the severity scores was fairly evenly distributed across the four groups. There were very few reports of clinically significant findings (either moderate or severe). Of the ten categories of discomfort symptoms, only three had any really notable findings.

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For the category of blurry vision, at Day 7, 4.3% (1/23) of the REFRESH group and 4.2% (1/24) of the (b) (4) reported severe blurry vision, while 4.2% (1/24) of the (b) (4) group reported mild blurry vision (Table 11.2). There were no reports of any degree of blurry vision in the 9464X group at either Day 7 or Day 30.

For the category of dry eye feeling, there was only one report (1/24, 4.2%) of severe dry eye feeling and this was in the (b) (4) (Table 11.3). Moderate dry eye feeling was reported in 8.7% (2/23) of subjects in the REFRESH group at Day 7 and in 4.3% (1/23) of subjects in the (b) (4). The few other reports of dry eye feeling were all mild in severity.

Reports of increased lens awareness were few during the study. There was one report (1/23, 4.3%) of moderate increased lens awareness at Day 30 in the (b) (4) and one report of moderate increased lens awareness among the three subjects with an unscheduled visit for the 9464X group (Table 11.7). The one other report of increased lens awareness (non-baseline) was of mild severity in the (b) (4) (1/24, 4.2%).

For the other categories of symptoms of discomfort, the report rates were very low and were not clinically significant.

6.3.3 SUBJECTIVE VISION QUALITY

At each study visit, subjects were asked to evaluate their overall subjective vision quality while wearing their contact lenses, using an 11-point scale from 0 to 10, where 0 meant that overall vision quality was poor and 10 indicated that overall vision quality was excellent. Data for the right and left eyes of each subject were averaged at each visit for the purposes of data analysis.

Table 12 presents the results for mean changes from baseline in overall vision quality at each follow-up visit. For the among-group comparisons, there were no statistically significant differences at any visit. In general, overall vision quality tended to decrease slightly for each of the four treatment groups as time progressed. This may be reflective of the aging of the lenses as the study progressed, since vision quality typically tends to decrease the longer a soft (hydrogel) contact lens is worn.

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Table 13 presents the results for the mean end-of-day vision quality compared to baseline. Again, for the among-group comparisons, there were no statistically significant differences at any visit. Interestingly, at Day 7 all three of the investigational rewetter groups evidenced a slight increase from baseline in mean end-of-day vision quality while the REFRESH group demonstrated a decrease (-0.37 units). At Day 30, there was a slight decrease from baseline for three of the four groups, with no change from baseline for the (b) (4). A significant group by-site interaction was found at the Day 7 visit indicating that differences among the groups were not consistent across the four investigational sites. For example, at the first site, REFRESH subjects showed an average loss of 2 points whereas at the other sites the average loss was less than 0.5 points and at one site there was a gain of 0.7 points. This interaction was not noted at the Day 30 visit and no significant difference among groups was found at this visit. The reason for the apparent site interaction effect for the Day 7 visit is not known.

Subjects were asked at each scheduled visit to rate the effect of the drops on their quality of vision approximately 2-3 minutes after instilling the drops. Results of this evaluation are provided in Table 14. At Day 7, there was no statistically significant among-group difference, whereas there was at Day 30 ($p = 0.0164$). The REFRESH group had a significantly higher rating of improvement in quality of vision after using the drops compared to the (b) (4) and (b) (4), but the REFRESH group was not significantly different from the (b) (4). At Day 30, the REFRESH group had the highest percentage (42.9%, 9/21) of subjects reporting that it “definitely improved” the quality of vision, followed by the (b) (4), (b) (4) and the (b) (4). For subjects reporting a “somewhat improved” quality of vision, the order (from highest to lowest) was 9464X (45.5%, 10/22), REFRESH (38.1%, 8/21), (b) (4) Confidential and Proprietary Information. Only two groups had responses in the categories of “somewhat decreased” or “definitely decreased” quality of vision: (b) (4). In this regard, (b) (4).

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Table 15 presents the results for average length of time (in minutes) that subjects experienced a perceived change in the quality of vision after using the drops, whether that change was positive (improved) or negative (decreased). For the category of improved quality of vision, the longest mean time at Day 7 was for the (b) (4) (101.5 minutes) and the shortest time was for the 9464X group (46.9 minutes). At Day 30, the longest mean time was again for the (b) (4) and the shortest mean time was again for the (b) (4). There was a notable decrease (23.5 minutes) in the mean length of perceived effect for the (b) (4) between the Day 7 and Day 30 visits, whereas the perceived mean duration of effect for the 9464X group was virtually identical for both visits. For the category of decreased quality of vision, there were no reports in either the (b) (4) or REFRESH groups at Day 7, while there was one report in the 9464X group (5 minutes) and three reports in the (b) (4). At Day 30, there were no reports of decreased quality of vision in the 9464X or REFRESH groups, while there was one report in the (b) (4) and five reports in the (b) (4) group (mean of 7.2 minutes). Overall, for those few cases where a decrease in vision quality was reported, the mean duration was markedly shorter than for the cases where an increase in vision quality was reported.

6.3.4 LENS WEARING TIME

Subjects who were enrolled into the study were required to be able to wear study lenses at least eight hours per day, seven days per week. At each follow-up visit, subjects were asked to report on their perception of whether their lens wearing time had increased or decreased since the previous visit, and if so, to characterize the extent of that change using one of five descriptive categories provided. Table 16 presents the results for these assessments for the intent-to-treat population. For the among-group comparisons at both Day 7 and Day 30, there were no statistically significant differences. For both visits, the overwhelming majority of responses for all four treatment groups fell into the “not changed” category, ranging from 75.0% (9463X, Day 7) to 90.5% (REFRESH, Day 30). At Day 30, the (b) (4) had the highest response rate for “increased a lot” (2/23, 8.7%), but this group also had the only report of a decrease in wearing time (“decreased somewhat,” 1/23, 4.3%). For the combined categories of “increased a lot/increased somewhat” at Day 30, (b) (4) had the

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highest response rate (5/23, 21.7%), followed closely by the 9464X group (4/22, 18.2%), then the REFRESH group (2/21, 9.5%) (b)(4) Confidential and Proprietary Information

6.3.5 TEAR BREAK-UP TIME

Investigators were asked to perform an assessment of the apparent tear-break up time over the front surface of the contact lens. This measurement is normally performed for a non-contact-lens-wearing eye using sodium fluorescein dye viewed under cobalt blue light to enhance viewing of the break-up of the tear film. In this study, to avoid the occurrence of staining of the soft contact lenses with fluorescein, this assessment was conducted under the slit lamp using white light without the use of fluorescein, which somewhat compromised the investigators' ability to view the first break in the tear film integrity. Therefore, the results for this measurement may not be representative of the results that would have been obtained had fluorescein been employed.

Table 17 present the results for the mean tear break-up time in seconds as measured by the investigators. There were no statistically significant among-group differences at baseline or Day 7, but there was at Day 30 ($p = 0.0044$), with the (b)(4) having the shortest mean break-up time (11.83 seconds) and the (b)(4) having the longest mean break-up time (16.87 seconds). At Day 30, the REFRESH group was found to have a significantly longer mean tear break-up time compared to the (b)(4), but was not significantly different from the (b)(4) Confidential and Proprietary Information, respectively). The 9464X group was nearly equal to the 9463X group at 16.23 seconds, followed by the REFRESH group at 13.48 seconds. It is possible that the 5-second time difference between the (b)(4) might be clinically meaningful in terms of enhanced lens wearing comfort.

It should be noted that a significant group by-site interaction was found, indicating that differences among groups were not consistent across sites. When evaluated further, it was noted that at the Day 30 visit, the (b)(4) had substantially lower times reported compared to the other three groups at the first site, but relatively comparable results compared to the other groups at the other three sites. This group by-site interaction was also

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noted at baseline with much lower values reported for (b) (4) as compared to the other groups for the first site but not for the other three sites.

6.3.6 PRODUCT ACCEPTABILITY

At the end of the study, each subject was asked several questions regarding his/her overall vision quality, lens wearing comfort (overall and end-of-day), and product preference with regard to the investigational product used compared to the pre-study lens rewetter used.

With regard to the assessment of the effect of the drops on overall vision quality during the study, Table 18 reveals that there was a statistically significant difference among the four treatment arms ($p = 0.0155$). The REFRESH group had a significantly higher rating for vision quality compared to the (b) (4), but not compared to the (b) (4)

(b)(4) For the category of “definitely improved,” the (b)(4) had the highest response rate (31.8%, 7/22), followed by the REFRESH group (27.3%, 6/22), the (b)(4)

(b)(4) When the two categories of “definitely improved/somewhat improved” are combined, the results were distributed as follows, from highest to lowest: REFRESH,

(b)(4)

The REFRESH and 9464X groups closely parallel each other, while the other two groups fall notably lower in this regard.

Regarding the effect of the drops on overall lens wearing comfort during the study as assessed at study exit, there was a statistically significant difference among the four treatment groups ($p = 0.0313$, Table 19). The REFRESH group had a significantly higher rating of lens wear comfort compared to the (b)(4)

(b)(4) but not compared to the (b)(4) The highest response rate for subjects who reported that the rewetter definitely or somewhat improved their lens wearing comfort was in the REFRESH group (90.9%, 20/22), (b)(4)

(b)(4) Conversely, the highest combined response rate for subjects reporting that the rewetter drops somewhat or definitely decreased their lens wearing comfort was in the (b)(4) while the lowest combined response

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for these two categories was in the REFRESH group (0.0%, 0/22), followed closely the 9464X group (4.5%, 1/22).

Subjects were also asked to compare their average end-of-the-day lens wearing comfort during the study to their average end-of-the-day lens wearing comfort just before they started the study. In response to this question, there was not a statistically significant difference among the four treatment arms, although the value did closely approach significance ($p = 0.0604$, Table 19). For the combined categories of “much better” and “somewhat better” end-of-day comfort, the highest percentage was in the REFRESH group (68.2%, 15/22), followed by (b)(4)

(b)(4) Conversely, for the combined responses for the categories of “somewhat worse” and “much worse,” (b)(4)

(b)(4)

Subjects were also asked to state their level of agreement with the statement: “use of the study drops generally allowed me to wear my lenses longer and more comfortably compared to before I started the study.” Five response categories were provided, ranging from “definitely agree” to “definitely disagree.” Table 19 provides the results for the responses to this statement. There was a statistically significant among-group difference for the four rewriter groups ($p = 0.0113$). The REFRESH group had a significantly higher level of agreement with the statement compared to (b)(4)

(b)(4) but not compared to the (b)(4) In the category of “definitely agree,” the REFRESH group had the highest response rate (45.5%, 10/22), followed by 9464X (27.3%, 6/22), (b)(4) category of “definitely disagree,” (b)(4)

(b)(4)

The (b)(4) and REFRESH groups had no responses in this category (0.0%, 0/22 for each).

Additionally, subjects were asked to compare their assigned study rewriter to their pre-study rewriter and express a preference, if any, and to rate the level of that preference. The results for this survey are provided in Table 20. The among-group differences approached, but did not attain, statistical significance ($p = 0.0841$). In the category of “definitely better” (for the

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study rewetter), the (b)(4) scored highest (31.8%, 7/22), (b)(4) 7/24), REFRESH (22.7%, 5/22), and (b)(4)

(b)(4) followed by the (b)(4) with the (b)(4) and REFRESH groups having no responses in this category (0.0%, 0/22 for each).

Lastly, subjects were asked whether they would continue to use their assigned study rewetter solution if it was commercially available. There was a statistically significant among-group difference for the responses to this question ($p = 0.0427$). Subjects in the REFRESH group were significantly more likely to say they would continue to use the product compared to subjects using (b)(4)

(b)(4) The differences between the REFRESH group (b)(4) were not statistically significant ($p = 0.0582$ and 0.1062 , respectively). The REFRESH group had the highest percentage of YES responses (86.4%, 19/22), followed by (b)(4)

(b)(4) For the NO responses, the highest percentage was in the (b)(4) 9/23), with the lowest percentage in the REFRESH group (9.1%, 2/22). The highest percentage of "uncertain" responses occurred in the (b)(4) and the lowest percentage occurred in the REFRESH group (4.5%, 1/22).

6.3.7 UNSCHEDULED LENS REPLACEMENTS

There were only two occurrences of unscheduled lens replacement in this study (Table 21). One occurred in the (b)(4) and was due to the loss of a lens. This would not be attributable to either the rewetter product or the care regimen used during the study. The other unscheduled lens replacement was in the REFRESH group and was due to poor surface quality of the lens (not caused by deposits). The exact description was not provided, but this could have been a manufacturing defect or some induced irregularity due to lens wear or lens handling.

6.4 SAFETY

The safety evaluations performed during this study consisted of adverse event documentation, slit lamp examination, and assessment of study-lens-corrected visual acuity.

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6.4.1 ADVERSE EVENTS

For the purposes of this study, the term adverse event was used as a general term that encompasses the more specific terms of unanticipated adverse device effects, serious adverse events, ocular adverse events, and atypical clinical findings that may occur during a clinical study.

6.4.1.1 Unanticipated Adverse Device Effects

An unanticipated adverse device effect was defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects.

No subject treated during the study experienced an unanticipated adverse device effect.

6.4.1.2 Serious Adverse Events (SAEs)

A serious adverse event was defined as any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

During this study, there were no serious adverse events reported.

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6.4.1.3 Ocular Adverse Events

Ocular adverse events include, but are not 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. In addition, adverse events include slit lamp findings and symptoms, problems, or complaints that require treatment, including temporary or permanent discontinuation of lens wear, to maintain ocular health.

In this study there was only one reported ocular adverse event in any of the four treatment groups. This occurred in the 9464X group and was due to the subject (#4439) getting paint flakes in her eyes just prior to the last scheduled study visit. This resulted in trace bulbar hyperemia and trace palpebral conjunctiva irritation, as well as some corneal infiltrates. The investigator classified the severity of the adverse event as mild. Refer to Appendix B for a more detailed case history for this subject.

Listings 3.1 through 3.4 provide a summary of the adverse events in this study. As noted above, only the 9464X group had a reported adverse event.

No subject in any of the four treatment groups experienced a sight-threatening event, iritis, corneal infiltrate, ulcer, ocular infection, or two-grade change in corneal neovascularization.

6.4.1.4 Atypical Clinical Findings

Atypical clinical findings are adverse events thought possibly related to the use of investigational products which are not typically encountered in routine clinical use of marketed contact lens care products. Examples would include, but are not limited to, contact dermatitis, an unacceptable taste in the mouth/nausea after use of the product, and discoloration or permanent distortion of contact lenses.

There were no atypical clinical findings reported during this study.

6.4.1.5 Findings Requiring Treatment

Investigators could have chosen one of five actions when treating a significant occurrence:

1) lens wear or study regimen temporarily discontinued; 2) treatment with prescription

medication; 3) re-challenge with the study drops; 4) no treatment; or 5) some other treatment not previously listed. As noted in Section 6.4.1.3 above, only one subject required treatment, and this consisted only of cessation of lens wear and replacement of the study lenses with new lenses. No other therapy was undertaken.

6.4.2 SLIT LAMP EXAMINATION FINDINGS

At each study visit, subjects were evaluated by slit lamp examination for six parameters: corneal edema, corneal neovascularization, corneal staining, bulbar hyperemia, palpebral conjunctival observations, and other complications. The classification of slit lamp observations was performed as detailed in Appendix C. Findings were graded on a scale of 0 to 4 (none, trace, mild, moderate, severe).

For the intent-to-treat population, Tables 22.1 through 22.6 present the results for all six categories of slit lamp findings by treatment group and by visit based on the maximum reported severity grade for the two eyes per subject for each visit. There were no statistically significant differences among the four treatment groups for the proportion of subjects with any grade of slit lamp finding for any of the six categories of slit lamp evaluation. Overall, there was a low incidence rate for any category of slit lamp finding during the study. Throughout the study, there were no reports of any moderate or severe findings (which would be considered clinically significant). All findings were either trace or mild in severity. The most frequently reported findings were corneal neovascularization, corneal staining, bulbar hyperemia, and palpebral conjunctival observations. However, the rates reported during the study were not substantially different from those reported at baseline, indicating little induced change as a result of study participation by the subjects. In fact, for corneal staining, the reported rates at Day 30 were actually considerably lower than at baseline for all but the (b)(4) treatment arm. This general reduction in corneal staining may have been due to the rewetters keeping the contact lenses more hydrated and reducing the punctuate staining that can occur secondary to lens dehydration during wear.

For the category of corneal neovascularization, examination of Table 22.2 reveals that for all four groups the reported rate of findings at Days 7 and 30 are very nearly the same as their values at baseline. This generally reflects the fact that experienced contact lens wearers may

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already have some level of neovascularization due to chronic low-grade corneal hypoxia caused solely by wear of the contact lenses, and not due to other factors. None of the findings in this category exceeded trace severity at any timepoint.

For the category of corneal staining (Table 22.3), the results indicate that there were already present some notable levels of trace staining at baseline, but there were no reports of any staining of worse severity. By Day 7, the incidence of corneal staining had noticeably decreased for all four treatment groups, and by the Day 30 visit, continued to decrease even further for all but the (b)(4). At this visit, the (b)(4) had the same incidence as at baseline. As noted above, this reduction in corneal staining may have been a function of increased contact lens hydration and/or corneal hydration secondary to rewetter use.

For bulbar hyperemia, all reported findings at baseline were of trace severity, and at all follow-up visits, the severity never exceeded the trace level (Table 22.4). At Day 30, the incidence rates remained very similar to baseline for all groups except the (b)(4), which rose to 30.4% (7/23) from 20.8% (5/24) at baseline, while the 9464X and REFRESH groups decreased slightly from baseline.

The findings for palpebral conjunctival observations mirror those for the corneal neovascularization category, i.e., the incidence rates at baseline are generally reflective of a history of contact lens wear. Lens wear of itself often induces some changes in the superior tarsal conjunctiva, so it is not unusual that experienced lens wearers would have some of these findings at baseline. In this case, all of the baseline findings were of trace severity, and remained so throughout the study for all visits for all four groups. At Day 30, the incidence rates were quite similar to the baseline values for all four groups with the exception of the (b)(4) which demonstrated nearly a 10% increase in the incidence of trace reports. However, given that all reports were of trace severity, this probably does not indicate a truly clinically significant change.

A separate analysis of slit lamp findings by FDA lens material group was not conducted for this study for two reasons: 1) the lens distribution of Group 1 and Group 4 materials was virtually identical within all four treatment groups, and 2) the relatively small sample sizes of each treatment group would be reduced even further (by half) in order to analyze the

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results by lens material group. Evaluation of such small numbers would be of limited statistical validity. Given that there were so few positive slit lamp findings in this study and that most reports were of trace severity, there would be little or no value in such a sub-analysis in trying to determine if there were any lens material-related slit lamp findings.

6.4.3 STUDY LENS CORRECTED VISUAL ACUITY

Tables 23.1.1 through 23.4.2 present the results by eye for baseline and final visual acuity with contact lenses for the four treatment groups, for both completed and discontinued subjects. It can be seen that most of the subjects had a final visual acuity at least equal to their baseline visual acuity. With regard to clinically significant loss of two or more lines of lens-corrected acuity, there were two eyes (b)(4), no eyes (0/46, 0.0%) in the 9464X group, two eyes (b)(4), and one eye (1/46, 2.2%) in the REFRESH group with this level of acuity loss. Table 24 presents the distribution of subjects with changes in visual acuity from baseline (gain or loss) at the final study evaluation. There was only one subject (#4147) in the (b)(4) who experienced a bilateral loss of two or more lines of best corrected acuity, which occurred at Day 7. Provided in Listing 4 is the information on those subjects who lost two or more lines of lens-corrected visual acuity at any time during the study. Subjects with clinically significant decreases in lens-corrected visual acuity are presented in more detail in Appendix D.

There were also occurrences of gains in final lens-corrected visual acuity. There was one eye (1/48, 2.1%) in the (b)(4) that gained two lines of lens-corrected acuity. All other gains were for one line of acuity, with 9 eyes (9/48, 18.8%) in the (b)(4), 10 eyes (10/46, 21.7%) in the 9464X group, 9 eyes (9/48, 18.8%) in the (b)(4), and 8 eyes (8/46, 17.4%) in the REFRESH group.

6.4.4 TREND ANALYSIS PROFILES

Trend analysis profiles for the four treatment groups are presented in Tables 25.1 through 25.4. Key safety data were evaluated in order to determine if any obvious trends were occurring in the populations being treated with regard to the number of eyes being

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discontinued from the study, the number of adverse events occurring, the number of reports of moderate and severe slit lamp examination findings, and the number of missed visits.

Based on these profiles, there were no differences among the four treatment groups in the number of eyes discontinued from the study. Each group had one subject that was discontinued from the study. In terms of adverse events, there was only one reported during the study and that was in the 9464X group for a non-regimen-related cause. The slit lamp findings were fairly uniformly distributed across all four groups, and there were no occurrences in any group of slit lamp findings worse than mild in severity. In terms of study visits, the number of missed visits was very similar across all four groups, with only one missed visit in the 9464X group and one missed visit in the REFRESH group.

Overall, the trend analysis profiles indicate that there are no notable differences in any of the evaluated parameters for all four treatment groups.

7.0 DISCUSSION

Based on the results of this study, the three test rewetter formulations and the REFRESH rewetter solution were determined to be generally comparable to one another in terms of overall clinical performance. There were only a few occurrences of statistically significant differences in lens wearing comfort, symptoms of discomfort, vision quality, perceived lens wearing time, tear break-up time, or product acceptability. There were no significant differences in objective slit lamp findings or the reported rates of adverse events, complications, or effects on contact lens-corrected visual acuity.

Mean end-of-day comfort scores did not show any statistically significant differences by either among-group or pairwise comparison analyses. For the assessment of the change in lens wearing comfort immediately following instillation of the drops compared to baseline comfort, there also were no statistically significant differences between the test rewetters and the control. As well, for the rating of the cushioning effect of the drops immediately after instillation, there was not a significant among-group difference at either follow-up timepoint. When asked to rate lens wearing comfort right after drop instillation to that immediately before the drops were instilled, there was not a significant among-group difference at Day 7,

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but there was a significant among-group difference at Day 30. The REFRESH group had significantly better performance in this regard than the three investigational rewetter groups.

Ratings of the duration of the comfort effect following drop instillation revealed no statistically significant among-group differences at either Day 7 or Day 30, but the REFRESH group had the highest percentage of subjects reporting duration of effect greater than two hours at both these visits.

Drop usage rates per day were similar during the study, with no statistically significant among-group differences. Formulation (b)(4) had the highest usage rates at both Days 7 and 30, while (b)(4) had the lowest rate at Day 7 and (b)(4) had the lowest rate at Day 30.

