

Introduction

James Saviola, O.D.

FDA/Center for Devices and Radiological
Health/*Ophthalmic and
ENT Network Leader*

Outbreaks and Product Recalls

Rare pathogen Outbreaks

- *Fusarium* keratitis - Spring 2006
- *Acanthamoeba* keratitis – Spring 2007

Agenda

- Outbreak Updates
- CL wearers & Human factors
- Product Labeling
- Chemistry of Lens/Solution
- Microbiology
- Acanthamoeba disinfection
- Biocompatibility of Lens/Solution
- Clinical study methodology
- Discussion Questions

FDA's Ongoing Response To Product Recalls

- **Laboratory Studies**
- **Standards Development**
 - **ANSI**
 - **ISO**
- **Manufacturers Discussions**
- **Re-assess FDA Guidances**

Objectives

- FDA –obtain Panel comments for modifications to existing Guidance
- Industry – learn future regulatory pathways for these devices
- Consumers – help gain more knowledge in proper use of these devices

Fusarium Keratitis Outbreak Update

**Gene Hilmantel, O.D., M.S.
FDA/Center for Devices and Radiological
Health/Office of Device Evaluation**

Before the Outbreak

- Fungal Keratitis had generally been rare in contact lens wearers
- Generally < 5% of cases of contact lens related microbial keratitis

Beginning of Outbreak

- February 2006: significant numbers of cases in Hong Kong and Singapore
- Singapore cases reported to be related to use of Bausch and Lomb contact lens solutions
- March 2006: CDC began receiving reports of Fusarium cases in US
 - » Prompted CDC and FDA investigation

CDC

Case – Control study conducted

- Cases collected through active and passive means
- Controls – neighborhood-matched adult soft contact lens wearers
- Confirmed cases had positive corneal cultures
- Cases, controls, ophthalmologists were interviewed

Chang DC, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. JAMA. 2006 Aug 23;296(8):953-63.

U.S. Fusarium Cases

- Passive surveillance identified 180 confirmed *Fusarium* keratitis cases (June 1, 2005 – Sept.30, 2006)
- From 36 states and territories

Identified Risk Factors

(45 Cases, 78 Controls)

- ReNu with MoistureLoc
 - » Odds Ratio: 13.3
- Reuse of solution in case (“topping off”)
 - » Odds Ratio: 3.2

Investigation of Patient Products

- *Fusarium* -- NOT recovered from any unopened product
 - » contact lens solutions,
 - » lenses, or
 - » lens cases provided by case patients

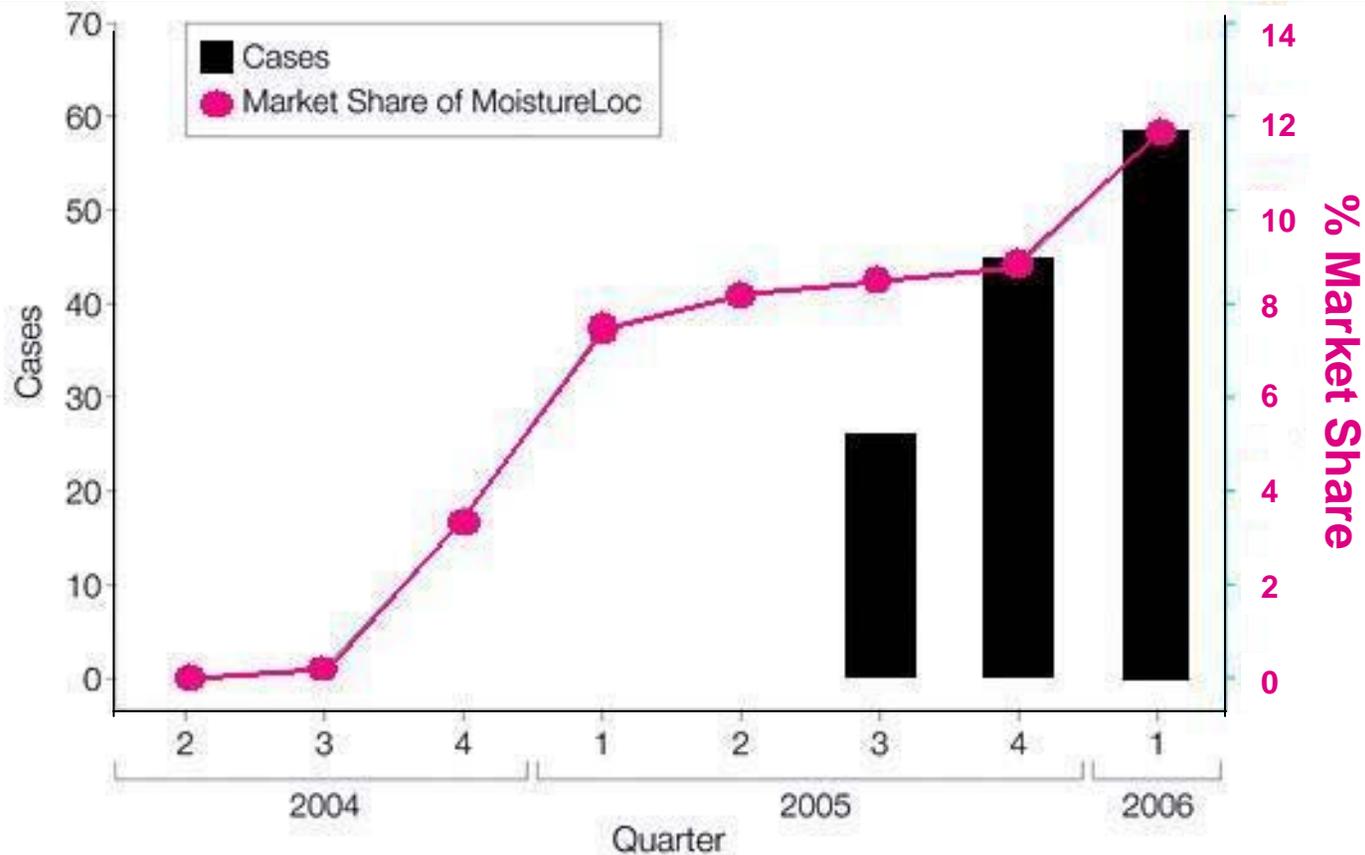
Genetic Typing of *Fusarium* Strains

- Genotyping scheme:
 - » High genetic diversity in *Fusarium* strains isolated
 - » Suggests that common source of contamination unlikely

FDA/CDC/B&L

- Investigated possible contamination at B&L manufacturing facility (Greenville, SC)
- No evidence for contamination found
- *Fusarium* -- NOT recovered from
 - » retained lots of care products;
 - » water samples (municipal water, de-ionized water, or distilled water)