Symptoms of discomfort were generally comparable across the four groups and were not statistically significantly different. The most often-reported symptoms were in the categories of blurry vision, dry eye feeling, and increased lens awareness, but there were very few reports overall that exceeded mild in severity.

Changes in vision quality from baseline were similar for all four groups and were not statistically significantly different at any visit. Changes from baseline in end-of-day vision quality also revealed no significant differences among the four groups. When asked to rate the effect of the drops on quality of vision within a few minutes after drop usage, there was a statistically significant among-group difference at Day 30, with REFRESH significantly better than the (b)(4), but not significantly different from the (b)(4) group. Interestingly, when subjects were asked to estimate how long the change in (improved) quality of vision persisted following drop usage, the (b)(4) formulation had the longest mean perceived duration of effect and (b)(4) had the shortest perceived duration at both Day 7 and Day 30.

With regard to perceived changes in lens wearing time compared to baseline, there were no statistically significant among-group differences for the four rewetters.

Assessment of product acceptability at the conclusion of the study indicated that for effect of the rewetter drops on overall vision quality, there was a significant difference among the four groups, with REFRESH being significantly better than (b)(4), but not significantly different

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from 9463X or 9464X. Overall lens wearing comfort as assessed at the end of the study also revealed a significant difference among the four groups, with REFRESH being significantly better than (b)(4), but not significantly different from 9464X. However, for rating of end-of-day comfort at study end compared to end-of-day comfort just before starting the study, there were no significant differences among the four groups.

When asked to compare their assigned study rewetter to their pre-study commercial rewetter and to express a preference, there was not a significant among-group difference. The (b)(4) group had the highest percentage of subjects who said that it was definitely better than their pre-study rewetter, while the (b)(4) had the highest percentage of subjects who said that it was definitely worse than their pre-study rewetter. Given that there was a rather wide distribution of commercial brands of pre-study rewetters, no attempt was made to analyze for a link of these outcomes to a particular brand of pre-study rewetter. When asked if they would continue to use their assigned drops if commercially available, there was a statistically significant among-group difference, with the REFRESH group having a significantly higher percentage of YES responses than the (b)(4), but not significantly different than the (b)(4).

Safety measures indicate that there was very little difference among the four products in terms of their safety profiles and there were no statistically significant differences among them for any category of slit lamp findings. For the category of corneal staining, there was an improvement from baseline for three of the four groups throughout the study, indicating that the additional lens hydration provided by the rewetter drops may have alleviated some signs of corneal dryness due to lens dehydration that otherwise may occur during lens wear. Reports of clinically significant decreases in lens-corrected visual acuity were few and were generally comparable across the four treatment groups.

One factor that must be kept in mind regarding a study of this type is that many of the outcome variables are based upon subjective responses by the study participants rather than upon objective measures as determined by the investigators. Given that individual subjects may well respond differently on subjective rating scales for a similar level of input, there is

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some inherent variability in these types of measures compared to measures of visual acuity, corneal staining, etc. which generally have more uniform and standardized grading scales.

8.0 CONCLUSION

The results of this study indicate that there were few statistically significant differences among the four tested products, although the REFRESH control product tended to have the best overall performance as a contact lens rewetter, followed closely by formulation 9464X. Again, while not statistically significantly different for most measures, the other two investigational formulations had somewhat lower performance as measured by the parameters evaluated in this study. Formulation (b)(4) generally had the lowest overall performance of all four rewetters evaluated. While there were some slight variations in performance attributes across the four groups, all four products in this study were demonstrated to be safe and effective for rewetting soft contact lenses during wear. Of the three investigational rewetter solutions, formulation (b)(4) generally had the best performance and was most nearly comparable to the REFRESH control product. Because of its overall performance relative to the REFRESH control, formulation (b)(4) is the recommended formula of choice to pursue for marketing clearance.

9.0 REFERENCES

None

10.0 APPENDICES

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APPENDIX A

SCHEDULE OF VISITS AND PROCEDURES

Study Period	Baseline	Day 7	Day 30
Procedures to Be Performed			
Informed Consent Form and Bill of Rights for Experimental Subjects ^a	X		
1. Subject Qualifications	X		
2. Demography	X		
3. Lens Wear History	X		
4. Pre-study Lens Care History	X		
5. Lens Wearing Time	X	X	X
6. Medications	X	X	X
7. Visual Acuity with Study Lenses	X	X	X
8. Lens Wear Comfort	X	X	X
9. Symptoms of Discomfort	X	X	X
10. Overall Subjective Vision Quality	X	X	X
11. Slit Lamp Examination	X	X	X
12. Tear Break-up Time	X	X	X
13. Lens Fit Quality	X	X	X
14. Adverse Events	X	X	X
15. Subject Status		(X)	X
16. General Comments	(X)	(X)	(X)
17. Product Acceptability		X	X
18. Exit Status		(X)	X

X = required

(X) = only if needed

^a The Bill of Rights for Experimental Subjects is only required for sites located in California.

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APPENDIX B

ADVERSE EVENT CASE HISTORIES

(b)(4)

Subject 4439, a 26-year-old white female with 10 years of previous contact lens wear experience and no significant history of contact lens difficulties, presented on Day 28 of the study complaining of red eyes and some discomfort of the lenses. Paint flakes had recently gotten into the subject's eyes. At the examination, visual acuity with the lenses in place was 20/20 OU. In the slit lamp examination, the investigator noted trace bulbar hyperemia and trace findings for the upper and lower palpebral conjunctiva OU, along with some small corneal infiltrates OS and the presence of some paint flakes on the front surface of the OD lens. There were no other remarkable slit lamp findings. The investigator attributed the findings to environmental irritation caused by the paint, and graded the severity of the adverse event as mild. The patient was exited from the study at this point as having completed the study (since this visit was within the Day 30 visit window) and given new contact lenses, but was not placed on any medications. The subject was followed by the investigator for another 2 weeks for resolution. At the last visit, the investigator noted that there was still trace palpebral conjunctival irritation OU, with some trace corneal infiltrates OS which she believed were resolving, but there were no other sequelae. Contact lens-corrected visual acuity was still 20/20 OU with the new lenses. No further action was taken, and the subject was instructed to contact the investigator's office if any further problems developed.

APPENDIX C

CLASSIFICATION OF SLIT LAMP OBSERVATIONS

The following slit lamp classification system was used to evaluate subjects during the study:

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.

GRADE

- 0 - NONE Normal transparency
 - a. No epithelial or sub-epithelial haziness
 - b. No microcysts
 - c. No stromal cloudiness

- 1 - TRACE a. Barely discernable localized epithelial or subepithelial haziness and/or
 - b. 1 to 20 microcysts and/or
 - c. barely discernable localized stromal cloudiness

- 2 - MILD a. Faint but definite localized or generalized epithelial or subepithelial haziness and/or
 - b. 21-50 microcysts and/or
 - c. Faint but definite localized or generalized stromal cloudiness

- 3 - MODERATE a. Significant localized or generalized epithelial or subepithelial haziness and/or
 - b. 51-100 microcysts and/or
 - c. Significant localized or generalized stromal cloudiness

- 4 - SEVERE a. Definite widespread, epithelial cloudiness giving dull glass appearance to cornea or numerous coalescent bullae (Note the number and location of bullae) and/or
 - b. >100 microcysts or bullae and/or
 - c. Definite widespread, stromal cloudiness, or numerous striae (Note the number and location of striae or folds)

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B. CORNEAL NEOVASCULARIZATION

Maximal corneal vascularization should be reported according to the following scale:

GRADE

- 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

The depth and location of vessel penetration was to be reported as follows:

DEPTH:

- Superficial
- Stromal

LOCATION:

- Nasal Temporal
- Inferior Superior
- Circumferential Other (describe)

C. CORNEAL STAINING

Maximal corneal staining should be reported according to the following scale:

GRADE

- 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

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- 3 - MODERATE Dense, coalesced staining up to 2 mm in diameter
 - a. Corneal abrasion
 - b. Foreign body track

- 4 - SEVERE Dense, coalescent staining >2 mm in diameter or full thickness abrasion

LOCATION:

Nasal	Temporal
Inferior	Superior
Central	

NOTE: recurrent erosion and corneal ulceration should be recorded under OTHER COMPLICATIONS

D. BULBAR HYPEREMIA

Maximal limbal and bulbar hyperemia should be recorded on a 5-point scale as follows:

GRADE

- 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 the maximal conjunctival response should be documented according to the following scale:

GRADE

- 0 - NONE Uniform satin appearance of conjunctiva
- 1 - TRACE Elevation of the small normal papillae (≤0.5mm) with slight injection of palpebral conjunctiva

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- 2 - MILD Mild or scattered papillae/follicles >0.5mm but <1mm in diameter
- 3 - MODERATE a. Significant papillae/follicles <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 in diameter
- b. Staining of the top of more than one papilla

The conjunctival response should be recorded for each of the four lid areas:

Upper Lid

Lower Lid

Superior tarsal conjunctiva
 Middle tarsal conjunctiva
 Inferior (lid margin region) tarsal conjunctiva

Palpebral conjunctiva of lower lid

F. OTHER FINDINGS

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, epidemic keratoconjunctivitis (EKC), corneal ulcers, iritis, lens adhesion, and recurrent erosion. The complication should be identified according to the following generic scale. Example provided for infiltrates, but the concept is applicable to all findings:

GRADE

- 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 findings such as marked infiltrates with overlying staining

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APPENDIX D**SUBJECTS WITH CLINICALLY SIGNIFICANT CHANGES IN CORRECTED VISUAL ACUITY**

(b)(4)

Subject **4147**, a 53-year-old white male, was reported with a two-line loss of acuity OD and a 3-line loss of acuity OS at the Day 7 visit. Visual acuity was 20/40 OU compared to 20/25 OD and 20/20 OS at baseline. The subject reported that he had accidentally slept in his standard daily wear lenses the night before. The slit lamp examination revealed mild corneal staining OU with trace bulbar hyperemia OU. The decrease in acuity was likely due to the unintended overnight wear of the lenses. The subject was instructed to avoid sleeping in his lenses and to maintain his daily wear routine. However, the subject elected to discontinue his participation in the study due to discomfort and there are no follow-up data after this visit.

(b)(4)

There were no subjects in this group who experienced a loss of two or more lines in contact lens-corrected visual acuity during the study.

(b)(4)

Subject **1407**, a 38-year-old white female, was reported with a loss of two lines of acuity in the left eye at Day 7 (from 20/20 to 20/30) and a two-line loss of acuity in the right eye at Day 30 (from 20/20 to 20/30). For both visits, there are no indications of any adverse slit lamp findings or other complications that would account for this change. It is possible that the decreases were due to some problems with the lenses such as deposits or something similar, but these are not noted. The left eye acuity returned to the baseline value of 20/20 at the Day 30 visit. It is not known if the right eye acuity improved following the subject's exit from the study as no further data are available.

Subject **4143**, a 31-year-old white female, was reported with a loss of two lines of acuity in the right eye at Day 30 (from 20/20 at baseline to 20/30). At this visit, the slit lamp examination revealed trace corneal neovascularization OU, trace changes in the palpebral conjunctiva OU, and trace circumferential limbal epithelial hypertrophy OU. The investigator attributed all of these findings to the contact lenses, but there is no comment on the supposed cause of the decreased acuity in the right eye.

REFRESH Group

Subject **1402**, a 29-year-old white female, presented at the Day 7 visit with a two-line reduction in acuity from 20/20 at baseline to 20/30. There were no remarkable slit lamp findings at this visit, and the only notable finding was a report of symptomatic mild itching OU. The cause of the decreased acuity is unknown, but might have been somehow related to the reported itching (e.g., repeated rubbing of the eyes could have distorted her vision).

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Subject **3429**, an 18-year-old white male, was reported with a loss of two lines of acuity OS (from 20/20 to 20/30) at Day 7 and a three-line loss of acuity OS (from 20/20 to 20/40) at Day 30. There were no abnormal slit lamp findings or symptoms, but inspection of the contact lens for the left eye at Day 30 revealed that it had poor surface quality and a new lens was dispensed. As this was the last study visit, no further data are available, but it is presumed that the acuity improved following lens replacement.

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11.0 TABLES AND LISTINGS

**Table 1
Subject Disposition**

	(b)(4)	9464X	(b)(4)	REFRESH	TOTAL
Intent-to-treat [a]					
Enrolled				23	94
Completed		22 (95.7%)		22 (95.7%)	90 (95.7%)
Discontinued:		1 (4.3%)		1 (4.3%)	4 (4.3%)
Not Regimen Related		1 (4.3%)		0 (0.0%)	2 (2.1%)
Regimen Related		0 (0.0%)		1 (4.3%)	2 (2.1%)
Findings of Uncertain Etiology		0 (0.0%)		0 (0.0%)	0 (0.0%)

[a] Modified Intent-to-Treat population – including all randomized subjects who received the assigned treatment at least once.

Table 2
Number (Percent) of Subjects Included in Analyses

	(b)(4)	9464X	(b)(4)	REFRESH	TOTAL
Intent-to-Treat Population [a]	(b)(4)	23 (24.5%)	(b)(4)	23 (24.5%)	94 (100.0%)
Per Protocol Population [b]	(b)(4)	23 (25.3%)	(b)(4)	22 (24.2%)	91 (100.0%)

[a] Modified Intent-to-Treat population - Including all randomized subjects who received the assigned treatment at least once.

[b] Per protocol population excludes the randomized subjects who did not meet the evaluation criteria at any timepoint.

Table 3
Demographics
(Intent-to-Treat Population)

	9464X (N = 23)	(b)(4)	REFRESH (N = 23)	TOTAL (N = 94)	P-value[a]
Age (years)					
N	23		23	94	0.9074
Mean	37.8		37.1	38.3	
Std	13.63		11.84	12.78	
Median	35.0		35.0	36.0	
Min	18.0		18.0	18.0	
Max	69.0		71.0	71.0	
Sex					
N	23		23	94	0.3239
Female	17 (73.9%)		13 (56.5%)	64 (68.1%)	
Male	6 (26.1%)		10 (43.5%)	30 (31.9%)	
Race					
N	23		23	94	0.9664
White	19 (82.6%)		18 (78.3%)	77 (81.9%)	
Non-White	4 (17.4%)		5 (21.7%)	17 (18.1%)	
Black	3 (13.0%)		3 (13.0%)	10 (10.6%)	
Asian	1 (4.3%)		0 (0.0%)	3 (3.2%)	
Hispanic	0 (0.0%)		2 (8.7%)	4 (4.3%)	
Other	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Iris Color					
N	23		23	94	0.3818
Dark (Brown)	12 (52.2%)		7 (30.4%)	38 (40.4%)	
Light	11 (47.8%)		16 (69.6%)	56 (59.6%)	
Blue	6 (26.1%)		5 (21.7%)	29 (30.9%)	
Green	1 (4.3%)		2 (8.7%)	8 (8.5%)	
Hazel	4 (17.4%)		9 (39.1%)	19 (20.2%)	
Other	0 (0.0%)		0 (0.0%)	0 (0.0%)	

[a] P Value for among-regimen comparison. Age was analyzed using 1-way ANOVA. Sex, race (white vs. Non-white) and eye color (dark vs. light) were analyzed using Pearson's chi-square test or Fisher's exact test.

Table 4
Prestudy Lens Care and Study Lens Information
(Intent-to-Treat Population)

	9464X (N = 23)	REFRESH (N = 23)	TOTAL (N = 94)	P-value[a]
Prestudy Rewetter Usage	(b)(4)	(b)(4)		
N	23	23	94	0.3424
Clerz Plus	1 (4.3%)	3 (13.0%)	5 (5.3%)	
OPTI-FREE Express	4 (17.4%)	5 (21.7%)	18 (19.1%)	
AMO Complete	2 (8.7%)	0 (0.0%)	10 (10.6%)	
Refresh Contacts	4 (17.4%)	6 (26.1%)	14 (14.9%)	
ReNu Multi-Plus Drops	3 (13.0%)	5 (21.7%)	15 (16.0%)	
Other	9 (39.1%)	4 (17.4%)	32 (34.0%)	
Prestudy Product Usage				
N	23	23	94	0.4486
COMPLETE	6 (26.1%)	3 (13.0%)	17 (18.1%)	
ReNu Multiplus	9 (39.1%)	6 (26.1%)	26 (27.7%)	
OPTI-FREE EXPRESS	7 (30.4%)	12 (52.2%)	42 (44.7%)	
UltraCare	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	1 (4.3%)	2 (8.7%)	9 (9.6%)	
FDA Lens Group				
N	23	23	94	0.9934
Group 1	12 (52.2%)	11 (47.8%)	47 (50.0%)	
Group 4	11 (47.8%)	12 (52.2%)	47 (50.0%)	

[a] P Value for among-regimen comparison using the Pearson's chi-square test or Fisher's exact test.

Table 5.1
Lens Wear Comfort at End-of-Day
Raw Values at Each Scheduled Visit
(Per Protocol Subjects)

Visit	9464X (N=23)	(b)(4)	REFRESH (N=22)
Baseline	N 23 Mean 7.5 SD 1.54 Median 8 Min 5 Max 10	(b)(4)	22 7.2 1.71 7 5 10
Day 7	N 22 Mean 7.8 SD 1.87 Median 8 Min 5 Max 10	(b)(4)	22 7.6 1.59 8 3 10
Day 30	N 22 Mean 8.2 SD 1.32 Median 8 Min 5 Max 10	(b)(4)	21 7.4 1.89 7 4 10

Note: Scale for comfort score is from 0 to 10 (from 'lens cannot be tolerated' to 'lens cannot be felt').
 The average score for OD and OS is used for analysis.

Table 5.2
Lens Wear Comfort at End-of-Day
Baseline and Change from Baseline at Each Scheduled Visit
(Per Protocol Subjects)

Visit	9464X (N=23)	REFRESH (N=22)	9464X vs. REFRESH P-value Difference 95% CI [a]
Baseline	N	(b)(4)	(b)(4)
	Mean	23	0.8350
	SD	7.5	0.3
	Median	1.54	(-0.8, 1.5)
	Min	8	
Day 7	Max	5	
	N	10	
	Mean	22	0.9793
	SD	0.4	0.2
	Median	1.25	(-1.1, 1.4)
Day 30	Min	0	
	Max	-2	
	N	3	
	Mean	22	0.7836
	SD	0.7	0.4
Baseline	Median	1.17	(-0.9, 1.8)
	Min	0	
	Max	-1	
	N	3	
	Mean	22	
Day 7	SD	0.3	
	Median	1.76	
	Min	0	
	Max	-4	
	N	4	

[a] For pairwise comparison, P-value and 2-sided simultaneous 95% CI are based on Dunnett's procedure using 2-way ANOVA model with fixed effects of regimen and site.

Note: Scale for comfort score is from 0 to 10 (from 'lens cannot be tolerated' to 'lens cannot be felt'). The average score for OD and OS is used for analysis.

Table 5.3
Lens Wear Comfort at End-of-Day
Pairwise Comparison of Investigational Rewettters for Baseline and Change from Baseline at Each Scheduled Visit
(Per Protocol Subjects)

	(b)(4)
Baseline	
Day 7	
Day 30	

[a] P-value for between-regimen comparison and 95% confidence interval on the difference are based on the least-square means using the 2-way ANOVA model with fixed effects of regimen and site, Type III sum of squares and error term pooled across 4 regimens.

Note: Scale for comfort score is from 0 to 10 (from 'lens cannot be tolerated' to 'lens cannot be felt'). The average score for OD and OS is used for analysis.

Table 6.1
Rating of Lens Comfort Immediately Post Drop Installation
Raw Values at Each Scheduled Visit
(Per Protocol Subjects)

Visit	(b)(4)	9464X (N=23)	(b)(4)	REFRESH (N=22)
Baseline				
		23		22
Mean		8.7		9.0
SD		1.32		1.02
Median		9		9
Min		7		7
Max		10		10
Day 7				
		22		22
Mean		8.8		9.1
SD		1.27		1.48
Median		9		10
Min		6		5
Max		10		10
Day 30				
		22		21
Mean		9.3		9.2
SD		0.83		1.09
Median		10		10
Min		8		7
Max		10		10

Note: Scale for comfort score is from 0 to 10 (from 'lens cannot be tolerated' to 'lens cannot be felt').
 The average score for OD and OS is used for analysis.

Table 6.2
Rating of Lens Comfort Immediately Post Drop Installation
Baseline and Change from Baseline at Each Scheduled Visits
(Per Protocol Subjects)

Visit	9464X (N=23)	REFRESH (N=22)	9464X vs. REFRESH P-value Difference 95% CI [a]
Baseline	N	23	(b)(4)
	Mean	8.7	0.7157
	SD	1.32	-0.3
	Median	9	(-1.1, 0.5)
	Min	7	
Day 7	Max	10	
	N	22	0.9760
	Mean	0.1	0.2
	SD	1.65	(-1.0, 1.4)
	Median	0	
Day 30	Min	-4	
	Max	3	
	N	21	0.9320
	Mean	0.6	0.2
	SD	1.38	(-0.9, 1.4)
	Median	0	
	Min	-2	
	Max	3	

[a] For pairwise comparison, P-value and 2-sided simultaneous 95% CI are based on Dunnett's procedure using 2-way ANOVA model with fixed effects of regimen and site.

Note: Scale for comfort score is from 0 to 10 (from 'lens cannot be tolerated' to 'lens cannot be felt'). The average score for OD and OS is used for analysis.

Table 6.3
Rating of Lens Comfort Immediately Post Drop Installation
Pairwise Comparison of Investigational Rewetters for Baseline and Change from Baseline at Each Scheduled Visit
(Per Protocol Subjects)

Baseline	(b)(4)
Day 7	
Day 30	

[a] P-value for between-regimen comparison and 95% confidence interval on the difference are based on the least-square means using the 2-way ANOVA model with fixed effects of regimen and site, Type III sum of squares and error term pooled across 4 regimens.

Note: Scale for comfort score is from 0 to 10 (from 'lens cannot be tolerated' to 'lens cannot be felt'). The average score for OD and OS is used for analysis.

Table 7
Rating of Cushioning Effect Immediately After Using Drops
Rated at Each Scheduled Visit
(Intent-to-treat Population)

Visit		(b)(4) 9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Day 7	N	22		23	0.7211
	Mean	8.45		8.35	
	SD	1.371		1.496	
	Median	8		8	
	Min	5		5	
	Max	10		10	
Day 30	N	22		21	0.3464
	Mean	8.18		8.71	
	SD	2.196		1.146	
	Median	8		9	
	Min	1		6	
	Max	10		10	

[a] P-values for among-regimen comparison using ANOVA.

Note: Cushioning rated on a scale of 0 to 10 with 0 = No real cushioning effect, 10 = Excellent cushioning effect; the average score for right and left eyes is used for analysis.

Table 8
Rating of Comfort After Using Drops versus Just Before Using Drops
Rated At Each Scheduled Visit
(Intent-to-treat Population)

Visit	Rating	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Day 7	N	22	23	0.0841
	Much Better	5 (22.7%)	7 (30.4%)	
	Somewhat Better	12 (54.5%)	11 (47.8%)	
	Same	4 (18.2%)	5 (21.7%)	
	Somewhat Worse	1 (4.5%)	0 (0.0%)	
	Much Worse	0 (0.0%)	0 (0.0%)	
Day 30	Missing	0 (0.0%)	0 (0.0%)	0.0079
	N	22	21	
	Much Better	5 (22.7%)	12 (57.1%)	
	Somewhat Better	13 (59.1%)	7 (33.3%)	
	Same	3 (13.6%)	2 (9.5%)	
	Somewhat Worse	1 (4.5%)	0 (0.0%)	
Much Worse	0 (0.0%)	0 (0.0%)		
Missing	0 (0.0%)	0 (0.0%)		

[a] Comparison among groups performed using Kruskal-Wallis test; the eye with the worse score is used for analysis.

For the outcomes at Day 30, the Wilcoxon 2-sample test was used to compare each of the treatment groups (9463X, 9464X, and 9467X) to the REFRESH control group. The p-values of the Wilcoxon tests are 0.0455, 0.0317 and 0.0012, respectively. REFRESH is significantly better than the other three treatment groups.

Table 9
Rating of Length of Comfort Effect After Using Drops
Rated At Each Scheduled Visit
(Intent-to-treat Population)

Visit	Rating	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Day 7	N	(b)(4)	(b)(4)	
	Less than 15 Minutes	22 1 (4.5%)	23 2 (8.7%)	0.8537
	15 to 30 Minutes	2 (9.1%)	2 (8.7%)	
	>30 to 60 Minutes	2 (9.1%)	1 (4.3%)	
	>60 Minutes to 2 Hours	5 (22.7%)	2 (8.7%)	
	>2 Hours	9 (40.9%)	13 (56.5%)	
Day 30	Not Needed for Additional Drops	3 (13.6%)	3 (13.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
	N	22	21	0.4169
	Less than 15 Minutes	0 (0.0%)	2 (9.5%)	
	15 to 30 Minutes	2 (9.1%)	2 (9.5%)	
	>30 to 60 Minutes	2 (9.1%)	1 (4.8%)	
>60 Minutes to 2 Hours	4 (18.2%)	4 (19.0%)		
>2 Hours	9 (40.9%)	11 (52.4%)		
Not Needed for Additional Drops	5 (22.7%)	1 (4.8%)		
Missing	0 (0.0%)	0 (0.0%)		

[a] Comparison among groups performed using Kruskal-Wallis test.

Table 10
Mean Number of Times Per Day Rewetter Drops were Used Since Last Visit
Rating at Each Scheduled Visit
(Intent-to-treat Population)

Visit		9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Day 7	N	22		23	0.7695
	Mean	3.27		3.30	
	SD	0.631		0.470	
	Median	3		3	
	Min	2		3	
Day 30	Max	5		4	
	N	22		21	0.2241
	Mean	3.14		3.48	
	SD	0.351		0.680	
	Median	3		3	
Min	3		3		
	Max	4		5	

[a] Among-regimen comparison performed using Kruskal-Wallis test.

Table 11.1
Number (Percent) of Subjects with Symptoms of Discomfort: Burning/Stinging
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Baseline	N	(b)(4)	(b)(4)	
	None	23 (100.0%)	23 (100.0%)	0.4047
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)		
Day 7	N	(b)(4)	(b)(4)	
	None	22 (100.0%)	23 (100.0%)	1.0000
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)		
Day 30	N	(b)(4)	(b)(4)	
	None	22 (100.0%)	21 (100.0%)	0.4122
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)		
Unscheduled [b]	N	(b)(4)	(b)(4)	
	None	3 (100.0%)	1 (100.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.2
Number (Percent) of Subjects with Symptoms of Discomfort: Blurry Vision
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	(b)(4)	9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Baseline	N		23 (100.0%)		23 (95.7%)	0.5675
	None		0 (0.0%)		1 (4.3%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 7	N		22 (100.0%)		23 (95.7%)	0.8124
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		1 (4.3%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 30	N		22 (100.0%)		21 (100.0%)	1.0000
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Unscheduled[b]	N		3 (100.0%)		1 (100.0%)	
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.3
Number (Percent) of Subjects with Symptoms of Discomfort: Dry Eye Feeling
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	(b)(4)	9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Baseline	N		23		23	0.2451
	None		17 (73.9%)		19 (82.6%)	
	Mild		5 (21.7%)		1 (4.3%)	
	Moderate		1 (4.3%)		3 (13.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 7	N		22		23	0.5302
	None		20 (90.9%)		21 (91.3%)	
	Mild		2 (9.1%)		0 (0.0%)	
	Moderate		0 (0.0%)		2 (8.7%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 30	N		22		21	0.5953
	None		22 (100.0%)		21 (100.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Unscheduled[b]	N		3		1	
	None		3 (100.0%)		1 (100.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.4
Number (Percent) of Subjects with Symptoms of Discomfort: Unusual Eye Secretions
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	(b)(4)	9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Baseline	N		23 (100.0%)		23 (100.0%)	1.0000
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 7	N		22 (100.0%)		23 (100.0%)	0.4113
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 30	N		22 (100.0%)		21 (100.0%)	1.0000
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Unscheduled[b]	N		3 (100.0%)		1 (100.0%)	
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.5
Number (Percent) of Subjects with Symptoms of Discomfort: Excessive Tearing
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Baseline	N	23 (100.0%)	23 (100.0%)	1.0000
	None	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Day 7	Missing	0 (0.0%)	0 (0.0%)	1.0000
	N	22 (100.0%)	23 (100.0%)	
	None	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Day 30	Severe	0 (0.0%)	0 (0.0%)	1.0000
	Missing	0 (0.0%)	0 (0.0%)	
	N	22 (100.0%)	21 (100.0%)	
	None	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
Unscheduled[b]	Moderate	0 (0.0%)	0 (0.0%)	1
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
	N	3 (100.0%)	1 (100.0%)	
	None	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
		0 (0.0%)	0 (0.0%)	

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.
 [b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.6
Number (Percent) of Subjects with Symptoms of Discomfort: Itching
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Baseline	N	23 (100.0%)	23 (100.0%)	1.0000
	None	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Day 7	Missing	0 (0.0%)	0 (0.0%)	0.5898
	N	22 (100.0%)	23	
	None	22 (100.0%)	22 (95.7%)	
	Mild	0 (0.0%)	1 (4.3%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Day 30	Severe	0 (0.0%)	0 (0.0%)	0.5326
	Missing	0 (0.0%)	0 (0.0%)	
	N	22 (100.0%)	21	
	None	22 (100.0%)	19 (90.5%)	
	Mild	0 (0.0%)	2 (9.5%)	
Unscheduled[b]	Moderate	0 (0.0%)	0 (0.0%)	1
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
	N	3 (100.0%)	1 (100.0%)	
	None	3 (100.0%)	0 (0.0%)	
Unscheduled[b]	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.
 [b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.7
Number (Percent) of Subjects with Symptoms of Discomfort: Increased Lens Awareness
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	(b)(4)	9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Baseline	N		23 (100.0%)		23 (100.0%)	0.4047
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 7	N		22 (100.0%)		23 (100.0%)	0.4113
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 30	N		22 (100.0%)		21 (100.0%)	0.4122
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Unscheduled[b]	N		3		1	
	None		2 (66.7%)		1 (100.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		1 (33.3%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.
 [b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.8
Number (Percent) of Subjects with Symptoms of Discomfort: Redness
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)

Visit	Severity	(b)(4)			
Baseline	N	24	23	24	23
	None	(100.0%)	(100.0%)	(100.0%)	(100.0%)
	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 7	N	24	22	24	23
	None	(95.8%)	(100.0%)	(100.0%)	(100.0%)
	Mild	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 30	N	23	22	23	21
	None	(100.0%)	(100.0%)	(95.7%)	(100.0%)
	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unscheduled[b]	N	0	3	0	1
	None		(66.7%)		(100.0%)
	Mild		0 (0.0%)		0 (0.0%)
	Moderate		1 (33.3%)		0 (0.0%)
	Severe		0 (0.0%)		0 (0.0%)

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.9
Number (Percent) of Subjects with Symptoms of Discomfort: Light Sensitivity
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	(b)(4)	9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Baseline	N		23 (100.0%)		23 (100.0%)	1.0000
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 7	N		22 (100.0%)		23 (100.0%)	1.0000
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 30	N		22 (100.0%)		21 (100.0%)	1.0000
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Unscheduled[b]	N		3 (100.0%)		1 (100.0%)	
	None		0 (0.0%)		0 (0.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 11.10
Number (Percent) of Subjects with Symptoms of Discomfort: Other
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Visit	Severity	(b)(4)	9464X (N = 23)	(b)(4)	REFRESH (N = 23)	P-value [a]
Baseline	N		23		23	0.7889
	None		22 (95.7%)		22 (95.7%)	
	Mild		1 (4.3%)		1 (4.3%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 7	N		22		23	0.2883
	None		19 (86.4%)		22 (95.7%)	
	Mild		3 (13.6%)		1 (4.3%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Day 30	N		22		21	0.5544
	None		22 (100.0%)		20 (95.2%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		1 (4.8%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		
Unscheduled[b]	N		3		1	
	None		3 (100.0%)		1 (100.0%)	
	Mild		0 (0.0%)		0 (0.0%)	
	Moderate		0 (0.0%)		0 (0.0%)	
	Severe		0 (0.0%)		0 (0.0%)	
Missing		0 (0.0%)		0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.
 [b] Pools data across all unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 12
Overall Subjective Vision Quality
Baseline and Change from Baseline at Each Scheduled Visit
(Intent-to-treat Population)

Visit	9464X (N=23)	(b)(4)	REFRESH (N=23)	P-value [a]
Baseline				
N	23		23	0.4795
Mean	8.96		8.89	
SD	0.976		0.953	
Median	9		9	
Min	7		7	
Max	10		10	
Day 7				
N	22		23	0.8757
Mean	-.05		-.07	
SD	0.999		1.368	
Median	0		0	
Min	-3		-4	
Max	2		2	
Day 30				
N	22		21	0.4383
Mean	-.16		-.43	
SD	0.864		1.087	
Median	0		0	
Min	-2		-3	
Max	2		2	

[a] P-values for among-regimen comparison using ANOVA.

Note: Vision Quality rated on a scale of 0 to 10 with 0 = Very poor, 10 = Excellent; the average score for right and left eyes is used for analysis.

Table 13
Subjective Vision Quality at End-of-Day
Baseline and Change from Baseline at Each Scheduled Visit
(Intent-to-treat Population)

Visit	9464X (N=23)	(b)(4)	REFRESH (N=23)	P-value [a]
Baseline	N 23 Mean 7.93 SD 1.479 Median 8 Min 5 Max 10	(b)(4)	23 7.54 1.405 8 5 10	0.6100
Day 7	N 22 Mean 0.20 SD 1.182 Median 0 Min -3 Max 2	(b)(4)	23 -.37 1.720 0 -7 2	0.3528*
Day 30	N 22 Mean -.25 SD 1.307 Median -0 Min -3 Max 2	(b)(4)	21 -.19 1.178 0 -2 2	0.8819

[a] P-values for among-regimen comparison using ANOVA.

The p-value with a "*" indicates that the interaction between regimen and site is significant with a p-value < 0.10.

Note: Vision Quality rated on a scale of 0 to 10 with 0 = Very poor, 10 = Excellent; the average score for right and left eyes is used for analysis.

Table 14
Rating of Effect on Quality of Vision After Using Drops At Each Scheduled Visit
 (Intent-to-treat Population)

Visit	Rating	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Day 7	N	(b)(4)	(b)(4)	
	Definitely Improved	22	23	0.1374
	Somewhat Improved	3 (13.6%)	4 (17.4%)	
	No Effect	11 (50.0%)	7 (30.4%)	
	Somewhat Decreased	7 (31.8%)	12 (52.2%)	
Day 30	Definitely Improved	1 (4.5%)	0 (0.0%)	
	Somewhat Improved	0 (0.0%)	0 (0.0%)	
	No Effect	0 (0.0%)	0 (0.0%)	
	Somewhat Decreased	0 (0.0%)	0 (0.0%)	
	Definitely Decreased	0 (0.0%)	0 (0.0%)	
[a] Comparison among groups performed using Kruskal-Wallis test.	N	22	21	0.0164
	Definitely Improved	3 (13.6%)	9 (42.9%)	
	Somewhat Improved	10 (45.5%)	8 (38.1%)	
	No Effect	9 (40.9%)	4 (19.0%)	
	Somewhat Decreased	0 (0.0%)	0 (0.0%)	
Definitely Decreased	0 (0.0%)	0 (0.0%)		
Missing	0 (0.0%)	0 (0.0%)		

For the outcomes at Day 30, the Wilcoxon 2-sample test was used to compare each of the treatment groups (9463X, 9464X, and 9467X) to the REFRESH control group. The p-values of the Wilcoxon tests are 0.3695, 0.0440 and 0.0007, respectively. REFRESH is significantly better than 9464X and 9467X, but not significantly different from 9463X.

Table 15
Average Length of Time (in minutes) Subjects Experienced a Change in Quality of Vision
By Rating of Improvement at Each Scheduled Visit
(Intent-to-treat Population)

Visit	9464X (N = 23)	(b)(4)	REFRESH (N = 23)
Subjects Rating Day 7	Quality 14 46.9 50.30 25 0 120	(b)(4)	11 52.2 56.36 20 0 120
Day 30	N 13 Mean 46.2 SD 44.68 Median 30 Min 0 Max 120	(b)(4)	17 51.2 51.37 60 0 120
Subjects Rating Day 7	Quality 1 5.0	(b)(4)	0
Day 30	N 5 Mean 5 SD 5 Median 5 Min 0 Max	(b)(4)	0

Table 16
 Rating of Lens Wearing Time Since Starting Study to Before Starting Study
 Rated At Each Scheduled Visit
 (Intent-to-treat Population)

Visit	Rating	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Day 7	N	(b)(4)	(b)(4)	
	Increased a Lot	22 0 (0.0%)	23 0 (0.0%)	0.8435
	Increased Somewhat	4 (18.2%)	3 (13.0%)	
	Not Changed	18 (81.8%)	19 (82.6%)	
	Decreased Somewhat	0 (0.0%)	0 (0.0%)	
	Decreased a Lot	0 (0.0%)	1 (4.3%)	
	Missing	0 (0.0%)	0 (0.0%)	
Day 30	N	(b)(4)	(b)(4)	
	Increased a Lot	22 0 (0.0%)	21 0 (0.0%)	0.4568
	Increased Somewhat	4 (18.2%)	2 (9.5%)	
	Not Changed	18 (81.8%)	19 (90.5%)	
	Decreased Somewhat	0 (0.0%)	0 (0.0%)	
	Decreased a Lot	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	

[a] Comparison among groups performed using Kruskal-Wallis test.

Table 17
Tear Break-up Time (in Seconds) with Lenses On
Reported at Each Visit
(Intent-to-treat Population)

Visit	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Baseline	N	23	0.2121*
	Mean	13.17	
	SD	10.080	
	Median	10	
	Min	3	
Day 7	Max	40	
	N	22	0.2506
	Mean	14.36	
	SD	9.820	
	Median	10	
Day 30	Min	5	
	Max	40	
	N	22	0.0044*
	Mean	16.23	
	SD	10.506	
	Median	13	
	Min	3	
	Max	40	

[a] P-values for among-regimen comparison using ANOVA. The p-value with a "*" indicates that the interaction between regimen and site is significant with a p-value < 0.10.

For the outcomes at Day 30, the Dunnett's procedure of ANOVA was used to compare each of the treatment groups (9463X, 9464X, and 9467X) to the REFRESH control group. The p-values are 0.8500, 0.8152, and 0.0446, respectively. REFRESH is significantly better than 9467X, but not significantly different from 9463X or 9464X.

Table 18
Rating of Overall Effect of Drops on Vision Quality
Rated at Study Exit for Overall Study Experience Compared to Before Study
(Intent-to-treat Population)

Item	Rating	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Vision Quality	N	(b)(4)	(b)(4)	
	Definitely Improved	7 (31.8%)	6 (27.3%)	0.0155
	Somewhat Improved	9 (40.9%)	11 (50.0%)	
	No Effect	6 (27.3%)	5 (22.7%)	
	Somewhat Worse	0 (0.0%)	0 (0.0%)	
Definitely Worse	0 (0.0%)	0 (0.0%)		
Missing	0 (0.0%)	0 (0.0%)		

[a] Among regimen comparison performed using Kruskal-Wallis test.

The Wilcoxon 2-sample test was used to compare each of the treatment groups (9463X, 9464X, and 9467X) to the REFRESH control group. The p-values of the Wilcoxon tests are 0.2381, 1.0000, and 0.0009, respectively. REFRESH is significantly better than 9467X, but not significantly different from 9463X or 9464X.

Table 19
Rating of Overall Effect of Drops on Overall Comfort, End-of-Day Comfort and Lens Wear Comfort
Rated at Study Exit for Overall Study Experience Compared to Before Study
(Intent-to-treat Population)

Item	Rating	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Overall Comfort	N	22	22	0.0313
	Definitely Improved	7 (31.8%)	10 (45.5%)	
	Somewhat Improved	12 (54.5%)	10 (45.5%)	
	No Effect	2 (9.1%)	2 (9.1%)	
	Somewhat Decreased	1 (4.5%)	0 (0.0%)	
	Definitely Decreased	0 (0.0%)	0 (0.0%)	
End-of-day Comfort	Missing	0 (0.0%)	0 (0.0%)	
	N	22	22	0.0604
	Much Better	3 (13.6%)	3 (13.6%)	
	Somewhat Better	8 (36.4%)	12 (54.5%)	
	Same	11 (50.0%)	6 (27.3%)	
	Somewhat Worse	0 (0.0%)	1 (4.5%)	
Much Worse	0 (0.0%)	0 (0.0%)		
Wear Lenses Longer and More Comfortably	Missing	0 (0.0%)	0 (0.0%)	
	N	22	22	0.0113
	Definitely Agree	6 (27.3%)	10 (45.5%)	
	Somewhat Agree	7 (31.8%)	6 (27.3%)	
	Neither Agree/Disagree	7 (31.8%)	5 (22.7%)	
	Somewhat Disagree	2 (9.1%)	1 (4.5%)	
Definitely Disagree	0 (0.0%)	0 (0.0%)		
Missing	0 (0.0%)	0 (0.0%)		

(b)(4)

(b)(4)

[a] Among regimen comparison performed using Kruskal-Wallis test.

The Wilcoxon 2-sample test was used to compare each of the treatment groups REFRESH control group. For overall comfort, the p-values of the Wilcoxon tests are 0.0248, 0.3645, and 0.0104, respectively. REFRESH is significantly better than 9463X and 9467X, but not significantly different from 9464X. For lens wear comfort, the p-values of the Wilcoxon tests are 0.0311, 0.2191, and 0.0017, respectively. REFRESH is significantly better than 9463X and 9467X, but not significantly different from 9464X.

(b)(4)

Table 20
Rating of Rewetter Preference and Desire to Continue Using Drops
Rated at Study Exit
(Intent-to-treat Population)

Item	Rating	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Study Drops Compared to Pre-Study Drops	N	22	22	0.0841
	Definitely Better	7 (31.8%)	5 (22.7%)	
	Somewhat Better	6 (27.3%)	9 (40.9%)	
	Same	7 (31.8%)	7 (31.8%)	
	Somewhat Worse	2 (9.1%)	1 (4.5%)	
	Definitely Worse	0 (0.0%)	0 (0.0%)	
Drops Commercially Available - Use Them Regularly	Missing	0 (0.0%)	0 (0.0%)	
	N	22	22	0.0427
	Yes	13 (59.1%)	19 (86.4%)	
	No	3 (13.6%)	2 (9.1%)	
	Uncertainly	6 (27.3%)	1 (4.5%)	
Missing	0 (0.0%)	0 (0.0%)		

[a] Among regimen comparison performed using Kruskal-Wallis test for ordinal data and Fisher's Exact test for yes/no response.

For the use of drops if commercially available, the Fisher's Exact Test was used to compare each of the treatment groups (9463X, 9464X, and 9467X) to the REFRESH control group. The p-values from this test are 0.0582, 0.1062, and 0.0162, respectively. REFRESH is significantly different from 9467X, but not significantly different from 9463X or 9464X.

Table 21
Unscheduled Lens Replacement
Number (Percent) of Lenses in Each Category
(Intent-to-treat Population)

	9464X (N = 23)	REFRESH (N = 23)
Total Lens Replacements	0	1
Refractive change(s) - power, base curve, diameter, etc.		0 (0.0%)
Damage - torn, chopped, abraded, etc.		0 (0.0%)
Deposits		0 (0.0%)
Discoloration or change in tint color		0 (0.0%)
Loss		0 (0.0%)
Irritation (not due to damage)		0 (0.0%)
Bad edge		0 (0.0%)
Poor surface quality		1 (2.1%)
Requested by AMO (not end of study)		0 (0.0%)
Subject permanently discontinued		0 (0.0%)

Note: The percent is calculated using the total number of lenses (N x 2 + Total Lens Replacements) within each regimen as the denominator.