Fusarium Cases and Market Share of B&L MoistureLoc



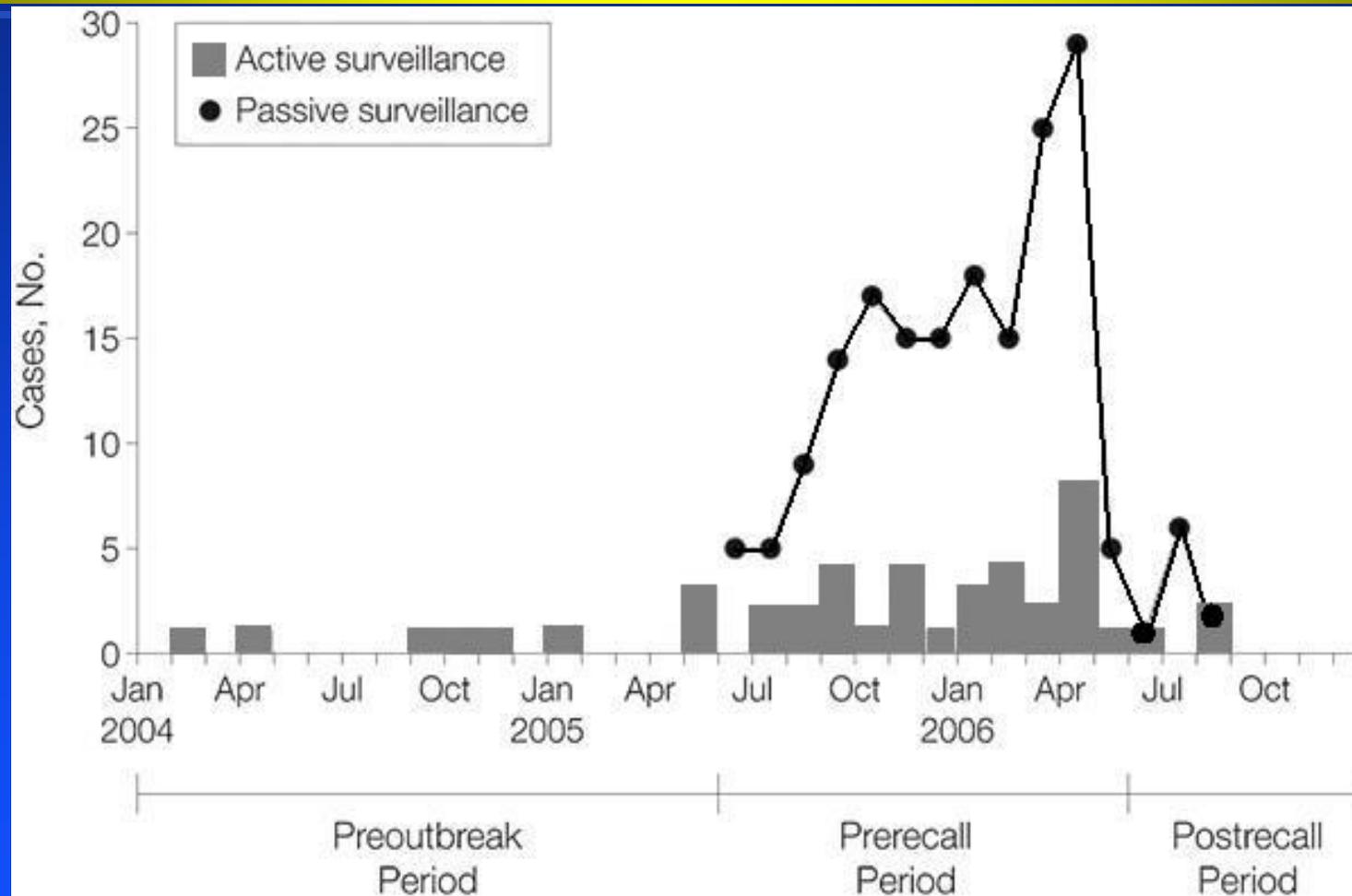
Chang DC, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. JAMA. 2006 Aug 23;296(8):953-63.

High Morbidity

- Corneal transplantation needed for ~30% of cases in U.S.

ReNu with MoistureLoc

- » US product sales stopped -- April 13, 2006
- » Worldwide recall -- May 15, 2006



From: Grant: JAMA, Volume 298(24).December 26, 2007.2867-2868

End of Outbreak

- Surveillance data show that the *Fusarium* outbreak ended within 2 months of the product recall

MoistureLoc Formula

- Contained 2 ingredients not in others:
 - » alexidine (a disinfectant)
 - » polyquartermium 10 (a moisture-retaining polysaccharide)
- Also a high content of poloxamer 407 (surfactant)
- Premarket testing had shown a high level of efficacy against *Fusarium*

CDC

Acanthamoeba Keratitits

What Do We Know About Contact Lens Wearers?

Bernard P. Lepri, OD, MS, MEd
FDA/Center for Devices and Radiological Health/Office of Device Evaluation

Demographics

- Over 30 million Americans wear contact lenses
- 67.7% are female
- 10% < age 18 or under
- 15% are between the ages of 18-24
- 50% are 25 to 44 years old
- Predominantly myopic
- 80% wear daily wear soft lenses
- >50% wear 1 to 2-week disposable lenses
- 15% wear extended wear soft lenses

American Optometric Association 2003

Care Regimens: Evolved but Complicated

- Cleaning
- Disinfecting
- Protein removal
- Hygiene of hands and lens cases
- Wearing time and replacement schedules

Origin of Complications

- 80% of contact lens complications are related to deficient compliance with wear and maintenance care

Ky W, Scherick K, Stenson S. Clinical Survey of lens care in contact lens patients. *CLAO J* 1998;24:216-219.

- Wearer's perception of own behavior is essential to minimizing and/or preventing complications.
- Several studies verify these facts

Studies on Medical Noncompliance

- In 2000, 759.3 million physician visits
 - » 188.3 million resulting from not following physician's advice
 - » Noncompliance rate of 24.8%

DiMatteo, MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care* 2004;42:200-209.

- Patients forget as much as 50% of what they heard within minutes of leaving a medical visit
- Retention depends on the doctor-patient relationship and repetition, and any measures that improve these two factors should improve compliance

Davidson, Si, Akingbehin T. Compliance in Ophthalmology. *Trans Ophthalmol soc UK* 1980;100:286-290.

- Contact lens field
 - » Noncompliance ranges from 50% to 79%

De Oliveira PR, Temporini-Nastari ER, Ruiz Alves M, Kara-Jose N. Self-evaluation of contact lens wearing and care by college students and health care workers. *Eye Contact Lens*. 2003 July;29(3):164-7.

Factors Affecting Compliance

- Complexity of treatment
- Frequency and duration
- Cost of regimen/treatment
- Medical literature:
 - There is a higher incidence of noncompliance in conditions that are asymptomatic, is prophylactic, or suppressive in nature.
- Factors necessary for contact lens safety are those identified as contributing to noncompliance

Donshik PC, Ehlers WH, Anderson LD, Suchecki JK. Strategies to better engage, educate, and empower patient compliance and safe lens wear: compliance: what we know, what we do not know, and what we need to know. *Eye Contact Lens*. 2007 Nov;33(6 Pt 2): 430-3; discussion 434.

Contact Lens Compliance Study Findings

- 54.2% considered themselves poor wearers
 - » Inadequate cleaning of lenses or case (44.3%)
 - » Noncompliance with medical orientation (15.1%)
- Contact lens care procedures
 - » 79.1% failing in implementation of procedures
 - » 30.0% poorly prepared for cleaning and maintenance awareness
 - Lack of knowledge

De Oliveira PR, Temporini-Nastari ER, Ruiz Alves M, Kara-Jose N. Self-evaluation of contact lens wearing and care by college students and health care workers. Eye Contact Lens. 2003 July;29(3):164-7.

Others

- Habitual wearers; avg. 2.6 years of wear; 74% were noncompliant;
 - 20% didn't understand chemical disinfection;
 - 8% didn't understand purpose of rinsing;
 - 18% didn't comprehend function of daily cleaner;
 - 22% did not wash their hands before handling their lenses
 - Reinforcement at follow up visits improved this behavior

Collins MJ, Carney LG. Compliance with care and maintenance procedures amongst contact lens wearers. *Clin Exp Optom* 1986;9:174-177

- 91% of patients failed in following at least one procedure regarding the use of a multipurpose solution, despite the ease of use!

Turner FD, Stein JM, Sager DP, et al. A new method to assess contact lens care compliance. *CLAO J* 1993;19:108-113

Human Factors Engineering

Goal: make products efficient, safe, and easy to learn and use

- Relies heavily on methods of the behavioral sciences
- Accomplishes goals by trying to understand HOW the device is used by the consumer.

Synonyms: ergonomics, usability engineering, user experience design, etc.

Use Error

Previously known as “User” Error

- Recognition that the “User” should not shoulder the blame
- Manufacturer has responsibility to reduce “Use Error” through proper design, testing and labeling.

Special challenges for contact lenses

Summary of Use Errors in Contact Lens Wearers

- Irregular cleaning of lenses
 - » Skipping daily cleaning or not following recommended disinfection times
 - » Inadequate rinse times
- Poor hand hygiene (lack of hand washing)
- Using tap water or saliva to wet lenses
- Not following lens replacement schedules
 - » Extending wear of lenses beyond manufacturers or eye care professionals recommendations
- Lack of regular eye exams and/or follow up contact lens exams
- Irregular replacement of disinfecting solutions
 - » Includes topping off and reuse of solutions
 - » Using solutions beyond their expiration date

Recommendations

- Labeling should provide written instructions along with the reasons for the various procedural steps and the consequences for not following them.
- Eye care professionals should reinforce lens care regimens with their patients and utilize both the patient and practitioner guides provided with the care products.
- Care products should be designed and tested consistent with consumer use patterns.
 - » Product labeling should include a discard date for use after opening of the product.

Question

Please discuss our proposal for specifying a discard date on lens care product labeling in addition to an expiration date.

Patient Labeling for Contact Lenses and Care Products



Carol Clayton

FDA/Center for Devices and Radiological Health/Office of
Communication, Education and Radiation Programs

Overview

- Patient labeling principles
- Advice for Patients
 - » *Fusarium* Keratitis
 - » *Acanthamoeba* Keratitis
- Proposed new patient labeling for consideration

Patient Labeling Principles

Guidance on Medical Device Patient Labeling

(<http://www.fda.gov/cdrh/ohip/guidance/1128.pdf>)

Patient Labeling Principles

- Appropriate content of an effective warning or precaution:
 - » Signal word (**WARNING, CAUTION**)
 - » **Hazard avoidance directive (Do Not, Never, Avoid, or Do, if more appropriate, followed by the action to avoid (or perform))**
 - » **Clear statement of the nature of the hazard**
 - » Consequences

Advice for Patients

- *Advice for Patients With Soft Contact Lenses: Risk of Serious Fungal Infection*
(April 10, 2006; Updated with New Information on April 21, 2006)
- *Advice for Patients with Soft Contact Lenses: Acanthamoeba Keratitis Infections Related to Complete® MoisturePlus Multi Purpose Contact Lens Solution* (May 31, 2007)

Reuse or “Top-off”

Current Instructions for Use:

- Use only fresh multipurpose solution each time you soak your lenses.

Proposed WARNING:

- Do not reuse or “top – off” old solution left in your lens case since solution reuse reduces effective lens disinfection and could lead to serious eye infection.



Question

Please discuss whether our proposed warning on reuse and topping-off is warranted. If yes, please identify any other message that should be conveyed in this warning.

Rub and Rinse Time

Current Instructions for Use:

- Rinse your lens for 10 seconds and repeat with the second side for a total of 20 seconds.
- Follow the complete recommended lens rubbing and rinsing times in the labeling to adequately disinfect your lenses and reduce the risk of contact lens contamination.

Proposed WARNING:

- Rub and rinse your lenses for the correct amount of time to help prevent serious eye infections.
- Never use saline solution or rewetting drops to disinfect your lenses. These solutions will not disinfect your lenses. Not using the recommended disinfectant can lead to serious eye infection.

Question

Please discuss whether our proposed warning on rub and rinsing time is warranted. If yes, please identify any other message that should be conveyed in this warning.

Lens Case Care

Current Instructions for Use:

- Rinse your lens case with sterile contact lens solution (never use tap water) and leave the lens case open to dry after each use.
- Replace your lens cases at least once every three months. Contact lens cases can be a source of bacterial growth.

Proposed WARNING:

- Do not store your lenses or rinse your lens case with tap water, bottled water or any non-sterile solution. Only use fresh multipurpose solution so you don't contaminate your lenses or lens case. Use of non-sterile solution can lead to serious eye infection.

Question

Please discuss whether our proposed warning on lens case care is warranted. If yes, please identify any other message that should be conveyed in this warning.

Water Activity

Proposed Instructions for Use:

- Remove your lenses before any activity involving water, including showering, using a hot tub, or swimming.

Proposed WARNING:

- Do not wear your lenses during any water activity such as showering, using a hot tub, or swimming. There can be a risk of eye infection from these sources.

Question

Please discuss whether our proposed instructions for use and warning on water activities are warranted. If yes, please identify any other message that should be conveyed.