Table 22.1
Number (Percent) of Subjects with Slit Lamp Findings: Edema
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)

Slit Lamp Examination	Severity	All Subjects		P-value [a]
		9464X (N = 23)	REFRESH (N = 23)	
Baseline	N	23 (100.0%)	23 (100.0%)	1.0000
	None	0 (0.0%)	0 (0.0%)	
	Trace	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Day 7	Missing	0 (0.0%)	0 (0.0%)	
	N	22 (100.0%)	23 (95.7%)	0.3850
	None	0 (0.0%)	1 (4.3%)	
	Trace	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)		
Day 30	Missing	0 (0.0%)	0 (0.0%)	
	N	22 (100.0%)	21 (100.0%)	0.4122
	None	0 (0.0%)	0 (0.0%)	
	Trace	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)		
Unscheduled[b]	Missing	0 (0.0%)	0 (0.0%)	
	N	3	1	
	None	2 (66.7%)	1 (100.0%)	
	Trace	1 (33.3%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Includes all data from unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 22.2
Number (Percent) of Subjects with Slit Lamp Findings: Corneal Neovascularization
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)
All Subjects

Slit Lamp Examination	Severity	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Baseline	N	(b)(4)	(b)(4)	0.1088
	None	22 (95.7%)	18 (78.3%)	
	Trace	1 (4.3%)	5 (21.7%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Day 7	Missing	0 (0.0%)	0 (0.0%)	
	N	22	23	0.4139
	None	20 (90.9%)	18 (78.3%)	
	Trace	2 (9.1%)	5 (21.7%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)		
Day 30	Missing	0 (0.0%)	0 (0.0%)	
	N	22	21	0.1919
	None	21 (95.5%)	16 (76.2%)	
	Trace	1 (4.5%)	5 (23.8%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)		
Unscheduled[b]	Missing	0 (0.0%)	0 (0.0%)	
	N	3	1	
	None	3 (100.0%)	1 (100.0%)	
	Trace	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Severe	0 (0.0%)	0 (0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Includes all data from unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 22.3
Number (Percent) of Subjects with Slit Lamp Findings: Corneal Staining
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)

Slit Lamp Examination	Severity	9464X (N = 23)		REFRESH (N = 23)		P-value [a]
		N	(%)	N	(%)	
Baseline	None	19	(82.6%)	17	(73.9%)	0.2773
	Trace	4	(17.4%)	6	(26.1%)	
	Mild	0	(0.0%)	0	(0.0%)	
	Moderate	0	(0.0%)	0	(0.0%)	
	Severe	0	(0.0%)	0	(0.0%)	
Missing	0	(0.0%)	0	(0.0%)		
Day 7	None	20	(90.9%)	19	(82.6%)	0.5650
	Trace	2	(9.1%)	4	(17.4%)	
	Mild	0	(0.0%)	0	(0.0%)	
	Moderate	0	(0.0%)	0	(0.0%)	
	Severe	0	(0.0%)	0	(0.0%)	
Missing	0	(0.0%)	0	(0.0%)		
Day 30	None	21	(95.5%)	19	(90.5%)	0.5246
	Trace	1	(4.5%)	2	(9.5%)	
	Mild	0	(0.0%)	0	(0.0%)	
	Moderate	0	(0.0%)	0	(0.0%)	
	Severe	0	(0.0%)	0	(0.0%)	
Missing	0	(0.0%)	0	(0.0%)		
Unscheduled[b]	None	3	(100.0%)	1	(100.0%)	
	Trace	0	(0.0%)	0	(0.0%)	
	Mild	0	(0.0%)	0	(0.0%)	
	Moderate	0	(0.0%)	0	(0.0%)	
	Severe	0	(0.0%)	0	(0.0%)	
Missing	0	(0.0%)	0	(0.0%)		

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Includes all data from unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

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Table 22.4
Number (Percent) of Subjects with Slit Lamp Findings: Bulbar Hyperemia
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)

Slit Lamp Examination	Severity	All Subjects		P-value [a]
		(b)(4)	9464X (N = 23)	
Baseline	N	(b)(4)	23	0.6882
	None	(b)(4)	17 (73.9%)	
	Trace	(b)(4)	6 (26.1%)	
	Mild	(b)(4)	0 (0.0%)	
	Moderate	(b)(4)	0 (0.0%)	
	Severe	(b)(4)	0 (0.0%)	
Day 7	N	(b)(4)	22	0.5929
	None	(b)(4)	16 (72.7%)	
	Trace	(b)(4)	6 (27.3%)	
	Mild	(b)(4)	0 (0.0%)	
	Moderate	(b)(4)	0 (0.0%)	
	Severe	(b)(4)	0 (0.0%)	
Day 30	N	(b)(4)	22	0.4344
	None	(b)(4)	17 (77.3%)	
	Trace	(b)(4)	5 (22.7%)	
	Mild	(b)(4)	0 (0.0%)	
	Moderate	(b)(4)	0 (0.0%)	
	Severe	(b)(4)	0 (0.0%)	
Unscheduled [b]	N	(b)(4)	3	1
	None	(b)(4)	2 (66.7%)	
	Trace	(b)(4)	1 (33.3%)	
	Mild	(b)(4)	0 (0.0%)	
	Moderate	(b)(4)	0 (0.0%)	
	Severe	(b)(4)	0 (0.0%)	
REFRESH (N = 23)	N	(b)(4)	23	0.6882
	None	(b)(4)	19 (82.6%)	
	Trace	(b)(4)	4 (17.4%)	
	Mild	(b)(4)	0 (0.0%)	
	Moderate	(b)(4)	0 (0.0%)	
	Severe	(b)(4)	0 (0.0%)	

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Includes all data from unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 22.5
Number (Percent) of Subjects with Slit Lamp Findings: Palpebral Conjunctival Observation
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)

Slit Lamp Examination	Severity	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
Baseline	N	23	23	0.7396
	None	16 (69.6%)	17 (73.9%)	
	Trace	7 (30.4%)	6 (26.1%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Day 7	Missing	0 (0.0%)	0 (0.0%)	0.6621
	N	22	23	
	None	15 (68.2%)	18 (78.3%)	
	Trace	7 (31.8%)	5 (21.7%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Day 30	Severe	0 (0.0%)	0 (0.0%)	0.9974
	Missing	0 (0.0%)	0 (0.0%)	
	N	22	21	
	None	16 (72.7%)	15 (71.4%)	
	Trace	6 (27.3%)	6 (28.6%)	
	Mild	0 (0.0%)	0 (0.0%)	
Unscheduled[b]	Moderate	0 (0.0%)	0 (0.0%)	1
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
	N	3	1	
	None	2 (66.7%)	1 (100.0%)	
	Trace	1 (33.3%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.
 [b] Includes all data from unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 22.6
Number (Percent) of Subjects with Slit Lamp Findings: Other Complications
Based on Worse Severity of Eyes at Each Scheduled Visit
(Intent-to-treat Population)

Slit Lamp Examination	Severity	All Subjects		P-value [a]
		9464X (N = 23)	REFRESH (N = 23)	
Baseline	N	23 (100.0%)	23 (95.7%)	0.5763
	None	0 (0.0%)	1 (4.3%)	
	Trace	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
Day 7	Missing	0 (0.0%)	0 (0.0%)	0.5308
	N	22 (100.0%)	21 (91.3%)	
	None	0 (0.0%)	2 (8.7%)	
	Trace	0 (0.0%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	
Day 30	Severe	0 (0.0%)	0 (0.0%)	0.9077
	Missing	0 (0.0%)	0 (0.0%)	
	N	22 (90.9%)	21 (90.5%)	
	None	1 (4.5%)	2 (9.5%)	
	Trace	1 (4.5%)	0 (0.0%)	
	Mild	0 (0.0%)	0 (0.0%)	
Unscheduled [b]	Moderate	0 (0.0%)	0 (0.0%)	1
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
	N	3 (66.7%)	1 (100.0%)	
	None	2 (33.3%)	0 (0.0%)	
	Trace	0 (0.0%)	0 (0.0%)	
Unscheduled [b]	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	
	Severe	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	

[a] P-value for among-regimen comparison using the Kruskal-Wallis test.

[b] Includes all data from unscheduled visits. The worst severity was used if a subject was reported with more than one unscheduled visit.

Table 23.1.1.1
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
(Intent to Treat Population)

(b)(4) - Completed Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation						Total
	20/10	20/15	20/20	20/25	20/30	20/40	
20/10	0	0	0	0	0	0	0
20/15	0	0	0	0	0	0	0
20/20	0	0	25	0	0	0	27
20/25	0	0	7	5	1	0	13
20/30	0	0	0	2	4	0	6
20/40	0	0	0	0	0	0	0
Total	0	0	32	9	5	0	46

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

Table 23.1.1.2
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
(Intent to Treat Population)

(b)(4) - Discontinued Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation								Total
	20/10	20/15	20/20	20/25	20/30	20/40			
20/10	0	0	0	0	0	0	0	0	0
20/15	0	0	0	0	0	0	0	0	0
20/20	0	0	0	0	0	1	0	1	1
20/25	0	0	0	0	0	1	0	1	1
20/30	0	0	0	0	0	0	0	0	0
20/40	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	2	0	2	2

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

Table 23.2.1
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
(Intent to Treat Population)

Completed Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation								Total
	20/10	20/15	20/20	20/25	20/30	20/40			
20/10	0	0	0	0	0	0	0	0	0
20/15	0	0	0	0	0	0	0	0	0
20/20	0	0	26	1	0	0	0	0	27
20/25	0	0	7	4	0	0	0	0	11
20/30	0	0	0	3	3	0	0	0	6
20/40	0	0	0	0	0	0	0	0	0
Total	0	0	33	8	3	0	0	0	44

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

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Table 23.2.2
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
(Intent to Treat Population)

(b)(4) - Discontinued Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation							Total
	20/10	20/15	20/20	20/25	20/30	20/40		
20/10	0	0	0	0	0	0	0	
20/15	0	0	0	0	0	0	0	
20/20	0	0	2	0	0	0	2	
20/25	0	0	0	0	0	0	0	
20/30	0	0	0	0	0	0	0	
20/40	0	0	0	0	0	0	0	
Total	0	0	2	0	0	0	2	

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

Table 23.3.1
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
 (Intent to Treat Population)

(b)(4) - Completed Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation							Total
	20/10	20/15	20/20	20/25	20/30	20/40		
20/10	0	0	0	0	0	0	0	0
20/15	0	0	0	0	0	0	0	0
20/20	0	0	20	1	2	0	0	23
20/25	0	0	5	9	3	0	0	17
20/30	0	0	1	4	1	0	0	6
20/40	0	0	0	0	0	0	0	0
Total	0	0	26	14	6	0	0	46

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

Table 23.3.3.2
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
(Intent to Treat Population)

(b)(4) - Discontinued Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation								Total
	20/10	20/15	20/20	20/25	20/30	20/40			
20/10	0	0	0	0	0	0	0	0	0
20/15	0	0	0	0	0	0	0	0	0
20/20	0	0	2	0	0	0	0	0	2
20/25	0	0	0	0	0	0	0	0	0
20/30	0	0	0	0	0	0	0	0	0
20/40	0	0	0	0	0	0	0	0	0
Total	0	0	2	0	0	0	0	0	2

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

Table 23.4.1
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
(Intent to Treat Population)

(b)(4) - Completed Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation										Total	
	20/10	20/15	20/20	20/25	20/30	20/40	20/50	20/60	20/70	20/80		
20/10	0	0	0	0	0	0	0	0	0	0	0	0
20/15	0	0	0	0	0	0	0	0	0	0	0	0
20/20	0	0	29	1	0	0	0	0	0	0	0	31
20/25	0	0	6	3	0	0	0	0	0	0	0	9
20/30	0	0	0	2	2	0	0	0	0	0	0	4
20/40	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	35	6	2	2	0	0	0	1	0	44

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

Table 23.4.2
Visual Acuity Tabulated by Number of Eyes
Comparing Lens-Corrected Visual Acuity at Final Evaluation to Baseline
(Intent to Treat Population)

(b)(4) - Discontinued Subjects

Baseline Visual Acuity	Visual Acuity at Final Evaluation							Total
	20/10	20/15	20/20	20/25	20/30	20/40	Total	
20/10	0	0	0	0	0	0	0	0
20/15	0	0	0	0	0	0	0	0
20/20	0	0	2	0	0	0	2	2
20/25	0	0	0	0	0	0	0	0
20/30	0	0	0	0	0	0	0	0
20/40	0	0	0	0	0	0	0	0
Total	0	0	2	0	0	0	2	2

Total number of eyes is tabulated.

[b] Values above the diagonal (shaded area) represent a decrease in visual acuity; values below the diagonal (bold & italic) represent an increase in visual acuity.

Table 24
Lens-Corrected Visual Acuity
Number (Percent) of Subjects with 2 Lines or Greater Loss at Final Evaluation
Compared to Baseline
(Intent-to-treat Population)

Line Change From Baseline	9464X (N = 23)	REFRESH (N = 23)	P-value [a]
N	23	23	0.5763
≤ -2	0 (0.0%)	1 (4.3%)	
> -2 to < +2	23 (100.0%)	22 (95.7%)	
≥ +2	0 (0.0%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)	

[a] P-value for among regimen comparison performed using Kruskal-Wallis test.
 Note: The tabulation is based on the worst change of the right and left eyes.

Table 25.1
Trend Analysis Profile
(Intent-to-treat Population)

(b)(4)

Time in Study (days)	7	30	Unscheduled	Total
Total Number of Eyes	48	46	0	48
Discontinued Eyes	2	0	0	2
All Adverse Reactions	0	0	0	0
All Corneal Ulcers	0	0	0	0
All Iritis	0	0	0	0
Other Adverse Reactions	0	0	0	0
Total # Eye Reports of Corneal Staining	4	4	0	8
Corneal Staining Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Staining	6	6	0	6
Total # Eye Reports of Edema	0	0	0	0
Edema Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Edema	0	0	0	0
Total # Eye Reports of Bulbar Hyperemia (injection)	8	6	0	14
Injection Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Bulbar Hyperemia	8	6	0	8
Total # Eye Reports of Corneal Neovascularization	4	4	0	8
Corneal Neovascularization Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Neovascularization	4	4	0	4
Total # Eye Reports of Palpebral Conjunctival Observations	10	11	0	21
Palpebral Conjunctival Observations Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Palpebral Conjunctival Observations	11	11	0	11
Total Visits	24	23	0	47
Total Missed Visits	0	0	0	0

Note: Eyes with multiple unscheduled visits were tabulated once.

Table 25.2
Trend Analysis Profile
(Intent-to-treat Population)

(b)(4)

Time in Study (days)	7	30	Unscheduled	Total
Total Number of Eyes	44	44	6	46
Discontinued Eyes	0	0	2	2
All Adverse Reactions	0	1	1	2
All Corneal Ulcers	0	0	0	0
All Iritis	0	0	0	0
Other Adverse Reactions	0	1	1	2
Total # Eye Reports of Corneal Staining	3	2	0	5
Corneal Staining Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Staining				4
Total # Eye Reports of Edema	0	0	1	1
Edema Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Edema				1
Total # Eye Reports of Bulbar Hyperemia (injection)	12	10	1	23
Injection Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Bulbar Hyperemia				17
Total # Eye Reports of Corneal Neovascularization	3	1	0	4
Corneal Neovascularization Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Neovascularization				3
Total # Eye Reports of Palpebral Conjunctival Observations	14	12	2	28
Palpebral Conjunctival Observations Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Palpebral Conjunctival Observations				14
Total Visits	22	22	3	47
Total Missed Visits	1	0	0	1

Note: Eyes with multiple unscheduled visits were tabulated once.

Table 25.3
Trend Analysis Profile
(Intent-to-treat Population)

(b) (4) (6)

Time in Study (days)	7	30	Unscheduled	Total
Total Number of Eyes	48	46	0	48
Discontinued Eyes	0	0	2	2
All Adverse Reactions	0	0	0	0
All Corneal Ulcers	0	0	0	0
All Iritis	0	0	0	0
Other Adverse Reactions	0	0	0	0
Total # Eye Reports of Corneal Staining	9	7	0	16
Corneal Staining Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Staining				10
Total # Eye Reports of Edema	0	1	0	1
Edema Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Edema				1
Total # Eye Reports of Bulbar Hyperemia (injection)	12	14	0	26
Injection Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Bulbar Hyperemia				14
Total # Eye Reports of Corneal Neovascularization	9	9	0	18
Corneal Neovascularization Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Neovascularization				9
Total # Eye Reports of Palpebral Conjunctival Observations	8	12	0	20
Palpebral Conjunctival Observations Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Palpebral Conjunctival Observations				12
Total Visits	24	23	0	47
Total Missed Visits	0	0	0	0

Note: Eyes with multiple unscheduled visits were tabulated once.

Table 25.4
Trend Analysis Profile
(Intent-to-treat Population)

(b) (4), (b) (5)

Time in Study (days)	7	30	Unscheduled	Total
Total Number of Eyes	46	42	2	46
Discontinued Eyes	2	0	0	2
All Adverse Reactions	0	0	0	0
All Corneal Ulcers	0	0	0	0
All Iritis	0	0	0	0
Other Adverse Reactions	0	0	0	0
Total # Eye Reports of Corneal Staining	6	3	0	9
Corneal Staining Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Staining	6	3	0	6
Total # Eye Reports of Edema	1	0	0	1
Edema Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Edema	1	0	0	1
Total # Eye Reports of Bulbar Hyperemia (injection)	6	6	0	12
Injection Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Bulbar Hyperemia	6	6	0	6
Total # Eye Reports of Corneal Neovascularization	10	10	0	20
Corneal Neovascularization Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Corneal Neovascularization	10	10	0	10
Total # Eye Reports of Palpebral Conjunctival Observations	9	12	0	21
Palpebral Conjunctival Observations Eye Reports > Mild	0	0	0	0
Total # of Eyes Ever Reported with Palpebral Conjunctival Observations	9	12	0	12
Total Visits	23	21	1	45
Total Missed Visits	0	1	0	1

Note: Eyes with multiple unscheduled visits were tabulated once.

Listing 1.1
Discontinued Subject Listing with Exit Reason
(Intent-to-Treat Population)

Regimen: (b)(4)

Subject	Age	Sex	Race [a]	Dose	Date of First	Date of Exit	Study Days [b]	Reasons for Discontinuation
4147	53	M	C	26MAR03	04APR03	9	Related Regimen, Discomfort	

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.
[b] Number of days since the first dose of study medication.

**Listing 1.2
Discontinued Subject Listing with Exit Reason
(Intent-to-Treat Population)**

(b)(4)

Regimen:

Subject	Age	Sex	Race [a]	Dose	Date of First	Date of Exit	Study Days[b]	Reasons for Discontinuation
3427	27	F	C	28FEB03	12MAR03	12		Not Rel. Regimen, Slit lamp findings Not Rel. Regimen, Discomfort

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.
 [b] Number of days since the first dose of study medication.

**Listing 1.3
Discontinued Subject Listing with Exit Reason
(Intent-to-Treat Population)**

Regimen: (b)(4)

Subject	Age	Sex	Race [a]	Dose	Date of First	Date of Exit	Study Days [b]	Reasons for Discontinuation
1409	25	M	A	14MAR03	14APR03	31	Not Rel. Regimen, Missed visits	

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.
 [b] Number of days since the first dose of study medication.

**Listing 1.4
Discontinued Subject Listing with Exit Reason
(Intent-to-Treat Population)**

Regimen
(b)(4)

Subject	Age	Sex	Race [a]	Date of First Dose	Date of Exit	Study Days[b]	Reasons for Discontinuation
1410	53	F	C	18MAR03	24MAR03	6	Related Regimen, Discomfort Related Regimen, Reduced visual acuity

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.

[b] Number of days since the first dose of study medication.

Listing 2.1
Reason for Subject/Visit Excluded from Per Protocol Population
(Intent-to-Treat Population)

Regimen: (b)(4)

Subject	Age	Sex	Race [a]	Visit	Date of Exit	Study Days [b]	Study Days Window	Reasons for Exclusion
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No Subjects Fit This Criterion

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.
[b] Number of days in the study up to this visit (visit date - baseline date).

Listing 2.2
Reason for Subject/Visit Excluded from Per Protocol Population
(Intent-to-Treat Population)

Regimen: (b)(4)

Subject	Age	Sex	Race	[a] Visit	Date of Exit	Study Days	Study Days Window	Reasons for Exclusion
1109	48	F	C	Day 7	22APR03	10	5-9	Out of visit window

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.

[b] Number of days in the study up to this visit (visit date - baseline date).

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Listing 2.3
Reason for Subject/Visit Excluded from Per Protocol Population
(Intent-to-Treat Population)

Regimen: (b) (4) (b) (5)

Subject	Age	Sex	Race	[a]	Visit	Date of Exit	Study Days [b]	Study Window	Reasons for Exclusion
1110	46	F	C		Baseline	28APR03	0	0	Did not wear lenses as scheduled
					Day 7	28APR03	7	5-9	Did not wear lenses as scheduled
					Day 30	28APR03	26	26-34	Did not wear lenses as scheduled
1409	25	M	A		Baseline	14APR03	0	0	Discontinued due to missed visits
					Day 7	14APR03	7	5-9	Discontinued due to missed visits

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.
 [b] Number of days in the study up to this visit (visit date - baseline date).

Listing 2.4
Reason for Subject/Visit Excluded from Per Protocol Population
(Intent-to-Treat Population)

Regimen: (b)(4)

Subject	Age	Sex	Race [a]	Visit	Date of Exit	Study Days		Study Days Window	Reasons for Exclusion
						Days[b]	Days		
1103	34	F	C	Baseline	06MAY03	0		0	Day 30 out of visit window
				Day 7	06MAY03	7		5-9	Day 30 out of visit window
				Day 30	06MAY03	54		26-34	Day 30 out of visit window

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.

[b] Number of days in the study up to this visit (visit date - baseline date).