Summary

- Labeling does not solve all problems with contact lenses.
- Use of other types of communication with the user to relay good hygiene behavior:
 - » Eye care practitioner
 - » General practitioners
 - » School nurses
 - » Posters
 - » CDs
 - » Web sites
 - » Videos

Lens and Solution Compatibility Issues

**Joseph C. Hutter, Ph.D.
FDA/Center for Devices and Radiological
Health/Office of Device Evaluation**

Overview

Lens and Solution Compatibility Issues

- Lens Groupings
- Limitations
- Proposed Improvements

Current FDA Lens Groupings

History – July 1985 FDA draft guidance

Rationale for Groupings

Monomers

- Hydrophilic: H₂O interaction
- Hydrophobic: mechanical strength
- Crosslinkers: mechanical strength, thermal stability

Hydrophilic monomers: HEMA, GMA, VP, MA

Current FDA Lens Groupings

Rationale for Groupings (cont'd)

Properties:

- Ionic materials: increased uptake of proteins/preservatives
- Water content: porosity and hydrophilicity

Differences:

- Ionic: MA added to increase % H₂O
- Non-ionic low water (38-45%): HEMA, HEMA-VP or GMA
- Non-ionic High water (70-79%): VP-based

Current FDA Lens Groupings

- Group 1 – Nonionic hydrogels <50% water
- Group 2 – Nonionic hydrogels >50% water
- Group 3 – Ionic hydrogels <50% water
- Group 4 – Ionic hydrogels >50% water

Pre-Clinical Testing in an FDA Group

- 1994 – 30-cycle test with recommended care products, unless the lens is in a group and labeled with already approved care products for that lens group
- Poly(HEMA) lenses from Groups 1 and 4 are tested in a 30-cycle test
- Representative silicone hydrogels are tested

Limitations of Current Lens Groupings

1. Solution and Lens Incompatibilities

- AMO UltraCare Disinfecting System (peroxide catalase) with B&L PureVision (balafilcon A--*originally FDA Group 3*): *Precaution in labeling*
- Ciba SoloCare (PHMB) with Vistakon Acuvue Advance (galyfilcon A--*originally FDA Group 1*): *Precaution in labeling, SoloCare no longer marketed*

Causes of incompatibilities were never determined.

Limitations of Current Lens Groupings

2. Unique Features of Silicone Hydrogels

Conventional poly(HEMA) lenses	Silicone hydrogel lenses
Water filled pores	Water filled pores
	Silicone phase
	Surface treatments
	Water soluble polymers

Limitations of Current Lens Groupings

3. Care product formulations are more complex (*more than cleaning and disinfecting lenses*)

- Comfort
- Moisture retention
- Conditioning
- Lubrication

HA Ketelson, DL Meadows, RP Stone, Dynamic Wettability Properties of a Soft Contact Lens Hydrogel, Colloids and Surfaces B; Biointerfaces 40 1-9 (2005)

B Levy, D Heiler, S Norton, Report on Testing from an Investigation of Fusarium in Contact Lens Wearers, Eye & Contact Lens, 32(6) 256-261 (2006)

New Groupings for Consideration

ISO TC 172/SC7 Working Group 9 (Contact Lenses and Contact Lens Care Products) is in the process of amending the current classification standard, ISO 18369-1 to add a Group 5 for enhanced oxygen permeability materials (e.g. silicone hydrogels).

FDA Group 5: Is a Single Grouping Sufficient to Describe Si-Hy Performance? Joseph C. Hutter, Ph.D., Center for Devices and Radiological Health, FDA, Nov. 2007, siliconehydrogels.org

Limitations to Group 5:

- Pore size (water content)
- Ionic content
- Surface treatments
- Silicone phase properties

FDA Proposal for Consideration

Group 5 Representative Silicone Hydrogels

1. <i>Iotrafilcon B</i>	<i>Plasma polymerized surface</i>
2. <i>balafilcon A</i>	<i>Plasma oxidized surface, macropores</i>
3. <i>galyfilcon A</i>	<i>No surface treatment, semi-interpenetrating network of water soluble polymer</i>
4. <i>comfilcon A</i>	<i>No surface treatment, co-polymerized with substantial VP</i>

This list will grow as more silicone hydrogels are added to the market.

Question

Please discuss whether you agree with:

ISO's current consideration of having silicone hydrogel lenses as a separate group and;

FDA's plan to further stratify the silicone hydrogel lens group into subcategories.

Microbiology Issues

Myra Smith, MS

FDA/Center for Devices and Radiological
Health/Office of Device Evaluation

Overview

- Current Microbiology Test Methods
- Limitations to Current Test Methods
- Studies Related to the Limitations
- Microbiology Issues for Panel Consideration

Current Microbiology Test Methods

- Disinfection Efficacy Tests

ISO 14729

- » Stand Alone Test

- » Regimen Test

- Preservative Efficacy Test

ISO 14730

Current Test Method: ISO 14729 Disinfection Efficacy Tests

Test Organisms

- *Pseudomonas aeruginosa* ATCC 9027
- *Staphylococcus aureus* ATCC 6538
- *Serratia marcescens* ATCC 13880
- *Candida albicans* ATCC 10231
- *Fusarium solani* ATCC 36031

Current Test Method: ISO 14729 Stand Alone Test

- Potency measure of fresh solution
- No lenses
- Measures 'kill' during minimum recommended soak time
- High inoculum level (10^6 cfu/ml)

Current Test Method: ISO 14729 Stand Alone Test Performance Criteria

Established for Products with Digital ‘Rub and Rinse’ directions

- Primary Performance Criteria

Evaluation of entire care regimen not required due to higher level of microbial kill in Stand Alone testing

- Secondary Performance Criteria

Further evaluate entire care regimen’s ability to kill and remove organisms due to lower levels of microbial kill by product in Stand Alone testing

- Failure to Meet Secondary Performance Criteria

Product rejected for marketing

Current Test Method: FDA Modifications to ISO 14729

“No Rub” Directions

- FDA recommends adding organic soil to Stand Alone test
- FDA recommends evaluating entire care regimen’s ability to kill and/or remove organisms for all products with ‘No Rub’

Current Test Method: ISO 14729 Regimen Test

- Simulated use
- Measure both 'removal' and 'kill'
- High inoculum level (10^6 cfu/ml)
- Organic soil
- Conventional Hydrogel lenses
- No Silicone Hydrogel lenses
(marketed after FDA guidance & ISO 14729)

Current Test Method: ISO 14729 Regimen Test Performance Criteria

- Same performance criteria used for both 'Rub' and 'No Rub' cleaning directions
- Performance criteria allows for recovery of a very low number of organisms from both the lens and the soak solution remaining in the lens case
- Variability expected in performing care regimens which rely on both physical removal and kill

Current Test Method: ISO 14730 Antimicrobial Preservative Efficacy Test

- Measures preservative effectiveness for up to 30 days
- Microbial rechallenge added on Day 14
- Without lenses
- Initial and shelf-life testing
- Basis for 30 day lens storage

Current Test Method: ISO 14730 Preservative Efficacy Test

Test Organisms

- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Escherichia coli*
- *Candida albicans*
- *Aspergillus niger*

Limitations to Current Test Methods

- Recent microbial keratitis outbreaks (Fusarium and Acanthamoeba)
- Changes in lens materials, care product formulations and directions for use
- Improve predictability of 'real world' performance

Limitations: Microbial Keratitis Outbreaks (*Fusarium* and *Acanthamoeba*)

- Both care products met current FDA/ISO performance criteria (Cleaning and Disinfection)
- Efficacy against *Acanthamoeba* was not tested

Limitations: Changes in Lens Materials, Care Products and Directions for Use

- Disinfection efficacy is determined by complex interactions
- Effect of preservative uptake by lenses on disinfection efficacy is not adequately addressed by current methods
- No silicone hydrogel (SH) lenses used in Regimen test
- 'No Rub' (Rinse only) cleaning directions

Limitations: 'Real World' Performance Issues

Test methods may not reflect 'real world' experience:

- Regimen test rub and rinse times (e.g., total up to 20 seconds) exceed typical consumer use.
- Deviation from directions for use (e.g. topping off)
- Improper care of lens case/hygiene (e.g. biofilm)
- Organisms causing clinical infection may be more resistant than current test organisms

Limitations: 'Real World' Performance Issues (cont'd)

- Disinfection and Preservative Efficacy Testing not always done with product at low end of active ingredient specifications (worst case).
- May result in reduced efficacy in marketed lots.

Related Studies: Preservative Absorption FDA/CDC Study

Absorption of Alexidine by Contact Lenses and Lens Cases and its Effect on Disinfection Efficacy against Fusarium solani, K. Warburton, J. Noble-Wang, B. Henry, S. Holliday, M. Smith, J. Hutter and J. Saviola (May 2007). Poster presented at annual American Society for Microbiology Meeting.

Related Studies: FDA/CDC Study (cont.)

Summary of Test Method

- Both silicone hydrogel and conventional hydrogel lenses inoculated with *F. solani* in lens cases
- Soak times up to 7 days
- Alexidine and Antimicrobial Assays

Related Studies: FDA/CDC Study (cont.)

Study Conclusions

- Alexidine uptake by lenses reduced alexidine concentration over time in lens case solution
- Decreased alexidine concentration resulted in reduced antimicrobial activity against *F. solani*
- Similar studies needed with other care products and lenses

Related Studies: Additional Studies of Preservative Uptake

Additional preservative and lens materials studied in the literature

Decreases in preservative concentration during lens storage reduce disinfection efficacy

George M, et al. ARVO 2007; Lakkis C, et al. ARVO 2007; Rosenthal RA, et al. Eye & Contact Lens 2006

Levy B, et al. Eye & Contact Lens 2006; Sentell KB, Beaulieu EH. CLES 2006; Rosenthal RA, et al. Contact Lens Spectrum. July 2002

Donnelly KH, Waworuntu RV. Eye & Contact Lens 2004

Related Studies: Development of New Test Methods

ANSI/ISO currently developing new method to evaluate disinfection efficacy in the presence of lens and lens case.

- Includes measurement of preservative concentration at various storage times up to 7 days
- Uses a variety of lens types, including silicone hydrogels
- Measures log reduction of ISO 14729 challenge organisms

Related Studies: Microbial Attachment and Biofilm Formation

Microbial (bacterial and fungal) attachment to lenses may vary by lens type, and species and/or strain of organism

Biofilm on lenses or cases may be tightly attached, difficult to physically remove, more resistant to care product preservatives

Effect of biofilm on disinfection efficacy is not evaluated in current test methods.

Kodjikian et al. Graefes Arch Clin Exp Ophthalmol 2007,
Imamura, Y. et al. Antimicrobial Agents and Chemotherapy 2008
Zhang, S. et al. Cornea 2007
Beattie, TK et al. Ophthalmology 2006

Related Studies: The Role of Rubbing

Removal of additional microorganisms from lens prior to exposure to solution preservative

Shih et al 1985: Rubbing and Rinsing removes 4 logs bacteria, Rinsing alone removes 3 logs

Rosenthal et al 2004: Some solutions failed regimen test with rinse only (5 sec) regimens; all failed with soak only

Related Studies: The Role of Rubbing (cont.)

Removal of additional debris, deposits from lens

Nichols et al, 2006 observed lower levels of 3-4+ lens deposits when a rub regimen was used by "heavy depositors"

For Panel Consideration

Rubbing Potentially Increases Safety Margin For Lens Wearers:

- Reducing the microbial challenge during disinfection
- Fewer residual lens deposits on conventional and silicone hydrogel lenses entering the lens case to interfere with disinfection efficacy
- Less biofilm formation in lens case
- Decreased interference with disinfection efficacy
- Cleaner lenses

Question

Currently rub and no-rub care products have been cleared by the FDA for marketing in the United States. In light of all the data currently available, please discuss your recommendations for continuing to have no-rub directions in the product labeling.

For Panel Consideration

- Modifications to Regimen test to Improve Predictability of 'Real World' Performance
 - Test silicone hydrogel lenses
 - Establish realistic rub and rinse times
- FDA is currently working with members of ISO regarding modifications to the regimen test.

Question

Please discuss our proposal to revise the current Regimen Test in order to improve predictability of 'Real World' performance, and include the following topics in your discussion:

- Testing marketed silicone hydrogels
- Defining 'worst case' rub and rinse times (e.g., 5 sec. rub and 5 sec total rinse time)

For Panel Consideration

Acanthamoeba as a Challenge Organism in Disinfection Efficacy Tests

- Variability in methodologies. Need to identify species, stage (cyst, troph), challenge concentration, recovery methods, performance criteria used in efficacy testing
- Develop and standardize methodology in conjunction with ANSI and ISO

Question

Please discuss your recommendations for adding *Acanthamoeba* as a challenge organism in disinfection efficacy testing.

For Panel Consideration

Evaluating the Effects of Preservative Uptake by Contact Lenses on Disinfection Efficacy:

- Future FDA participation in planned studies for evaluating new test methodology
- Identify lens/solution incompatibilities
- Basis for recommended storage time

Question

Please discuss our proposal to develop standardized test methods to evaluate the effects of preservative uptake by contact lenses on disinfection efficacy.

For Panel Consideration

Conducting Microbiology Effectiveness Testing Using 'Worst Case' Conditions

- Disinfection and Preservative Efficacy testing at low end of active ingredient specification (worst case).
- Testing more resistant clinical isolates

Question

Please discuss our proposal for modifying Disinfection and Preservative Efficacy testing by:

- Testing at the lower end of the active ingredient specifications to simulate worst case conditions and;
- Including more resistant clinical isolates in these tests.