**Listing 3.1
All Adverse Events: Subject Listing
(Intent-to-Treat Population)**

Regimen: (b) (4) (b) (6)

Subject [a]	Age	Sex	Race	AE No.	Adverse Event (Investigator Term)	Discontinued from Study due to this AE	Type of Adverse Event [b]
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No Subjects Fit This Criteria

Subject	AE No.	Onset Day[c]	Onset Date	Stop Date	Duration of event (days)	Causality	Severity	Action Taken[d]	Outcome [e]
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No Subjects Fit This Criteria

- [a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other
- [b] O=Ocular, A=Atypical Clinical Finding, S=Serious, U=Unanticipated adverse device effect
- [c] Number of days since the first dose of study drops.
- [d] A=Lens Wear/study regimen temporarily discontinued, B=Treated with prescription drug, C=No treatment, D=Other
- [e] A=Ongoing, B=Recovered, C=Recovered with Sequelae

**Listing 3.2
All Adverse Events: Subject Listing
(Intent-to-Treat Population)**

Regimen: (b) (4) (c)

Subject No.	Age	Sex	Race	AE No.	Adverse Event (Investigator Term)	Discontinued from Study due to this AE	Type of Adverse Event [b]
4439	26	F	C	141		Yes	0

Subject No.	AE No.	Onset Day[c]	Onset Date	Stop Date	Duration of event (days)	Causality	Severity	Action Taken[d]	Outcome [e]
4439	141	28	04/17/03	04/30/03	13		Mild	A, D	A

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other
 [b] Ocular, A=Atypical Clinical Finding, S=Serious, U=Unanticipated adverse device effect
 [c] Number of days since the first dose of study drops.
 [d] A=Lens Wear/study regimen temporarily discontinued, B=Treated with prescription drug, C=No treatment, D=Other
 [e] A=Ongoing, B=Recovered, C=Recovered with Sequelae

**Listing 3.3
All Adverse Events: Subject Listing
(Intent-to-Treat Population)
Regimen: (b) (4)**

Subject [a]	Age	Sex	Race	AE No.	Adverse Event (Investigator Term)	Discontinued from Study due to this AE	Type of Adverse Event [b]
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No Subjects Fit This Criteria

Subject No.	AE	Onset Day[c]	Onset Date	Stop Date	Duration of event (days)	Causality	Severity	Action Taken[d]	Outcome [e]
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No Subjects Fit This Criteria

- [a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other
- [b] O=Ocular, A=Atypical Clinical Finding, S=Serious, U=Unanticipated adverse device effect
- [c] Number of days since the first dose of study drops.
- [d] A=Lens Wear/study regimen temporarily discontinued, B=Treated with prescription drug, C=No treatment, D=Other
- [e] A=Ongoing, B=Recovered, C=Recovered with Sequelae

**Listing 3.4
All Adverse Events: Subject Listing
(Intent-to-Treat Population)**

Regimen (b)(4)

Subject	Age	Sex	Race	AE No.	Adverse Event (Investigator Term)	Discontinued from Study due to this AE	Type of Adverse Event [b]
[a]							

No Subjects Fit This Criteria

Subject	AE No.	Onset Day[c]	Onset Date	Stop Date	Duration of event (days)	Causality	Severity	Action Taken[d]	Outcome [e]

No Subjects Fit This Criteria

- [a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other
- [b] Ocular, A=Atypical Clinical Finding, S=Serious, U=Unanticipated adverse device effect
- [c] Number of days since the first dose of study drops.
- [d] A=Lens Wear/study regimen temporarily discontinued, B=Treated with prescription drug, C=No treatment, D=Other
- [e] A=Ongoing, B=Recovered, C=Recovered with Sequelae

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Listing 4
Lens-Corrected Visual Acuity
(Intent-to-Treat Population)
Subjects with a 2 or More Line Loss in Either Eye

Regimen	Subject	Age	Sex	Race	[a]	Visit	Visual Acuity (OD)	Line Change [b] (OD)	Visual Acuity (OS)	Line Change [b] (OS)
(b)(4)	4147	53	M	C		Baseline	20/25	-2	20/20	-3
						Day 7	20/40		20/40	
	1407	38	F	C		Baseline	20/20	0	20/20	-2
						Day 7	20/20		20/30	0
						Day 30	20/30	-2	20/20	0
	4143	31	F	C		Baseline	20/20	0	20/20	0
						Day 7	20/20		20/20	0
						Day 30	20/30	-2	20/20	0
	1402	29	F	C		Baseline	20/20	-2	20/20	-1
						Day 7	20/30		20/25	0
						Day 30	20/25	-1	20/20	0
	3429	18	M	C		Baseline	20/20	0	20/20	-2
						Day 7	20/20		20/30	-3
						Day 30	20/20	0	20/40	-3

[a] Age in years. M=Male, F=Female. C=White, B=Black, A=Asian, H=Hispanic, O=Other.
 [b] Changes from baseline.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Memorandum

From: Reviewer(s) - Name(s) Daniel W. C. Brown, Ph.D. *DWCB*

Subject: 510(k) Number K032030

To: The Record - It is my recommendation that the subject 510(k) Notification:

- Refused to accept.
- Requires additional information (other than refuse to accept).
- Is substantially equivalent to marketed devices.
- NOT substantially equivalent to marketed devices.
- Other (e.g., exempt by regulation, not a device, duplicate, etc.)

- Is this device subject to Section 522 Postmarket Surveillance? YES NO
- Is this device subject to the Tracking Regulation? YES NO
- Was clinical data necessary to support the review of this 510(k)? YES NO
- Is this a prescription device? YES NO
- Was this 510(k) reviewed by a Third Party? YES NO
- Special 510(k)? YES NO
- Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers YES NO

- Truthful and Accurate Statement Requested Enclosed
- A 510(k) summary OR A 510(k) statement
- The required certification and summary for class III devices n/a
- The indication for use form

Combination Product Category (Please see algorithm on H drive 510k/Boilers) n/a N

Animal Tissue Source YES NO Material of Biological Origin YES NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

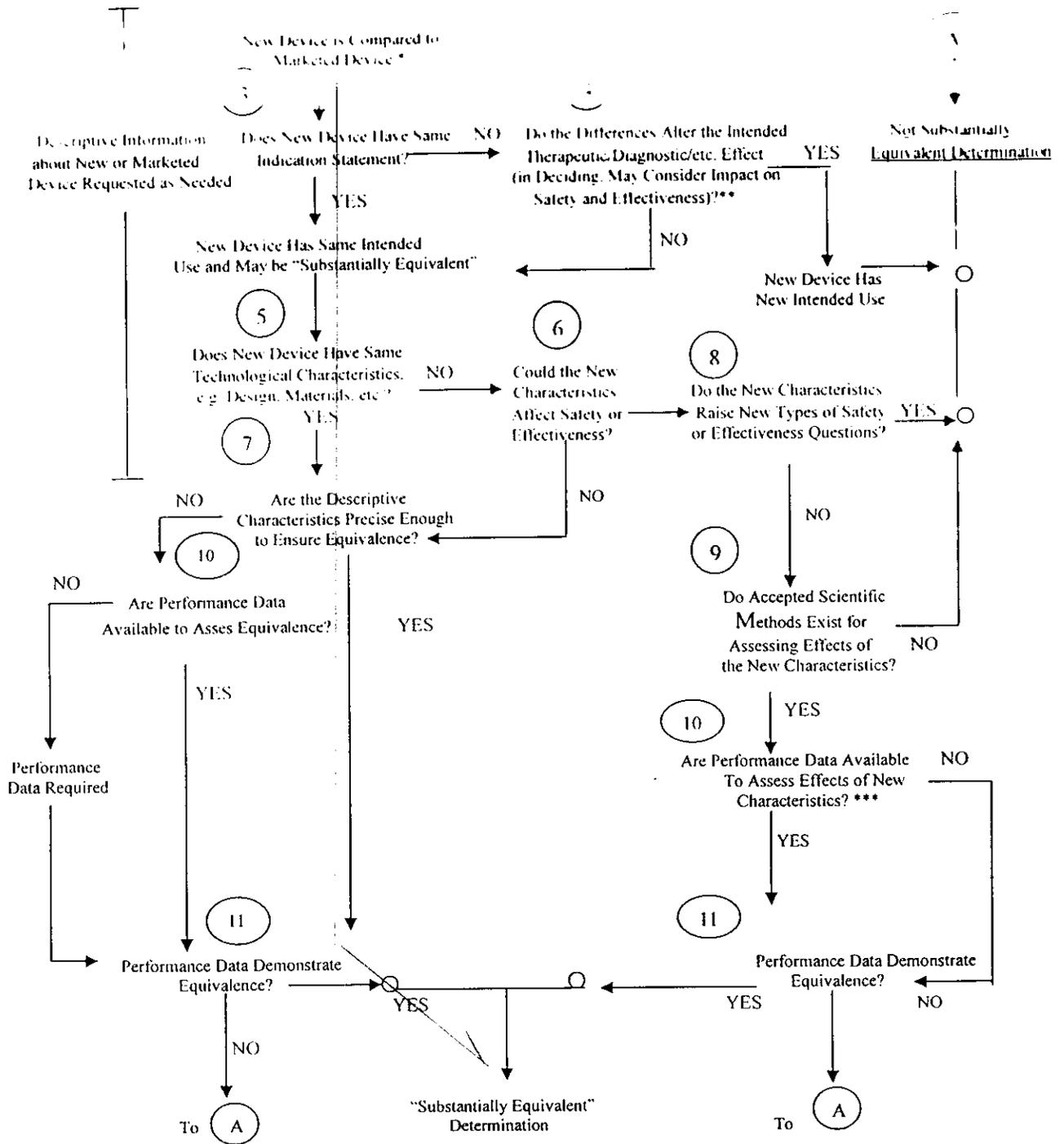
- No Confidentiality
- Confidentiality for 90 days
- Continued Confidentiality exceeding 90 days

Predicate Product Code with class: LPN/MRC II Additional Product Code(s) with panel (optional):
LPN 886.5928
MRC 886.5918

Review: Jarvis VAB 9/25/03
 (Branch Chief) (Branch Code) (Date)

Final Review: A. Ralph J. ... 9/25/03
 (Division Director) (Date)

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or call 301-796-8118.

REVISED: 3/14/95

THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).

"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K K032030

Reviewer: Daniel W. C. Brown, Ph.D. *DWCB*

Division/Branch: Ophthalmic & ENT/Vitreoretinal & Extraocular Devices

Device Name: blink CL Lubricant Eye Drops

Product To Which Compared (510(K) Number If Known): Aquify Lens Comfor Drops
Ciba Vision

	YES	NO	
1. Is Product A Device	X		If NO = Stop
2. Is Device Subject To 510(k)?	X		If NO = Stop
3. Same Indication Statement?	X		If YES = Go To 5
4. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If YES = Stop NE
5. Same Technological Characteristics?	X		If YES = Go To 7
6. Could The New Characteristics Affect Safety Or Effectiveness?			If YES = Go To 8
7. Descriptive Characteristics Precise Enough?	X		If NO = Go To 10 If YES = Stop SE
8. New Types Of Safety Or Effectiveness Questions?			If YES = Stop NE
9. Accepted Scientific Methods Exist?			If NO = Stop NE
10. Performance Data Available?			If NO = Request Data
11. Data Demonstrate Equivalence?			Final Decision:

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

DECISION MEMO:

Intended Use

Use *blink* CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses, to help relieve dryness, irritation and discomfort that may be associated with lens wear, and to cushion lenses by placing a drop on the lens prior to application on the eye.

Device Description:

Blink CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate), sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite (stabilized oxychloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients.

The Chemistry/Manufacturing, Toxicology, Microbiology and Clinical are all adequately stated and documented in this submission. The labeling of the device is well described and illustrated.

11. Conclusion: The sponsor has submitted adequate data/information in this document that is appropriate and supports the sponsor's contention that the device is substantially equivalent to the predicate device. Therefore, the device is APPROVED.

- Device as described and labeled complies with Special Controls for Class II Contact Lens Care Products
JS 9/25/03

SCREENING CHECKLIST FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS

510(k) Number: K02030

The cover letter clearly identifies the type of 510(k) submission as (Check the appropriate box):

- Special 510(k) - Do Sections 1 and 2
- Abbreviated 510(k) - Do Sections 1, 3 and 4
- Traditional 510(k) or no identification provided - Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present or Adequate	Missing or Inadequate
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510]] Manual.	X	
Table of Contents.	X	
Truthful and Accurate Statement.	X	
Device's Trade Name, Device's Classification Name and Establishment Registration Number.	X	
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).	X	
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510]] Manual.	X	
Statement of Indications for Use that is on a separate page in the premarket submission.	X	
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510]] Manual.	X	
510(k) Summary or 510(k) Statement.	X	
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.	X	
Identification of legally marketed predicate device. *	X	
Compliance with performance standards. * [See Section 514 of the Act and 21 CFR 807.87 (d).]	n/a	
Class III Certification and Summary. **	"	
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)]	"	
510(k) Kit Certification ***	"	

* - May not be applicable for Special 510(k)s.

** - Required for Class III devices, only.

*** - See pages 3-12 and 3-13 in the Premarket Notification [510]] Manual and the Convenience Kits Interim Regulatory Guidance.

Section 2: Required Elements for a SPECIAL 510(k) submission:

	Present	Inadequate or Missing
Name and 510(k) number of the submitter's own, unmodified predicate device.		
A description of the modified device and a comparison to the sponsor's predicate device.		
A statement that the intended use(s) and indications of the modified device, as described in its labeling are the same as the intended uses and indications for the submitter's unmodified predicate device.		
Reviewer's confirmation that the modification has not altered the fundamental scientific technology of the submitter's predicate device.		
A Design Control Activities Summary that includes the following elements (a-c):		
a. Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.		
b. Based on the Risk Analysis, an identification of the required verification and validation activities, including the methods or tests used and the acceptance criteria to be applied.		
c. A Declaration of Conformity with design controls that includes the following statements:		
A statement that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results of the activities demonstrated that the predetermined acceptance criteria were met. This statement is signed by the individual responsible for those particular activities.		
A statement that the manufacturing facility is in conformance with the design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review. This statement is signed by the individual responsible for those particular activities.		

Section 3: Required Elements for an ABBREVIATED 510(k)* submission:

	Present	Inadequate or Missing
For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type. (If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.)		
For a submission, which relies on a recognized standard, a declaration of conformity [For a listing of the required elements of a declaration of conformity, SEE Required Elements for a Declaration of Conformity to a Recognized Standard, which		

is posted with the 510(k) boilers on the H drive.) For a submission, which relies on a recognized standard without a declaration of conformity, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device.		
For a submission, which relies on a non-recognized standard that has <u>not</u> been historically accepted by FDA, a statement that the manufacturer intends to conform to a recognized standard and that supporting data will be available before marketing the device and any additional information requested by the reviewer in order to determine substantial equivalence.		
Any additional information, which is not covered by the guidance document, special control, recognized standard and/or non-recognized standard, in order to determine substantial equivalence.		

- * - When completing the review of an abbreviated 510(k), please fill out an Abbreviated Standards Data Form (located on the H drive) and list all the guidance documents, special controls, recognized standards and/or non-recognized standards, which were noted by the sponsor.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:	X	
b) Sterilization and expiration dating information:	X	
i) sterilization process	X	
ii) validation method of sterilization process	X	
iii) SAL	X	
iv) packaging	X	
v) specify pyrogen free	n/a	
vi) ETO residues	"	
vii) radiation dose	"	
viii) Traditional Method or Non-Traditional Method	"	
c) Software Documentation:	"	

Items with checks in the "Present or Adequate" column do not require additional information from the sponsor. Items with checks in the "Missing or Inadequate" column must be submitted before substantive review of the document.

Passed Screening X Yes _____ No _____
 Reviewer: Daniel W. C. Brown, Ph.D.
 Concurrence by Review Branch: J. Brown

Date:

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>

Internal Administrative Form

	YES	NO
1. Did the firm request expedited review?		X
2. Did we grant expedited review?		X
3. Have you verified that the Document is labeled Class III for GMP purposes? n/a		
4. If, not, has POS been notified?		
5. Is the product a device?	X	
6. Is the device exempt from 510(k) by regulation or policy?	X	X
7. Is the device subject to review by CDRH?	X	
8. Are you aware that this device has been the subject of a previous NSE decision?		X
9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?		
10. Are you aware of the submitter being the subject of an integrity investigation?		X
11. If, yes, consult the ODE Integrity Officer.		
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.		

12



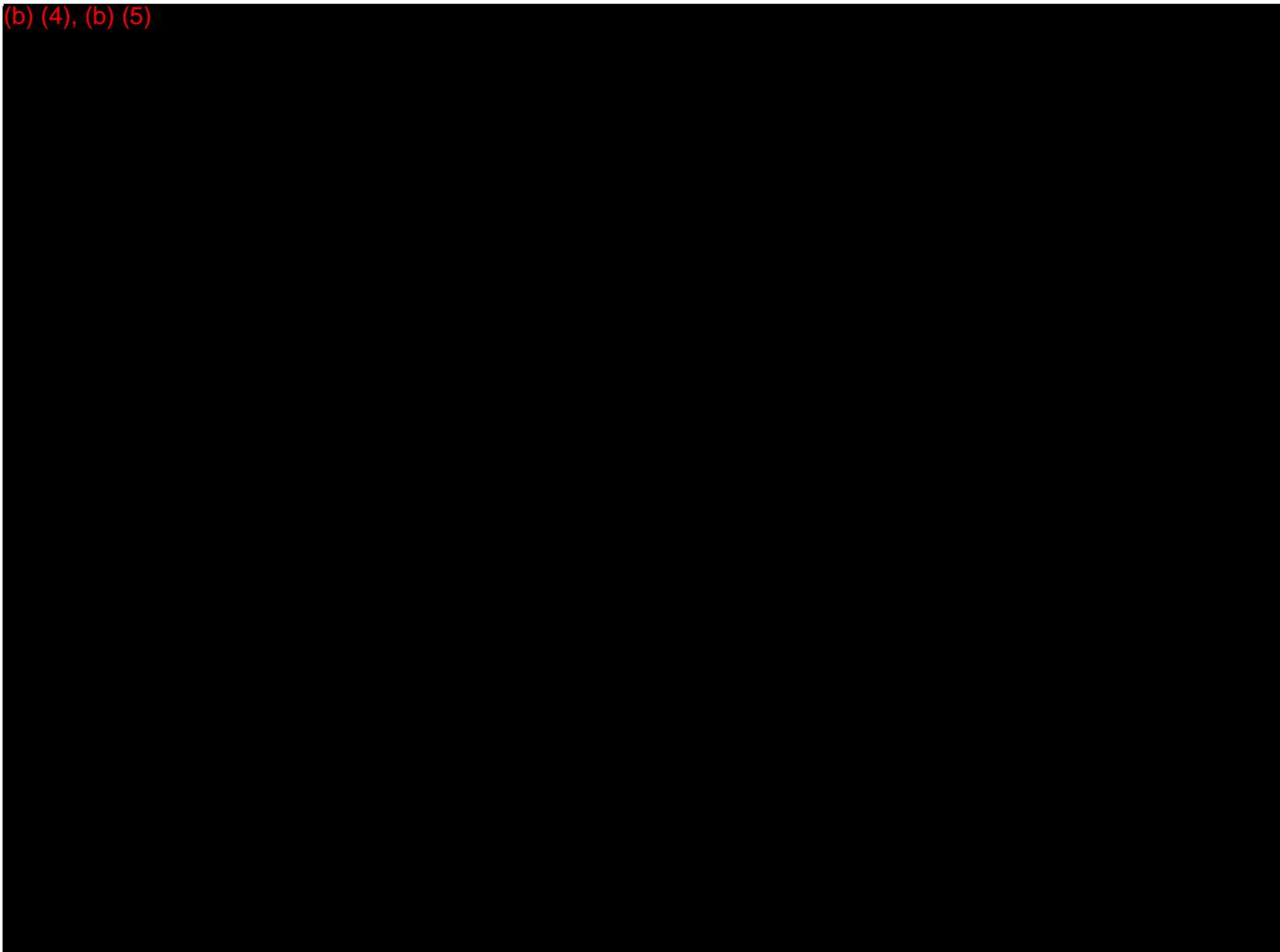
DEPARTMENT OF HEALTH & HUMAN SERVICES

**Public Health Service
Food and Drug Administration**

Date: September 16, 2003
From: Karen Warburton, Microbiologist *Karen Warburton*
Subject: K032030/A1, blink CL Lubricant Eye Drops—Microbiology review
To: The Record

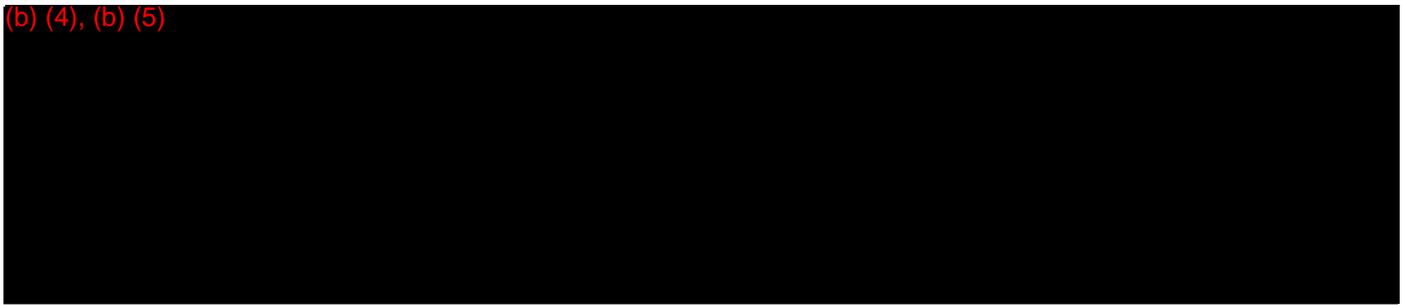
Amendment 1 responds to deficiencies that were faxed to the sponsor on September 9, 2003. The response to the microbiology deficiencies (noted in my review dated September 2) are discussed below.

(b) (4), (b) (5)



Page 2 of 2

(b) (4), (b) (5)



Comment: *Satisfactory*

Conclusion/recommendation

The sponsor has adequately responded to the microbiology deficiencies. A substantial equivalence determination is recommended.



DEPARTMENT OF HEALTH & HUMAN SERVICES

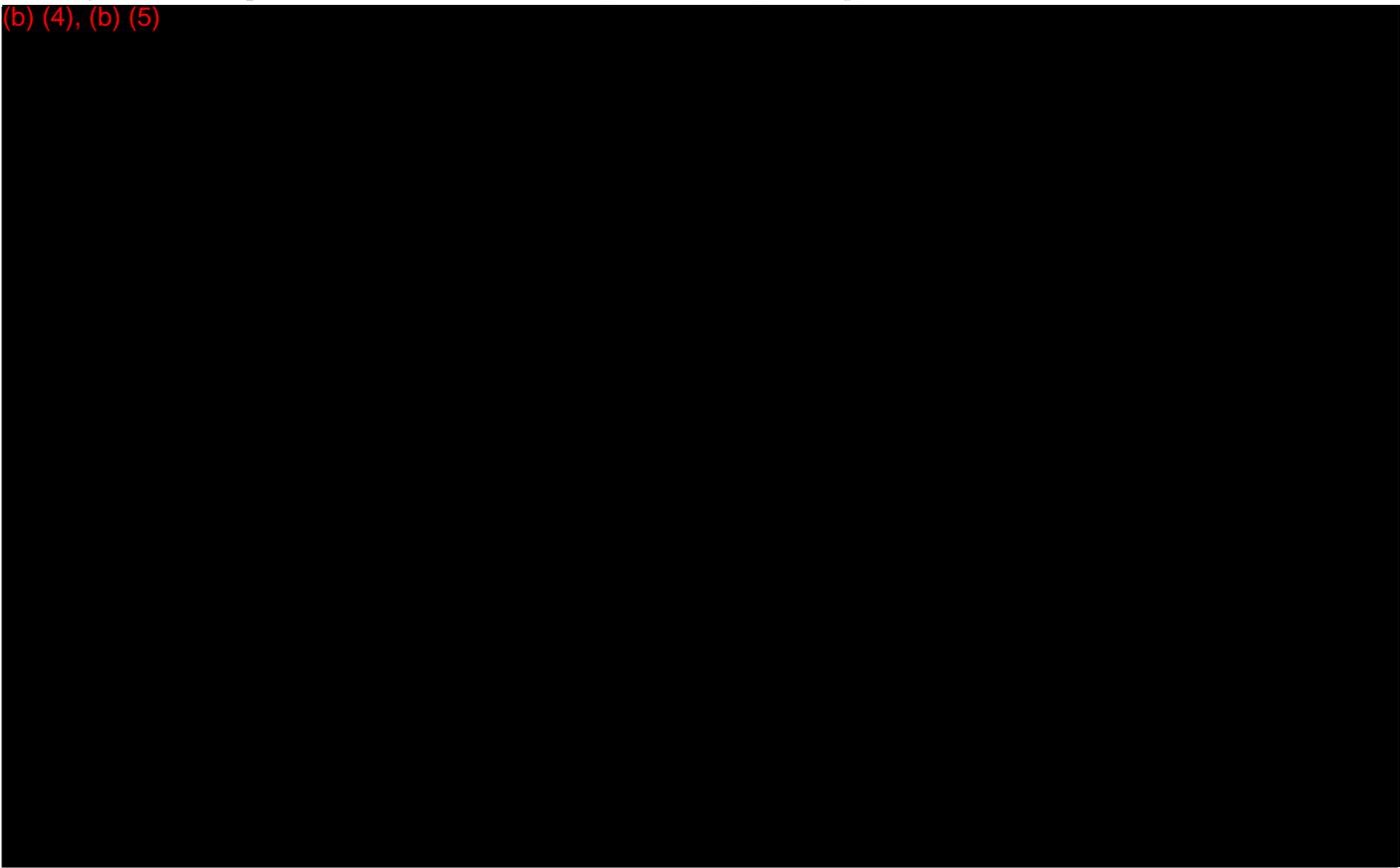
Public Health Service
Food and Drug Administration

Date: September 2, 2003
From: Karen Warburton, Microbiologist *Karen Warburton*
Subject: K032030, blink CL Lubricant Eye Drops—Microbiology review
To: The Record

Device Description

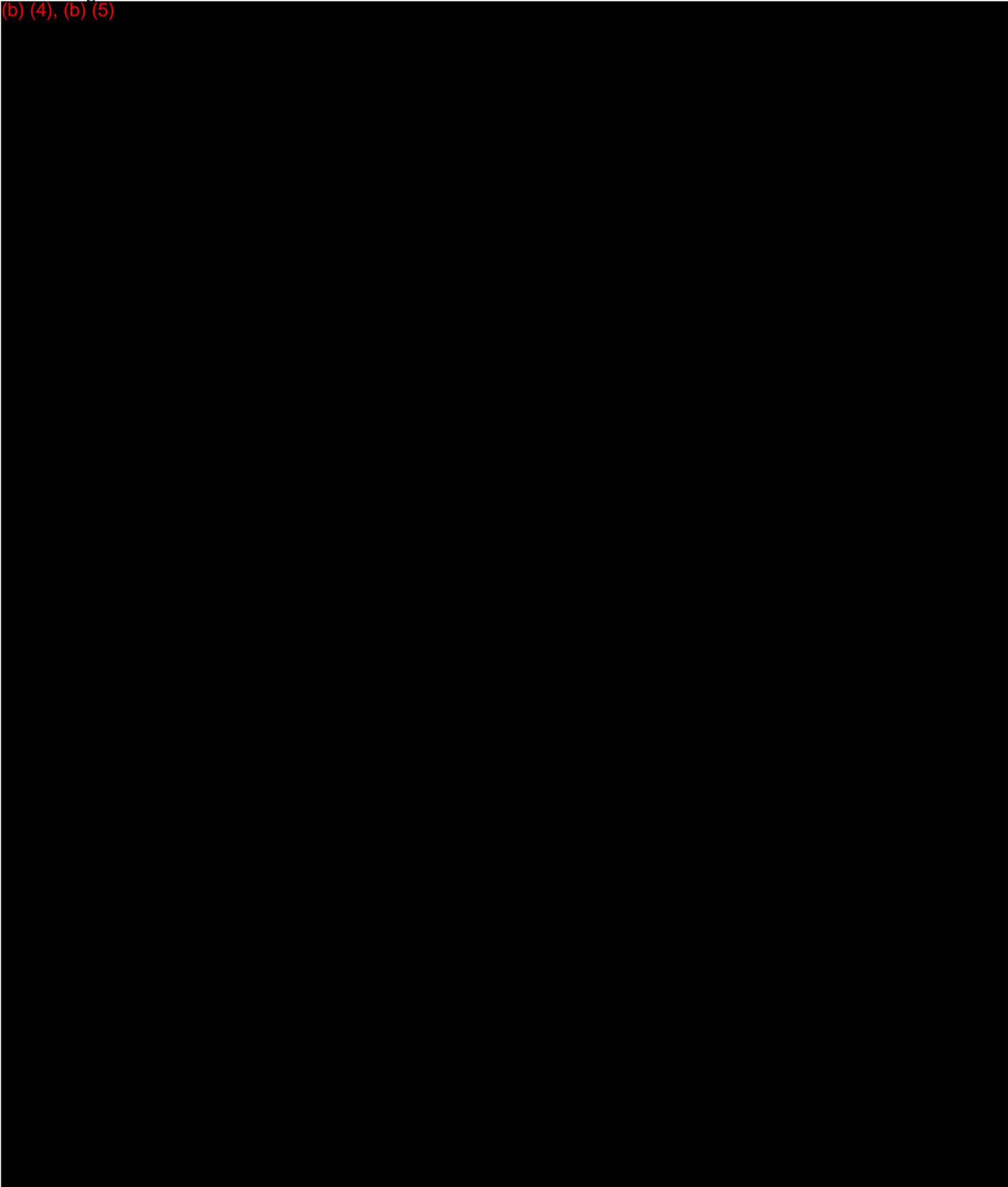
blink CL Lubricant Eye Drops are intended for use with both hydrophilic and gas permeable contact lenses to lubricate and rewet, to help relieve dryness irritation and discomfort that may be associated with lens wear, and to cushion lenses by placing a drop on the lens prior to application on the eye. This multi-dose solution contains sodium hyaluronate, sodium chloride, sodium borate decahydrate, boric acid, potassium chloride, magnesium chloride, Purite (stabilized oxychloro complex which functions as the preservative) , and purified water.

(b) (4), (b) (5)



Page 2 of 2

(b) (4), (b) (5)



16

Date: September 16, 2003

From: Chemist, VEDB/DOED

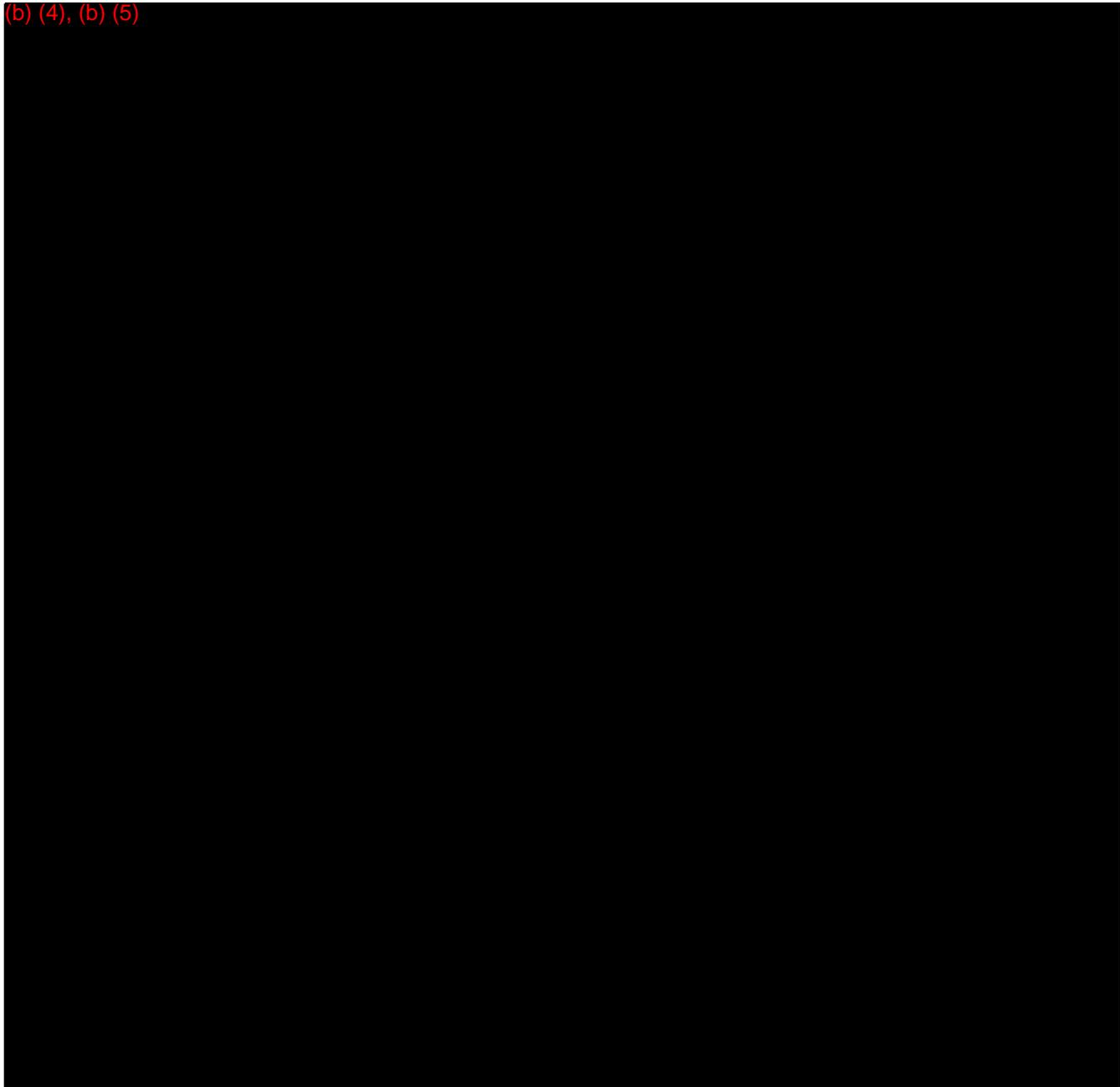
To: The Record

Subject: Manufacturing/Chemistry Review for blink CL Lubricant Eye Drops (K032030/A1), submitted by AMO

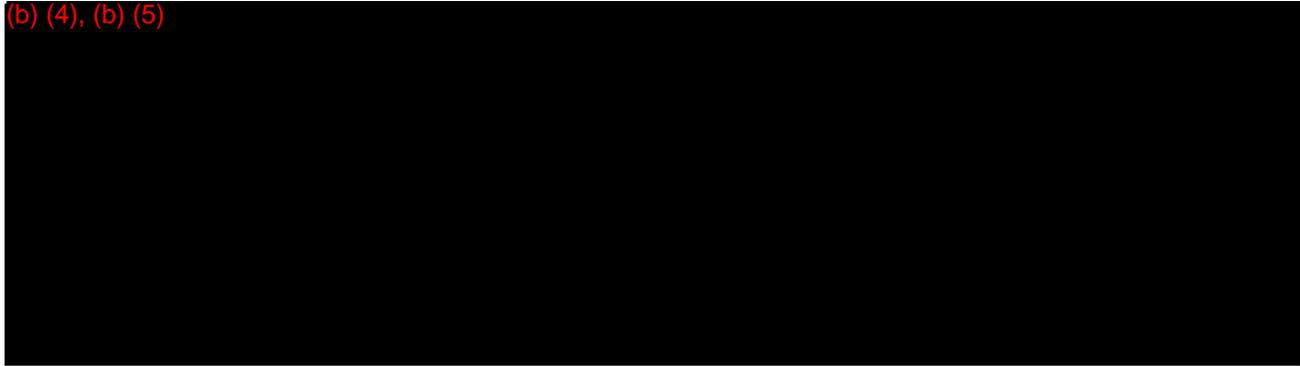
Introduction: This amendment is in response to additional information requested by FDA dated September 9, 2003.

Manufacturing/Chemistry Review

(b) (4), (b) (5)

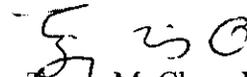


(b) (4), (b) (5)



Recommendation

The sponsor has satisfactorily supplied the origin and specifications for sodium hyaluronate. Clearance is recommended from a chemistry perspective.


Tzeng M. Chen, Ph.D.

Date: August 4, 2003

From: Chemist, VEDB/DOED

To: The Record

Subject: Manufacturing/Chemistry Review for blink™ CL Lubricant Eye Drops (K032030), submitted by AMO

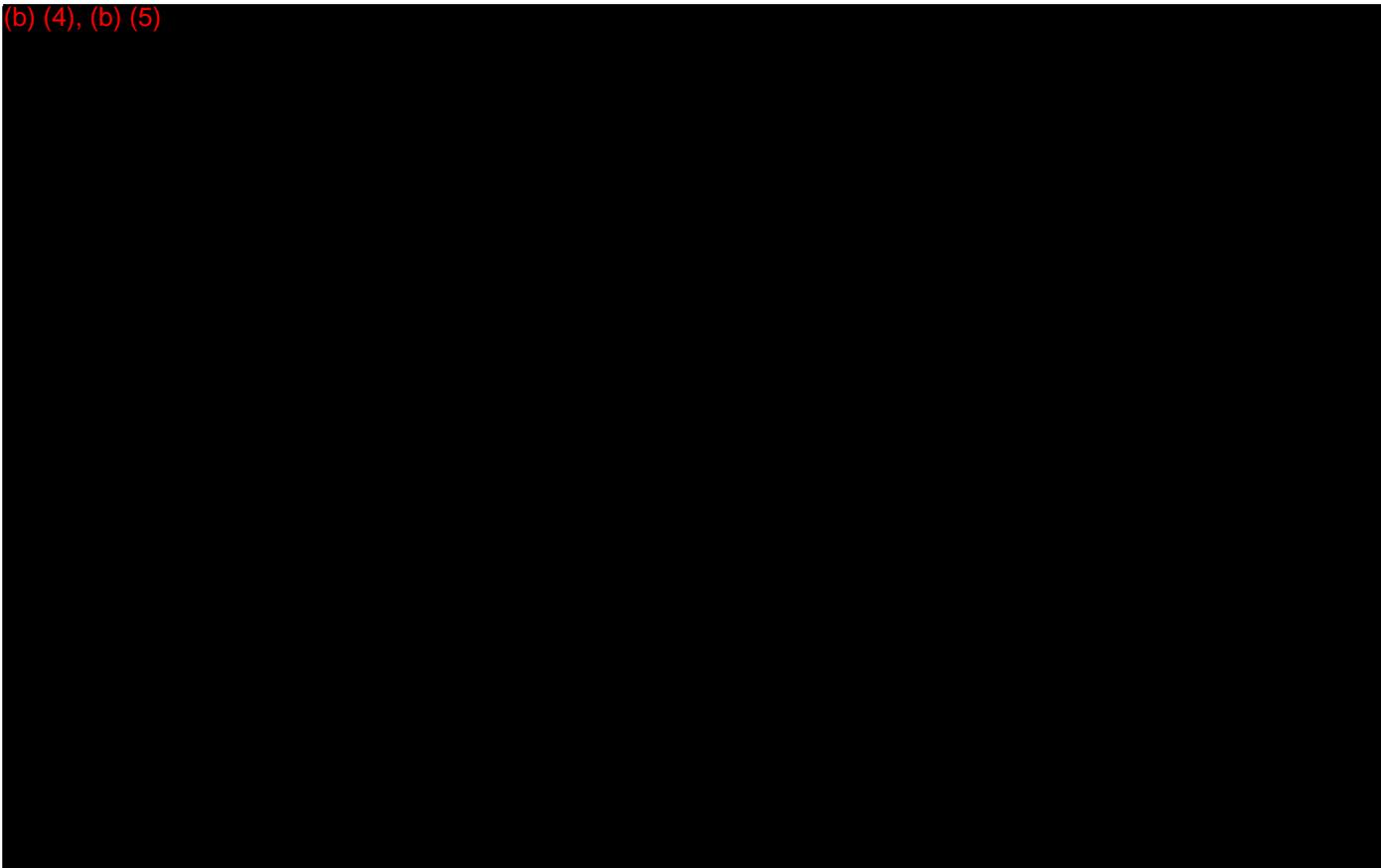
Indications for use:

Use blink™ CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses; to help relieve dryness, irritation and discomfort that may be associated with lens wear; and to cushion lenses by placing a drop on the lens prior to application on the eye.

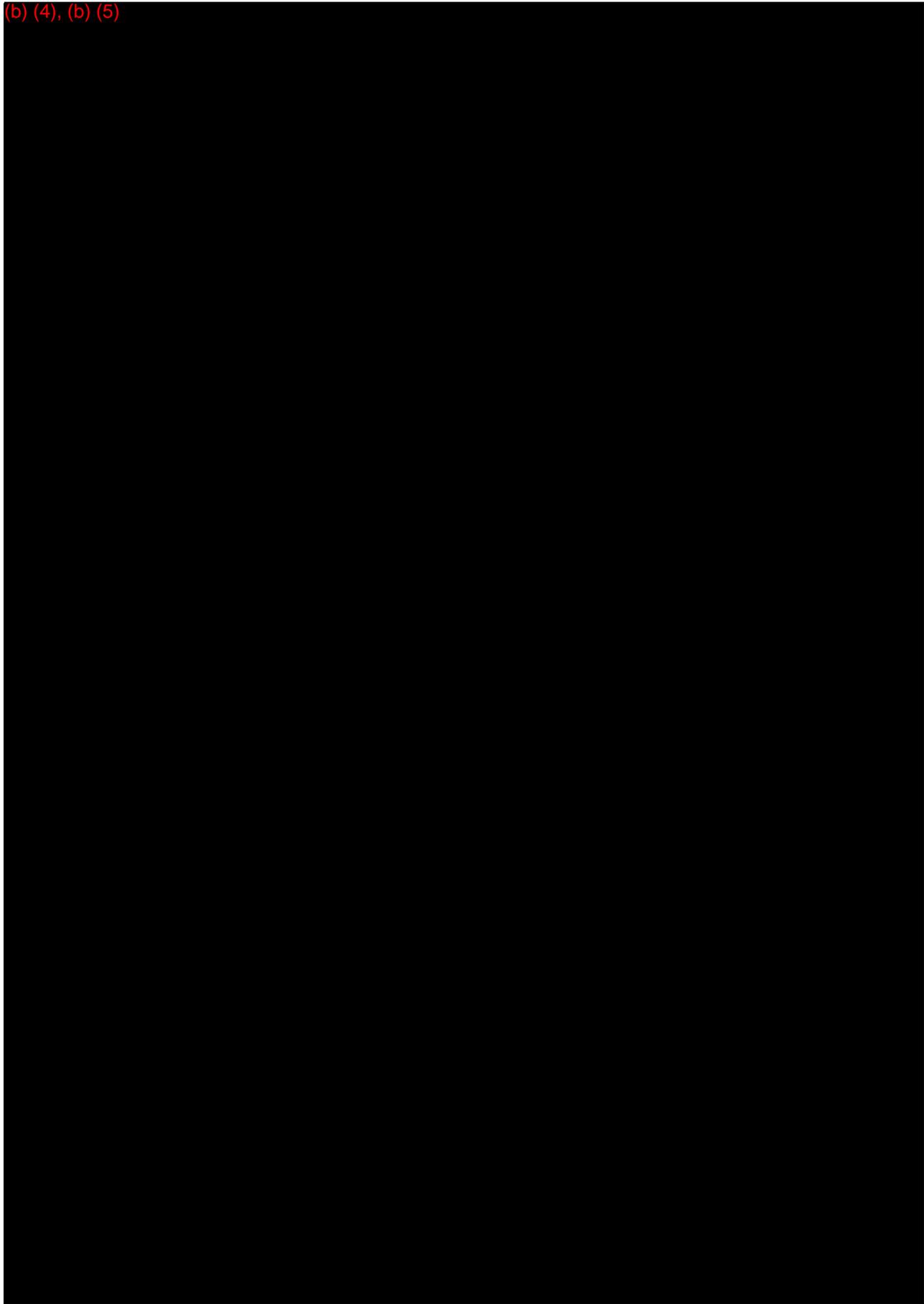
Predicate devices:

- Refresh Contacts Lubricating and Rewetting Drops (Allergan): containing carboxymethyl cellulose as a lubricant and Puite as a preservative.
- Aquify lens Comfort Drops (Ciba Vision): containing sodium hyaluronate as a Lubricant and sodium perborate as a preservative
- Hylashield CL Lubricating Eye Drop (Biomatrix): containing Hylan A (crosslinked sodium hyaluronate), un-preserved

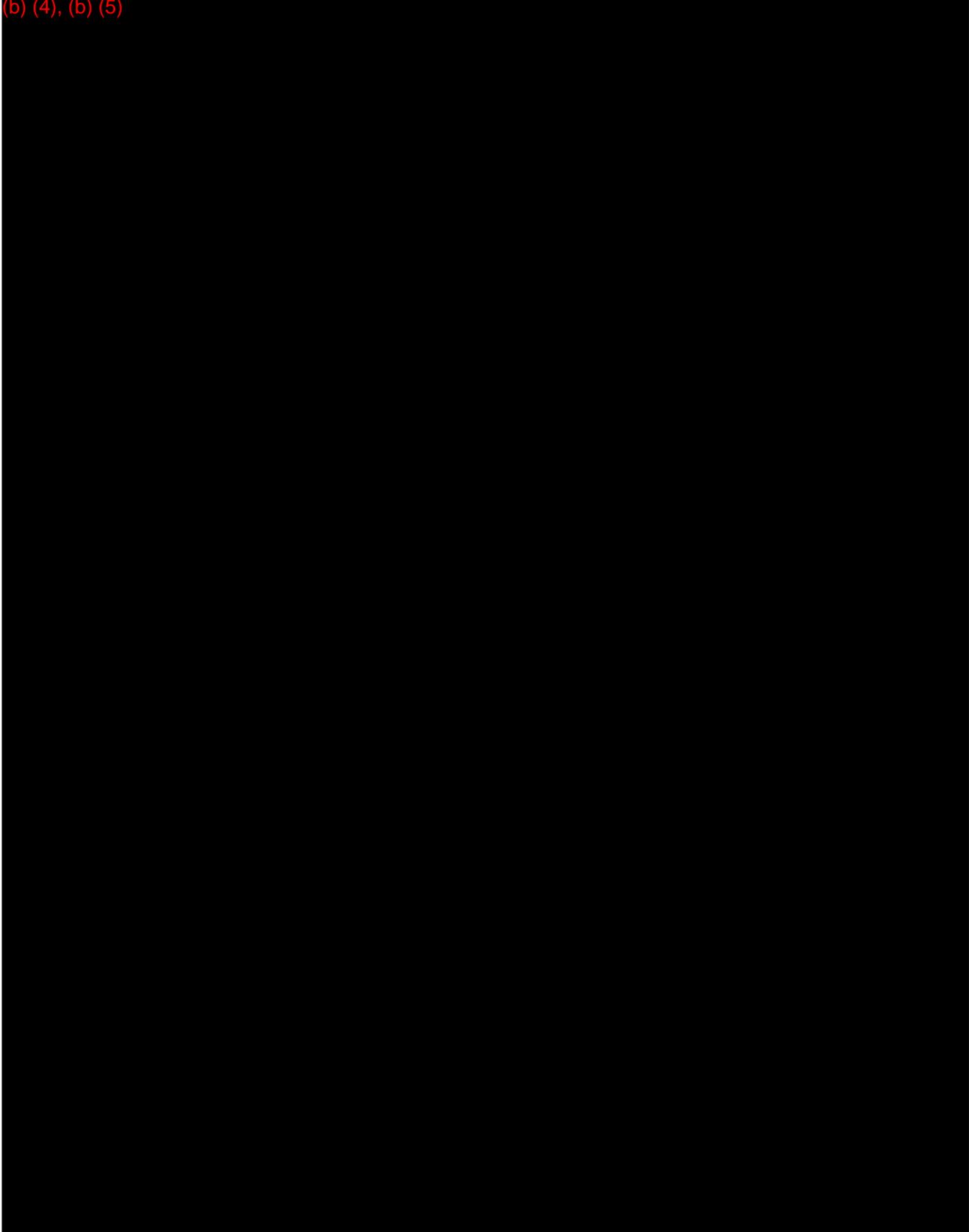
(b) (4), (b) (5)