CDC Acanthamoeba Keratitis Presentation

Lens – Solution Interactions: Impact on Biocompatibility

Molly Ghosh, PhD, DABT
FDA/Center for Devices and Radiological
Health/Office of Device Evaluation

Presentation Overview

- Background on Lens-Solution Interactions
- Testing Revision for Consideration
(Cytotoxicity test proposal)

Background

Preclinical Testing of Contact Lens Care Solutions

- FDA's 1997 Premarket Notification (510(k)) Guidance for Contact Lens Care Products
- Post 1997: Silicone Hydrogel Lenses (1999)
- Testing Revision for Consideration
 - » Preclinical and Clinical Study Designs to address potential lens-solution interaction and its impact on product safety

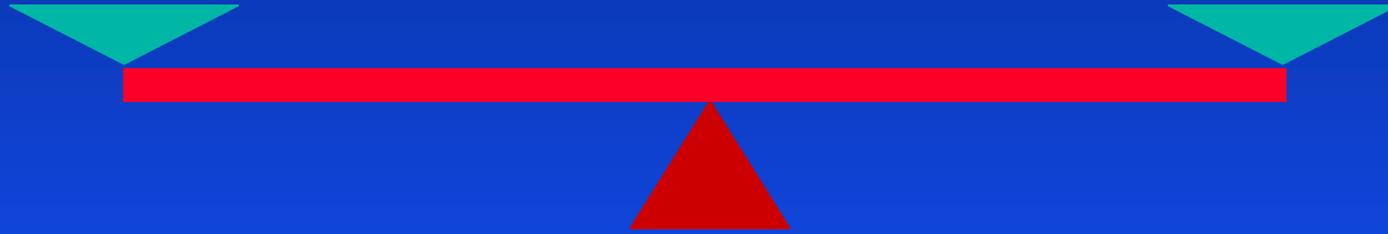
Fusarium Keratitis Outbreak

- Loss of antimicrobial activity during lens storage in cases
- Cytotoxic effects of MPS
 - Damage to epithelial barrier function
 - Increased risk of microbial infection
- Synergistic Effects
- Patient behavior – “topping off”

Contact Lens Care Solution

Efficacy

Toxicity



- Cytotoxic effects by direct contact with ocular tissues
- Cytotoxic effects by indirect contact through contact lenses

Lens-solution Interactions: Cytotoxic Effects

- Preservative uptake/release of ingredients from MPS by lenses
 - Water content
 - Ionic nature
 - Chemical functional groups
- Uptake of other chemical ingredients
- Corneal staining – could be mild, transient, asymptomatic
- Compromised corneal surface – increased risk for infection

Preclinical Testing of Contact Lens Care Solutions

ISO TC 172 / SC 7/ WG 9 “Contact Lens and Care products” Update:

- Draft proposal prepared by FDA on cytotoxicity testing of contact lens care solution
 - Discussed at ANSI Z80 SC7 Meeting on March 31, 2008
 - To be discussed at ISO TC 172 / SC 7/ WG 9 meeting in Paris, July 2008

Biocompatibility Testing for Multipurpose Solution (MPS)

- Testing on MPS (per FDA's 1997 guidance document)
- Testing on various groups of lenses soaked in MPS (FDA's testing revision for consideration)
 - Cytotoxicity Testing (*in vitro*)

Lens Groups to be Tested with MPS

1. Conventional Hydrogels:

- i. Group I (polymacon)
- ii. Group IV (e.g. etafilcon A)

2. Silicone Hydrogels:

- i. Surface modifications with plasma polymerization (recommend lotrafilcon B due to higher water content)
- ii. Plasma oxidation surface treatment (balafilcon A)
- iii. Not surface treated (recommend galyfilcon A due to higher water content)

Test Proposal: Points taken into consideration

- Both in vitro and in vivo studies necessary for evaluation of MPS
- Ocular tissue and cell-based in vitro models
- No single predictive in vitro assay validated for contact lenses and care solutions yet
- L-929 cell culture model (ISO/USP) for cytotoxicity test proposal

Testing Revision for Consideration

Cytotoxicity Test

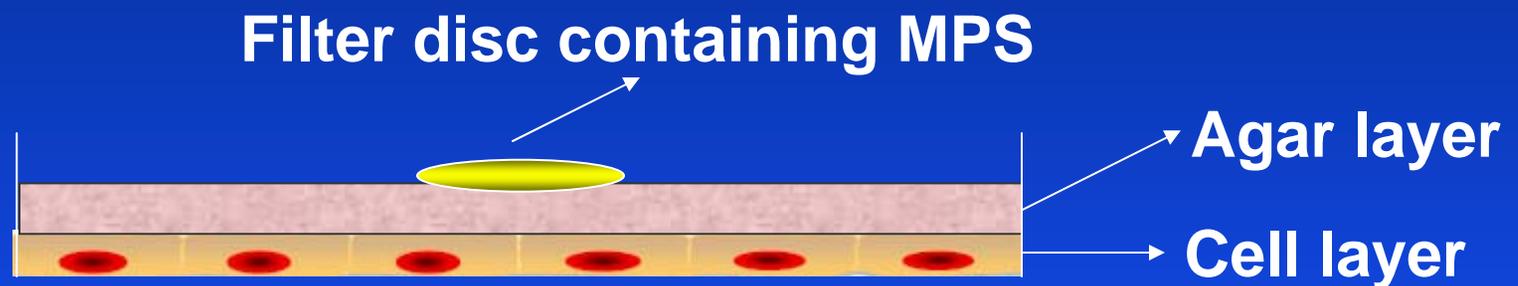
Salient Features of Cytotoxicity Test Proposal for Testing of MPS

- Standard ISO/USP test methods
- L-929 cell model
- Tests to evaluate direct exposure to MPS
- Test to evaluate indirect exposure to MPS through contact lenses
 - » Conventional hydrogels (Gr I and IV)
 - » Silicone hydrogels with different surface treatments

Cytotoxicity Testing on MPS

(to evaluate direct exposure)

- **Agar Diffusion Assay (currently used)**

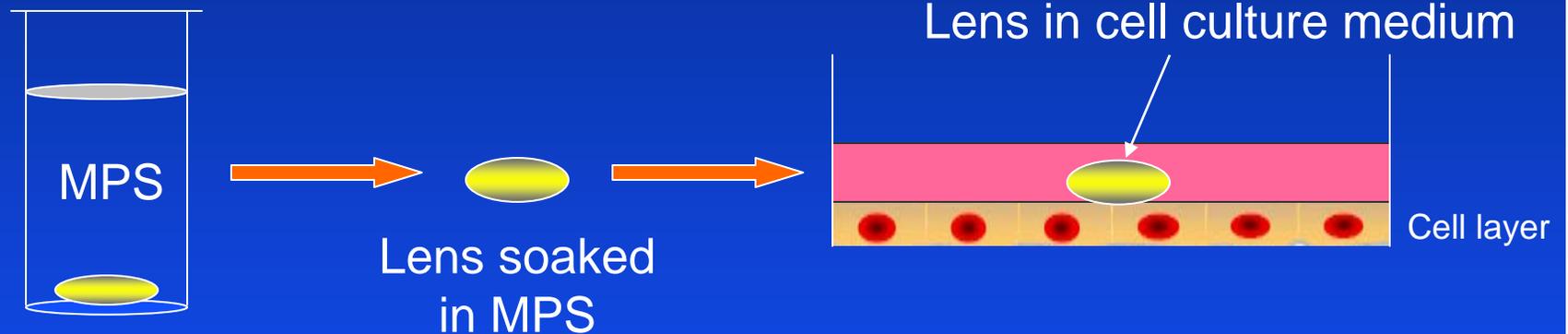


- **Modified Elution Assay (additional test)**



Cytotoxicity Testing of MPS-soaked Lenses (additional test to evaluate indirect exposure)

Direct Contact Assay



- Conventional hydrogel lens
- Silicone hydrogel lens

Non-cytotoxic response



Severe cytotoxic response



Question

The current cytotoxicity test involves testing on the multipurpose solution by itself, and not in conjunction with various groups of lenses.