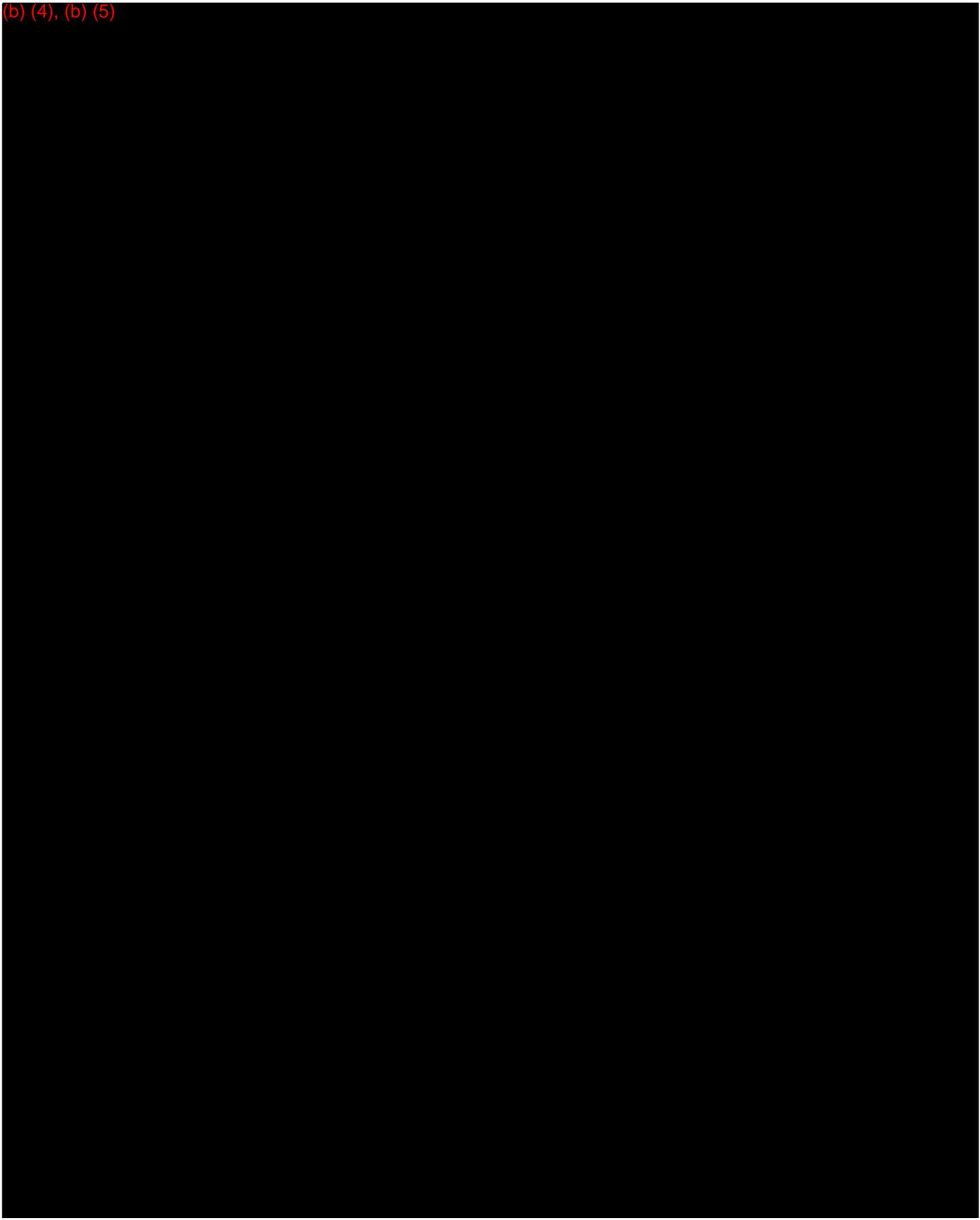
(b) (4), (b) (5)



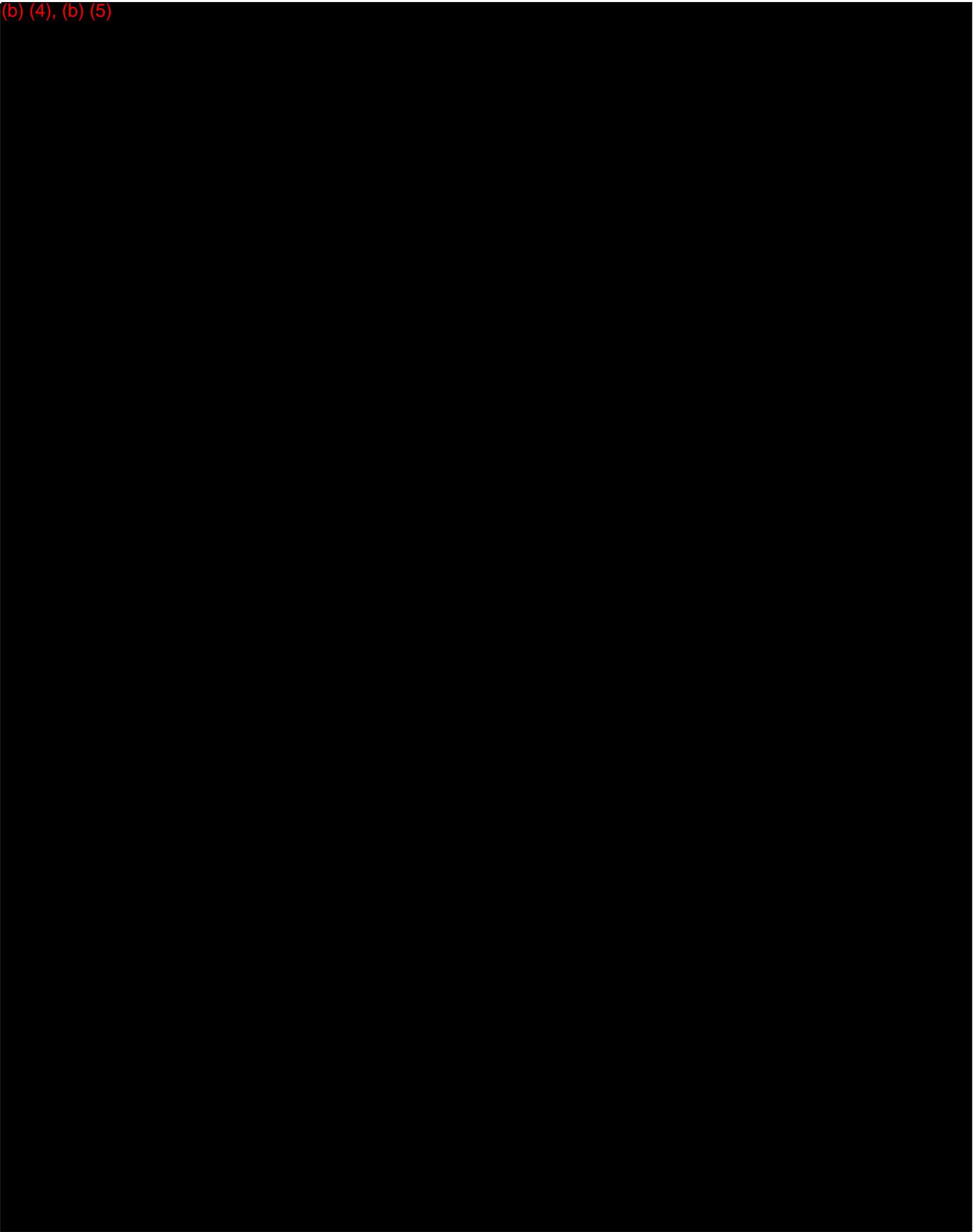
(b) (4), (b) (5)



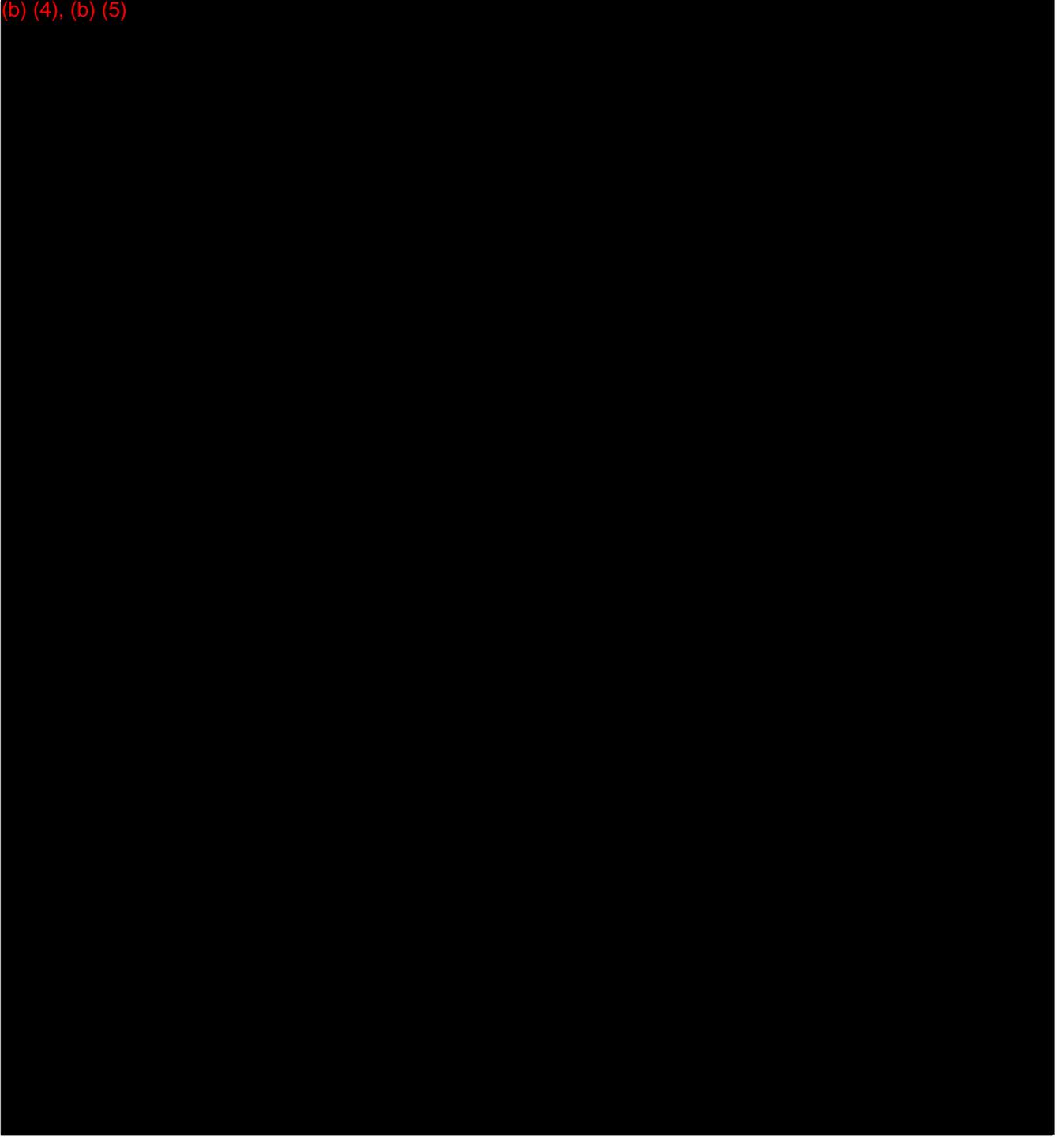
(b) (4), (b) (5)

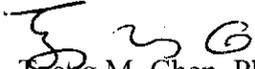


(b) (4), (b) (5)

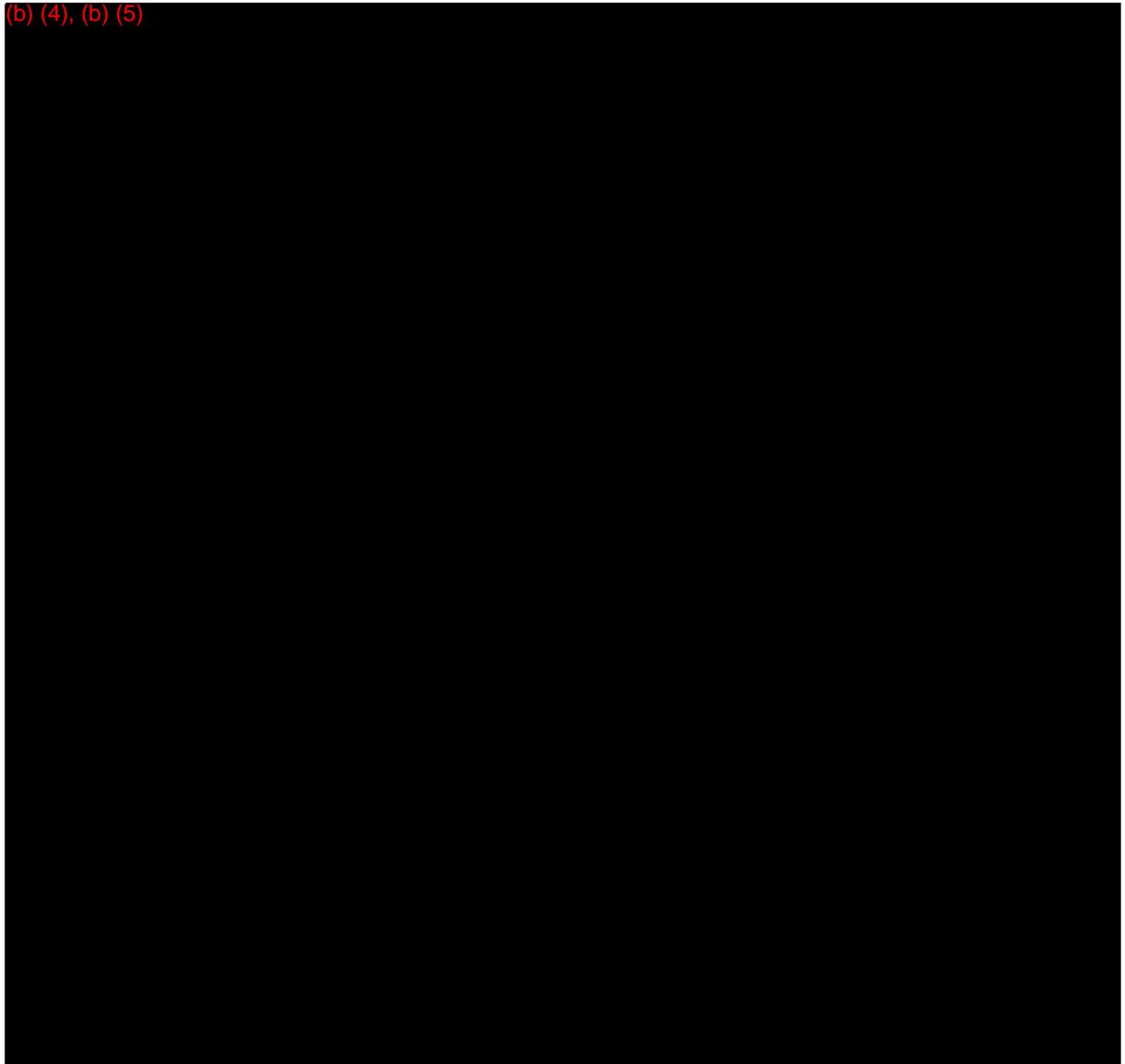


(b) (4), (b) (5)




Tzefg M. Chen, Ph.D.

(b) (4), (b) (5)



K032030

Premarket Notification – Clinical Review

Date: September 15, 2003

From: Gene Hilmantel, O.D., M.S.

To: The Record

Subject: K032030; clinical review

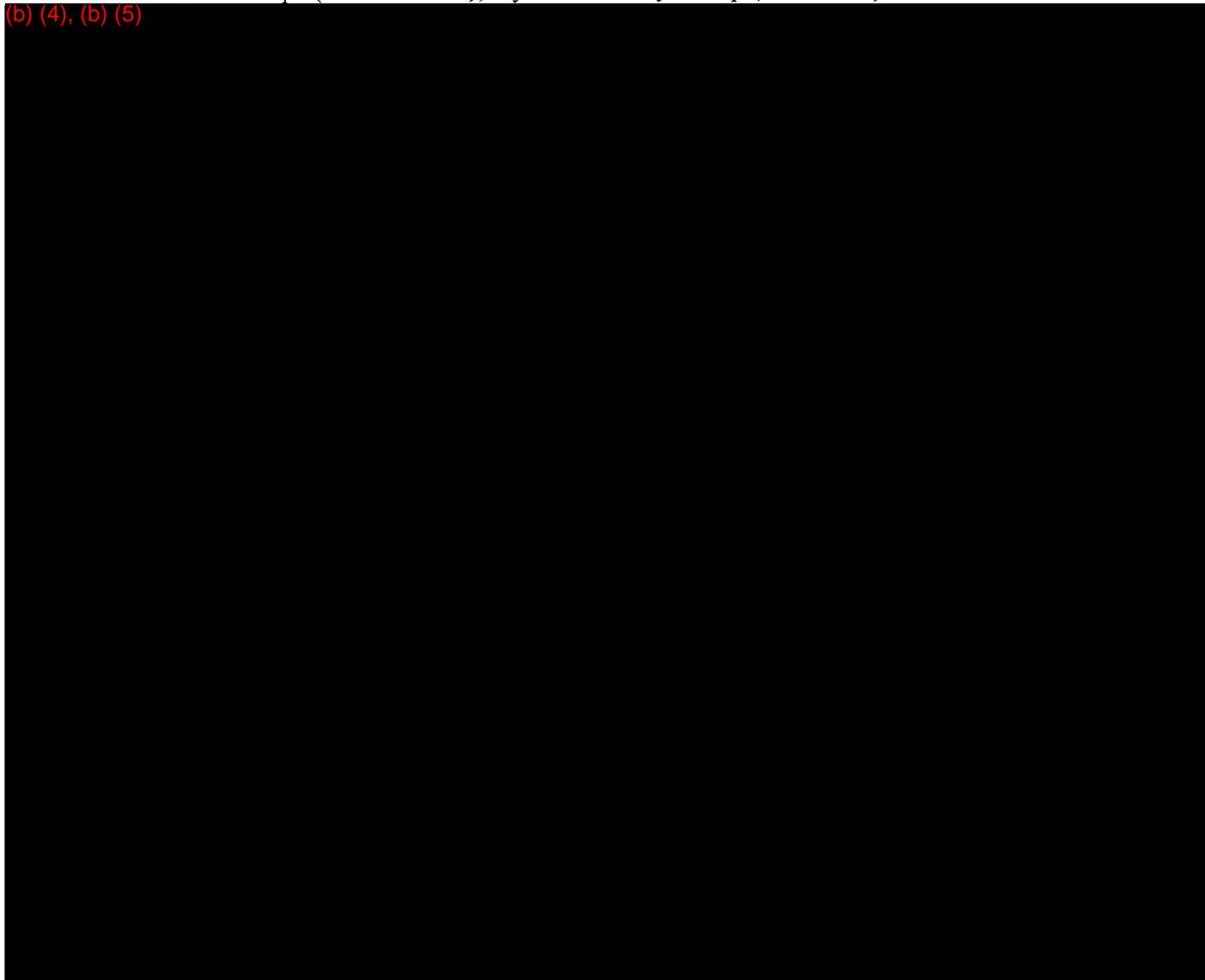
Device: blink™ CL Lubricant Eye Drops

Sponsor: Advanced Medical Devices (AMO)

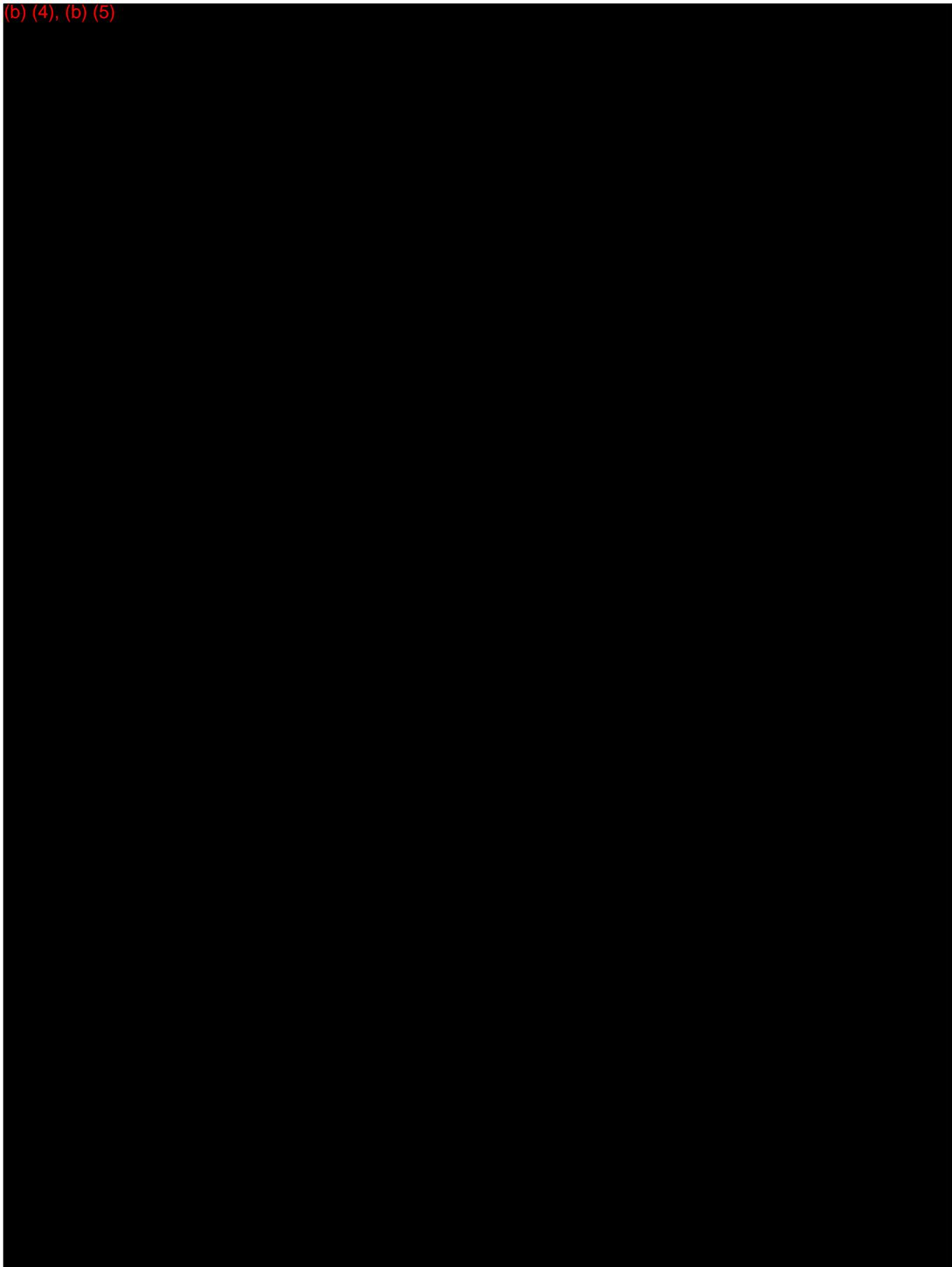
Indications for Use: Use blink™ to lubricate and rewet soft and rigid gas permeable contact lenses, to help relieve dryness, irritation and discomfort that may be associated with lens wear, and to cushion lenses by placing a drop on the lens prior to application on the eye. [p7]

Predicate: Refresh® Contacts™ Lubricating and Rewetting drops (Allergan); AQuify Lens Comfort Drops (CIBA Vision); Hylashield® Eye Drop (Biomatrix).

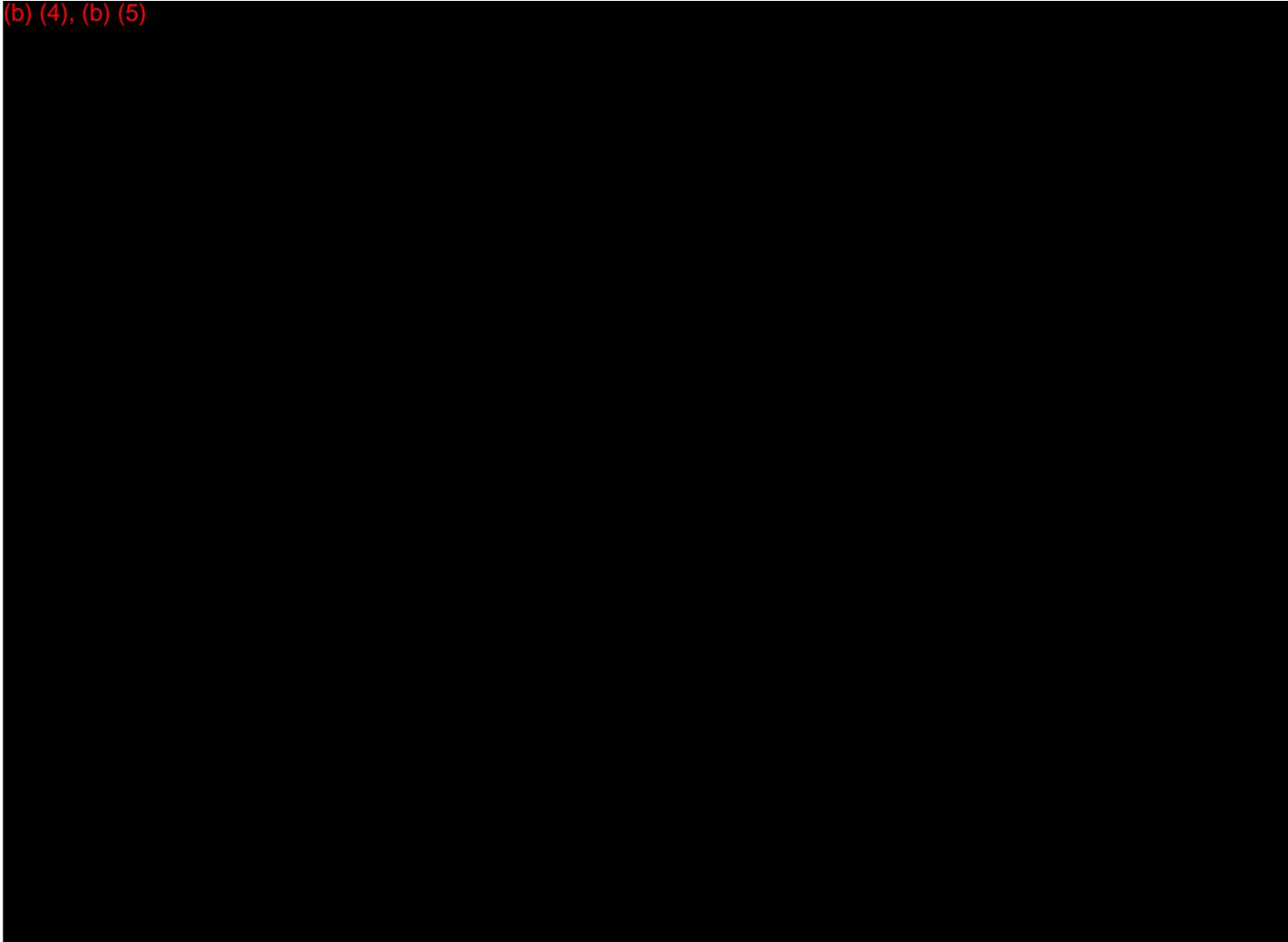
(b) (4), (b) (5)



(b) (4), (b) (5)



(b) (4), (b) (5)



Reviewer's Comment: The response is acceptable.

Conclusion/Recommendation

From a clinical perspective, I recommend a finding of Substantial Equivalence.

Jane Halmstedt
9/24/03

SINGLE LABEL

Front:

(logo) AMO

blink™ CL Lubricant Eye Drops
For Soft and RGP Lenses

USE ONLY IF BREAKSEAL ON BOTTLE CAP IS INTACT

10 mL (0.3 fl oz) STERILE

Back:

CONTENTS: **blink™** CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. If you are allergic to any ingredient in this product, DO NOT USE. **DIRECTIONS:** Apply 1 to 2 drops to each eye as needed. Blink several times. **PRECAUTIONS:** Store at room temperature. Use before the expiration date marked on the bottle and carton.

Distributed by:
Advanced Medical Optics, Inc
Santa Ana, CA 92705 U.S.A.
©2003 AMO, Inc.

XXXXX
9464X

Lot No.:

Exp. Date:



CDRH
**Division of Ophthalmic and Ear,
Nose and Throat Devices**
9200 Corporate Boulevard
Rockville, MD 20850
FAX NO. 301 480-4201
or 301 827-4601
PHONE NO. 301 594-2205

Date: 15 Sept 2003 Time: _____

To: Mr. Paul J. Nowacki Fax #: 714-247-8677

Organization: Advanced Medical Optics

From: Daniel W. C. Brown, Ph.D.

Department: FDA

Subject: K032030

No. of Pages (Including cover sheet): 2

Comments:

- As Requested FYI Read and Destroy
- Response Needed Signature Circulate
- For Correction Investigate File

Division Director's Office	301 594-2205
Ear, Nose and Throat Devices Branch	301 594-2080
Diagnostic and Surgical Devices Branch	301 594-2018
Intraocular and Corneal Implants Branch	301 594-2053
Vitreoretinal and Extraocular Devices Branch	301 594-1744
Mail Code: HFZ 460	

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Please advise if transmission is illegible

We recommend that the following should be added to the Warnings section of the labeling: "To avoid contaminating your solution, DO NOT transfer to other bottles or containers."

The bottle label does not contain any directions. Please modify the bottle label to include Directions.

At several places in the Package Insert, Bottle label, and Carton label, the statement is made that the product is, "For use with any contact lens." Please either remove the "**any**" statement from all labeling, or provide data showing the *clinical compatibility with ever currently marketed contact lens brand.*

Records processed under FOIA Request #2016-4847, Released by CDRH on 09-26-2016.

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO	2201	
CONNECTION TEL		917142478677
SUBADDRESS		
CONNECTION ID		
ST. TIME	09/09 10:39	
USAGE T	00'25	
PGS. SENT	2	
RESULT	OK	



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

CDRH
Division of Ophthalmic and Ear,
Nose and Throat Devices
 9200 Corporate Boulevard
 Rockville, MD 20850
 FAX NO. 301 480-4201
 or 301 827-4601
 PHONE NO. 301 594-2205

Date: 9 Sept 2003 Time: _____
 To: Mr. Paul J. Nowacki Fax #: 714-247-8677
 Organization: Advanced Medical Optics
 From: Daniel W. C. Brown, Ph.D.
 Department: FDA
 Subject: K032030
 No. of Pages (including cover sheet): 2

Comments:

- As Requested FYI Read and Destroy
- Response Needed Signature Circulate



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

CDRH
Division of Ophthalmic and Ear,
Nose and Throat Devices

9200 Corporate Boulevard
Rockville, MD 20850
FAX NO. 301 480-4201
or 301 827-4601
PHONE NO. 301 594-2205

Date: 9 Sept 2003 Time: _____

To: Mr. Paul J. Nowacki Fax #: 714-247-8677

Organization: Advanced Medical Optics

From: Daniel W. C. Brown, Ph.D.

Department: FDA

Subject: K032030

No. of Pages (Including cover sheet): 2

Comments:

- As Requested FYI Read and Destroy
- Response Needed Signature Circulate
- For Correction Investigate File

Division Director's Office	301 594-2205
Ear, Nose and Throat Devices Branch	301 594-2080
Diagnostic and Surgical Devices Branch	301 594-2018
Intraocular and Corneal Implants Branch	301 594-2053
Vitreoretinal and Extraocular Devices Branch	301 594-1744
Mail Code: HFZ 460	

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Please advise if transmission is illegible

33

Date: 9 September 2003

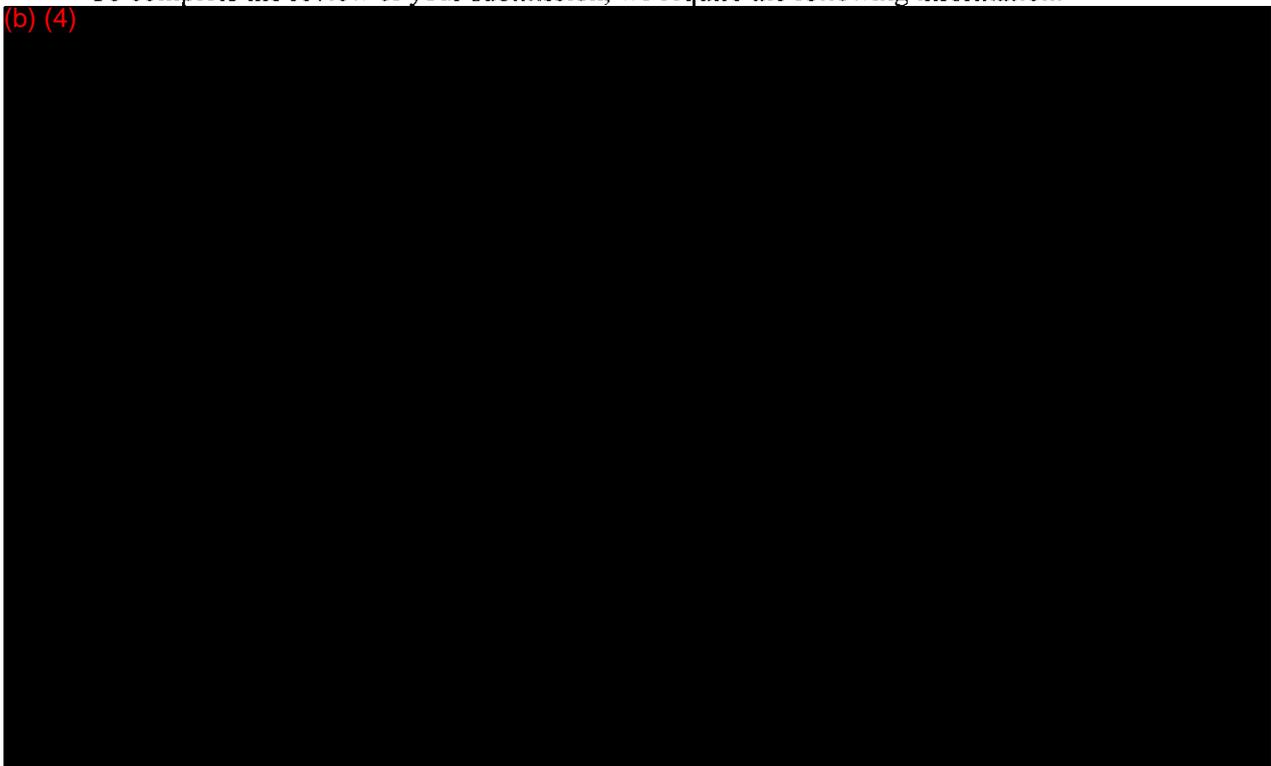
To: Mr. Paul J. Nowacki

From: Daniel W. C. Brown, Ph.D.

RE: K032030

To complete the review of your submission, we require the following information:

(b) (4)



Please provide the labeling for the Predicate Device.

Finally, "ANY" should be deleted in the labeling in the phrase "For Use With **ANY** Contact Lenses".

Saviola, James

From: Nowacki, Paul [Paul.Nowacki@amo-inc.com]
Sent: Wednesday, September 24, 2003 7:10 PM
To: Saviola, James; Hilmantel, Gene N; Brown, Daniel W. C.
Subject: RE: K032030
Importance: High

will be A2

Please note that we have sent the revised labeling to the 510k Document Mail Center on Wednesday, September 24 via overnight courier. Hopefully, they should have it by 10am on Thursday.

I have attached what we sent for your convenience.

Thanks,

Paul

-----Original Message-----

From: Saviola, James [mailto:JZS@CDRH.FDA.GOV]
Sent: Wednesday, September 24, 2003 9:05 AM
To: Nowacki, Paul; Hilmantel, Gene N; Brown, Daniel W. C.
Subject: RE: K032030

I like it. I like it very much. Thanks Paul.

*Jim Saviola, OD
CAPT US PHS
Chief VEDB/DOED
301-594-1744*

-----Original Message-----

From: Nowacki, Paul [mailto:Paul.Nowacki@amo-inc.com]
Sent: Wednesday, September 24, 2003 11:55 AM
To: Gene Hilmantel; DCB@CDRH.FDA.GOV; Jim Saviola
Subject: K032030
Importance: High

Gentleman,

Here is the revised bottle label copy per our conversation a few minutes ago. If it meets your requirements, please let me know by e-mail. I will then send duplicate copies to the 510k document mail center via overnight courier.

Paul

*Discussed concerns of no deviations on b. He label
to Mr. Nowacki. JS*



September 24, 2003

510k Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

**RE: K032030 – blink™ CL Lubricant Eye Drops
15 September 2003 FDA Request for Labeling Changes**

TO WHOM IT MAY CONCERN,

Advanced Medical Optics (AMO) hereby provides duplicate copies of a submission to the above-referenced 510k. This is being sent in response to a request for three (3) labeling changes from Daniel W.C. Brown, Ph.D. of FDA (facsimile dated 15 September 2003) and a teleconference with James F. Saviola, O.D. and Gene N. Hilmantel, O.D.

Number 1

We recommend that the following should be added to the Warnings section of the labeling: "To avoid contaminating your solution, DO NOT transfer to other bottles or containers."

AMO has revised the Warnings section of the labeling by combining the above statement with an already existing statement regarding contamination. The new Warning reads as follows:

"To avoid contamination do not touch dropper tip to any surface and DO NOT transfer contents to any other bottle or container."

Number 2

The bottle label does not contain any directions. Please modify the label to include Directions.

AMO has added the following to the bottle label:

"DIRECTIONS: Apply 1 to 2 drops to each eye as needed. Blink several times."

Number 3

At several places in the Package Insert, Bottle label and Carton label, the statement is made that the product is, "For use with any contact lens." Please either remove the "any" statement from all labeling, or provide data showing the clinical compatibility with every currently marketed contact lens brand.

AMO has replaced this statement throughout all the labeling with the following:

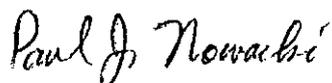
“For use with soft and RGP contact lenses.”

A copy of the labeling incorporating the changes discussed above is enclosed.

We ask that the existence of this 510k be kept confidential since:

- The intent to market the product covered by this 510k has been kept confidential. No disclosures have been made to persons other than those bound by secrecy agreements.
- Precautions have been taken to preserve confidentiality.
- FDA will be immediately notified of any disclosure of intent to market.

Sincerely,



Paul J. Nowacki
Manager
Worldwide Regulatory Affairs
And Medical Compliance

Phone: 714-247-8601
Facsimile: 714-247-8677
E-mail: paul.nowacki@amo-inc.com

blink™
CL Lubricant Eye Drops

PACKAGE INSERT

blink™ CL Lubricant Eye Drops

For Soft and RGP Contact Lenses

DESCRIPTION:

blink™ CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. This preparation contains no chlorhexidine, no thimerosal and no other mercury containing ingredients.

ACTIONS:

blink™ CL Lubricant Eye Drops has been formulated for use with both soft and rigid gas permeable (RGP) contact lenses; to rewet lenses before insertion and lubricate lenses during wear and to moisturize and refresh tired, dry eyes. It also relieves minor irritation, discomfort, dryness, blurring and itchiness, which may occur while wearing your lenses.

INDICATIONS:

Use **blink™** CL Lubricant Eye Drops to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses, to help relieve dryness, discomfort and irritation that may be associated with lens wear and to cushion lenses by placing a drop on the lens prior to application on the eye.

CONTRAINDICATIONS:

If you are allergic to any ingredient in **blink™** CL Lubricant Eye Drops, do not use this product.

WARNINGS:

PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS

COULD RESULT IN SERIOUS INJURY TO THE EYE. It is essential that you 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 that the risk of serious adverse reactions is increased when these lenses are worn overnight.

Extended wear lenses should be regularly removed for cleaning and disinfecting 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 disinfecting or for disposal and replacement.

Studies have also shown that smokers had a higher incidence of adverse reactions.

It is recommended that contact lens wearers see their eye care practitioner twice each year or if directed, more frequently.

To avoid contamination, do not touch the dropper tip of the bottle to any surface and DO NOT transfer contents to any other bottle or container. Replace cap after using.

PRECAUTIONS:

Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

ADVERSE REACTIONS (POSSIBLE PROBLEMS) AND WHAT TO DO:

The following may occur:

- Eyes stinging, burning or itching
- Excessive watering (tearing) of the eyes
- Unusual eye secretions
- Redness of the eyes
- Reduced sharpness of vision (visual acuity)
- Blurred vision
- Sensitivity to light (photophobia)
- Dry eyes

If you notice any of the above, **IMMEDIATELY** remove and examine your lenses.

If a lens appears to be damaged, do not reapply; consult your eye care practitioner. If the problem stops and the lenses appear to be undamaged, follow the "Directions" below, before reapplying the lens.

If the problem continues **IMMEDIATELY** remove your lenses, discontinue use of all lens care products that contact the eye, and consult your eye care practitioner.

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

DIRECTIONS:

TO LUBRICATE AND REWET LENSES DURING THE DAY:

With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT: Place 1 or 2 drops of **blink™** CL Lubricant Eye Drops on each side of each lens before application.

HOW SUPPLIED:

blink™ CL Lubricant Eye Drops is supplied in sterile 0.08 fl oz (2.5mL) and .03 fl oz (10mL) plastic bottles. The bottles are marked with the lot number and expiration date.

LENSES:

blink™ CL Lubricant Eye Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP) contact lenses.

September 2003

Distributed by:
Advanced Medical Optics, Inc.
Santa Ana, CA 92705 U.S.A.
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XXXXXX
9464X

SINGLE LABEL

Front:

(logo) AMO

blink™ CL Lubricant Eye Drops
For Soft and RGP Lenses

USE ONLY IF BREAKSEAL ON BOTTLE CAP IS INTACT

10 mL (0.3 fl oz) STERILE

Back:

CONTENTS: **blink™** CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%. If you are allergic to any ingredient in this product, **DO NOT USE.** **DIRECTIONS:** Apply 1 to 2 drops to each eye as needed. Blink several times. **PRECAUTIONS:** Store at room temperature. Use before the expiration date marked on the bottle and carton.

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XXXXX
9464X

Lot No.:

Exp. Date:

UNIT CARTON

Front Panel

(logo) AMO

blink™ CL Lubricant Eye Drops

For Soft and RGP Lenses

10mL (0.3 fl oz)

STERILE

Back Panel

blink™ CL Lubricant Eye Drops

For Soft and RGP Lenses.

DIRECTIONS:

TO LUBRICATE AND REWET LENSES DURING THE DAY:

With the lenses on the eye, apply 1 to 2 drops to each eye as needed, or as directed by your eye care practitioner. Blink several times.

FOR EXTRA COMFORT: Place 1 or 2 drops of **blink™** CL Lubricant Eye Drops on each side of each lens before application.

Top Flap

blink™ CL Lubricant Eye Drops

10mL (0.3 fl oz) STERILE

USE ONLY IF BREAKSEAL ON BOTTLE CAP IS INTACT.

Side Panel

blink™ CL Lubricant Eye Drops is used to lubricate and rewet soft and rigid gas permeable (RGP) contact lenses as well as to cushion lenses prior to application.

Questions or Comments? 1-800-347-5005

Distributed by Advanced Medical Optics, Inc.
Santa Ana, CA 92705 U.S.A.

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Side Panel

CONTENTS: **blink™** CL Lubricant Eye Drops is a sterile, buffered, isotonic, preserved solution. This aqueous formulation includes purified water, hyaluronic acid (sodium hyaluronate) sodium chloride, potassium chloride, calcium chloride, magnesium chloride, boric acid and is preserved with Purite® (stabilized oxychloro complex) 0.005%.

If you are allergic to any ingredient in this product, DO NOT USE.

PRECAUTIONS: Keep bottle tightly closed when not in use. For in-eye use only. Do not use in the lens case. Store at room temperature. Use before the expiration date marked on the bottle and carton. Keep out of the reach of children.

WARNING: SEE PACKAGE INSERT FOR ADDITIONAL AND IMPORTANT SAFETY INFORMATION.

LENSES:

blink™ CL Lubricant Eye Drops is for use with soft (hydrophilic) and rigid gas permeable (RGP) contact lenses.

Lot#

Part #

Expiration Date

XXXXXX