Please discuss our proposal to include both conventional and silicone-hydrogel contact lenses soaked in the multipurpose solution for Direct Contact cytotoxicity testing to evaluate the multipurpose solution.

The Impact of Silicone-Hydrogel Contact Lenses on Clinical Study Methodology

Marc Robboy, O.D.

FDA/Center for Devices and Radiological
Health/Office of Device Evaluation

Overview

- Current 510(k) Guidance
- Si-Hy CLs and Interactions
- Proposed Revisions to 510(k) Guidance
- Recent Events & Patient Labeling

May, 1997 Premarket Notification 510(k) Guidance for CL Care Products: Clinical Investigations

Lens Mat'l	Test	Control
Group IV	20	10
Group I	20	10

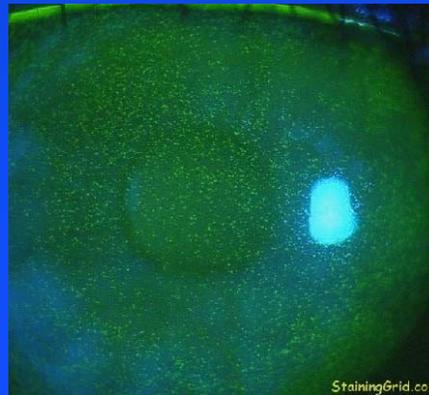
<http://www.fda.gov/cdrh/ode/contlens.pdf>

Silicone Hydrogel Contact Lenses: Interactions with CL Care Products Solution-related Corneal Staining

Preservative Uptake & Release:

- *Significantly more asymptomatic staining with PHMB-based care system, consistent with a classical solution-based toxicity reaction.*

Jones L, MacDougall N, et al. Asymptomatic corneal staining associated with the use of balafilcon silicone-hydrogel contact lenses disinfected with a PHMB-preserved care regimen. *Optom Vis Sci.* 2002; 79(12): 753-761.

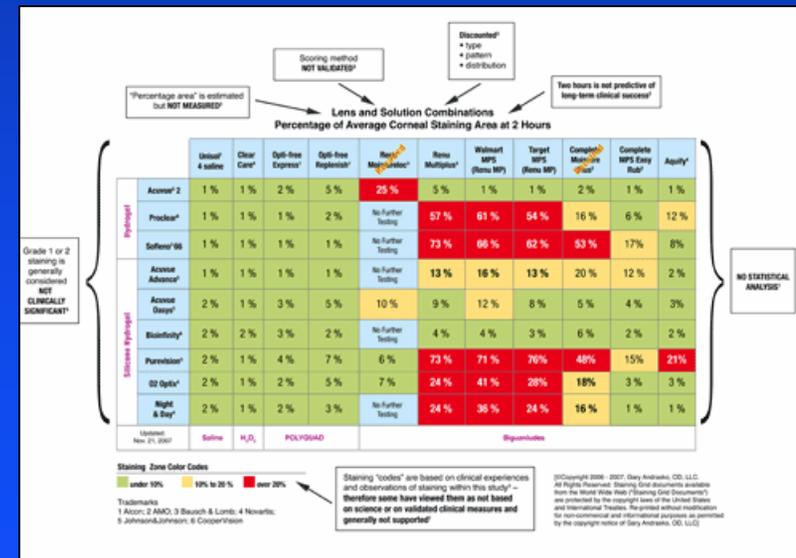


Silicone Hydrogel Contact Lenses: Interactions with CL Care Products Solution-related Corneal Staining

Lens and Solution Combinations
Percentage of Average Corneal Staining Area at 2 Hours

		Unisol ¹ 4 Saline	Clear Care ⁴	Opti-free Express ¹	Opti-free Replenish ¹	Renu Moistoretoc ²	Renu Multiplus ³	Walmart MPS (Renu MP)	Target MPS (Renu MP)	Complete Moisture Plus ²	Complete MPS Easy Rub ²	Aquify ⁴
Hydrogel	Acuvue ² 2	1%	1%	2%	5%	25%	1%	1%	1%	2%	1%	1%
	Proclear ⁶	1%	1%	1%	2%	No Further Testing	57%	61%	54%	16%	6%	12%
	Soflens ³ 66	1%	1%	1%	1%	No Further Testing	73%	66%	62%	53%	17%	8%
Silicone Hydrogel	Acuvue Advance ³	1%	1%	1%	1%	No Further Testing	13%	16%	13%	20%	12%	2%
	Acuvue Oasys ³	2%	1%	3%	5%	10%	9%	12%	8%	5%	4%	3%
	Biofinity ⁶	2%	2%	3%	2%	No Further Testing	4%	4%	3%	6%	2%	2%
	Purevision ³	2%	1%	4%	7%	6%	73%	71%	76%	48%	15%	21%
	O2 Optix ⁴	2%	1%	2%	5%	7%	24%	41%	28%	18%	3%	3%
	Night & Day ⁴	2%	1%	2%	3%	No Further Testing	24%	36%	24%	16%	1%	3%
Updated: Nov. 21, 2007		Saline	H ₂ O ₂	POLYQUAD			Biguanides					

<http://www.staininggrid.com/>



<http://www.truthaboutstaininggrid.com/>

Silicone Hydrogel Contact Lenses: Interactions with CL Care Products Solution-related Corneal Staining

- *Corneal infiltrative events were 3X more likely to occur in eyes exhibiting solution toxicity compared to unaffected eyes.*

Carnt N, Jalbert I, et al. Solution toxicity in soft contact lens daily wear is associated with corneal inflammation. *Optom Vis Sci.* 2007; 84(4): 309-315.

- *Significant difference in corneal epithelial permeability when effect on barrier function of different care systems were measured.*

Hall, J, Paugh J, et al. A pilot study of the effect of silicone-hydrogel lenses and marketed multi-purpose solutions on human epithelial barrier function. *ARVO 2007*, Ft. Lauderdale, FL.

Silicone Hydrogel Contact Lenses: Interactions with CL Care Products Solution-related Corneal Staining

- *The literature reflects that superficial punctate corneal staining does not reflect corneal injury or toxicity.*

Ward KW. Superficial punctate fluorescein staining of the ocular surface. *Optom Vis Sci.* 2008; 85(1): 8-16.

- *No increase in infections in presence of low-grade staining*
- *Highly unlikely that staining could disappear so rapidly if it compromised epithelial tissue.*
- *Apparent misuse of “solution cytotoxicity” warrants reevaluation.*

Levy B. Superficial corneal “staining”—clinical observation and risk assessment. *Eye Contact Lens.* 2007 33: 165–166.

Silicone Hydrogel Contact Lenses: Interactions with CL Care Products Solution-related Corneal Staining

Follow-up visits and corneal staining:

- *Maximum corneal staining occurs within 2-4 hours post-insertion.*

Garofalo R, Dassananyake N, et al. Corneal staining and subjective symptoms with multipurpose solutions as a function of time. *Eye Contact Lens*. 2005; 31(4): 166-174.

- *DW soft lens wearers should be routinely examined soon after lenses are inserted, and alternative solution/lens type combinations should be investigated.*

Carnt N, Jalbert I, et al. Solution toxicity in soft contact lens daily wear is associated with corneal inflammation. *Optom Vis Sci*. 2007; 84(4): 309-315.

May, 1997 Premarket Notification 510(k) Guidance for CL Care Products: Clinical Investigations

Current Assessment of Corneal Staining:

- Follow-up visit schedule contains target dates, but does not indicate specific time of day

Question

Please discuss your recommendation for an additional follow-up visit at 2 hours in order to assess for solution-related corneal staining.

Please discuss whether this should be included in lens care products and/or lens guidance.

May, 1997 Premarket Notification 510(k) Guidance for CL Care Products: Clinical Investigations

Proposed Interim Testing of Si-Hy Lenses

- Four lens types consisting of:

Silicone Hydrogels

- surface modification by plasma polymerization (lotrafilcon B, due to the higher H₂O content)
- plasma oxidation surface treatment (balafilcon A)
- not surface treated (galyfilcon A, due to the higher H₂O content)

Conventional Hydrogels

- Group IV (e.g., etafilcon)

**May, 1997 Premarket Notification
510(k) Guidance for CL Care Products:
Clinical Investigations
Proposal**

Lens Mat'l	Test	Control
Si-Hy:		
<i>Iotrafilcon B</i>	30	15
<i>balafilcon A</i>	30	15
<i>galyfilcon A</i>	30	15
Group IV	30	15

Question

Please provide your recommendations on the inclusion of silicone hydrogel lenses in the clinical investigations of contact lens care products.

May, 1997 Premarket Notification (510(k)) Guidance for CL Care Products: Labeling/Directions for Use

Role of Rubbing and Rinsing

- FDA has cleared both rub-and-rinse and no-rub MPS care products
- Microbiology references:
 - » *Removal of additional microorganisms from lens prior to exposure to solution preservative*
 - » *Removal of additional debris, deposits from lens*

Shih et al 1985: Rubbing and Rinsing removes 4 logs bacteria, Rinsing alone removes 3 logs

Rosenthal et al 2004 found some solutions failed regimen test with prototype rinse only (5 sec) regimens; all failed with soak only

Nichols et al, 2006 observed lower levels of 3-4+ lens deposits when a rub regimen was used by heavy depositors

May, 1997 Premarket Notification (510(k)) Guidance for CL Care Products: Labeling/Directions for Use

Role of Rubbing and Rinsing

- Professional organization recommendations
 - » American Academy of Ophthalmology
 - “Consider performing a "rub and rinse" lens cleaning method, rather than a no-rub method...”
 - » American Academy of Optometry
 - » American Optometric Association
- *Growing evidence supports digital rub component.*

Butcko V, McMahon T, et al. Microbial keratitis and the role of rub and rinsing. *Eye Contact Lens*. 2007; 33(6): 421-423.

Question

Currently rub and no-rub care products have been cleared by the FDA for marketing in the United States. In light of all the data currently available, please discuss your recommendations for continuing to have no-rub directions in the product labeling.

Overview

- Current 510(k) Guidance
- Si-Hy CLs and Interactions
- Proposed Revisions to 510(k) Guidance
- Recent Events & Patient Labeling

FDA Questions

Question 1

Please discuss whether our proposed directions for use and warnings below are warranted. If yes, please identify any other message(s) that should be conveyed in the proposed warnings:

- A. Reuse and topping-off
- B. Rub and rinsing time
- C. Lens case care
- D. Water activities
- E. Specifying a lens care product discard date

Please provide any additional recommendations for product labeling.

Question 2

Currently rub and no-rub care products have been cleared by the FDA for marketing in the United States. In light of all the data currently available, please discuss your recommendations for continuing to have no-rub directions in the product labeling.

Question 3

Regarding Clinical Issues

- A. Please discuss your recommendation for an additional follow-up visit at 2 hours in order to assess for solution-related corneal staining.
- B. Please discuss whether this additional follow-up should be included in lens care products and/or lens guidance.

Question 3 (cont')

Regarding Clinical Issues (cont')

- C. Please provide your recommendations on the inclusion of silicone hydrogel lenses in the clinical investigations of contact lens care products.

Question 4

Regarding Microbiology Issues

- A. Please discuss our proposal to revise the current Regimen Test in order to improve predictability of 'Real World' performance, and include the following topics in your discussion:
- Testing marketed silicone hydrogels
 - Defining 'worst case' rub and rinse times (e.g., 5 sec. rub and 5 sec total rinse time)

Question 4 (cont')

Regarding Microbiology Issues (cont')

B. Please discuss your recommendations for adding *Acanthamoeba* as a challenge organism in disinfection efficacy testing.

Question 4 (cont')

Regarding Microbiology Issues (cont')

- C. Please discuss our proposal for developing standardized test methods to evaluate the effects of preservative uptake by contact lenses on disinfection efficacy. Additionally, please comment on use of these tests to determine post-disinfection storage times in an unopened lens case.

Question 4 (cont')

Regarding Microbiology Issues (cont')

D. Please discuss our proposal for modifying Disinfection and Preservative Efficacy testing by:

- Testing at the lower end of the active ingredient specifications to simulate worst case conditions and
- Including more resistant clinical isolates in these tests.

Question 5

Please discuss whether you agree with:

- ISO's current consideration of having silicone hydrogel lenses as a separate group and
- FDA's plan to further stratify the silicone hydrogel lens group into subcategories.

Question 6

The current cytotoxicity test involves testing on the multipurpose solution by itself, and not in conjunction with various groups of lenses.

Please discuss our proposal to include both conventional and silicone-hydrogel contact lenses soaked in the multipurpose solution for Direct Contact cytotoxicity testing to evaluate the multipurpose solution.