Introduction

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FDA/CDRH/ODE
May 13, 2014

Contact Lens Safety

- First soft contact lens approval - 1971
- Significant public health impact - FDA safeguards:
  - » FDA website
  - » standards
  - » FDA guidance for contact lenses and lens care products
- Today - 38 million contact lens wearers (U.S.)[1]
  - » 12% of US population (2012)[2]

[1]Mark W. Swanson. Optometry and Vision Science; Vol. 89(6): pp. 839–848. 2012.
[2]www.census.gov/population/international/data/idb/worldpopinfo.php

Guidance Documents

- 1994: Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses[1]

- 1997: Guidance for Industry - Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products[2]

[1]http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080928.htm
[2]http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080218.pdf

Keratitis Outbreaks

- Rare Pathogen Outbreaks
  - » 2006: *Fusarium* keratitis
  - » 2007: *Acanthamoeba* keratitis

FDA's Reassessment of Safety and Contact Lens Standards and Guidance

- Identified new concerns due to:
  - » introduction of new lens materials
  - » different care product formulations
  - » greater potential for interaction between contact lens and contact lens care products
  - » different patterns of use (as compared to 1990's)

FDA's Response

- 2008: Ophthalmic Advisory Panel Meeting[1]
  - » recommendations for improving CL user safety
- 2009: CL Care Product Microbiology Workshop
  - » critical test method parameters for evaluating the activity of CL products against *Acanthamoeba*
  - » critical elements for disinfection efficacy test methods that simulate "real world" consumer use conditions
- 2008 - 2013: Research
- Revision to Guidance Documents

[1]http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=699

FDA's Response-Research

- Categorize the numerous silicone hydrogel lenses to address concerns with dimensional stability and toxicity

- Evaluate the efficacy of care product solution in the presence of lenses
  - » preservative depletion and efficacy study

- Develop *Acanthamoeba* test method

Today's Panel Meeting

- Bernard Lepri, O.D., M.S., M.Ed.
  - » demographics and patient noncompliance
- Joseph C. Hutter, Ph.D.
  - » silicone hydrogel grouping system for contact lenses
- J. Angelo Green, Ph.D.
  - » implications for preservative uptake on preclinical test recommendations

Today's Panel Meeting

- Jeffrey Brocious, M.S.
  - » microbiology research
- Marc Robboy, O.D.
  - » rigid gas permeable (RGP) lenses & use of water
- Jennifer Cope, M.D., M.P.H. (CDC)
  - » *Acanthamoeba* keratitis investigation
- FDA Questions

Contact Lens and Retinal Devices (CLRD)

- Denise Hampton, Ph.D. (Branch Chief)
- Bernard Lepri, O.D., M.S., M.Ed. (Optometrist)
- Gene Hilmantel, O.D., M.S. (Optometrist / Statistician)
- Marc Robboy, O.D. (Optometrist)
- Ming Shih, M.S. (Chemist)
- Leonid Livshitz, Ph.D. (Biomedical Engineer)
- Angelo Green, Ph.D. (Chemist)
- Mridulika Virmani, Ph.D. (Chemist)
- Joseph Hutter, Ph.D. (Chemical Engineer)
- Jeffrey Brocious, M.S. (Microbiologist)

Demographics & Patient Noncompliance

Bernard P. Lepri, O.D., M.S., M.Ed.
FDA/CDRH/ODE/DOED/CLRD

May 13, 2014

Demographics of Contact Lens Users

- Approximately 38 million Americans wear contact lenses[1]
  - » predominantly myopic[2]
  - » age
    - 14% younger than age 18[1]
    - 15% are between the ages of 18-24[2]
    - 50% are 25 to 44 years old[2]

[1]Mark W. Swanson. Optometry and Vision Science; Vol. 89(6): pp. 839–848. 2012.
[2]American Optometric Association

Demographics of Contact Lens Users

- Gender
  - » 68% are women[1]
  - » median age - 33 years[3]

- Wearing Type
  - » 80% wear daily wear soft lenses[1]
  - » >50% wear 1 to 2-week replacement lenses[1]
  - » 15% wear extended wear soft lenses[1]
  - » 48% wear silicone hydrogels[2]

[1]American Optometric Association
[2]Blue Book of Optometry
[3] Mark W. Swanson. Optometry and Vision Science; Vol. 89(6): pp. 839–848. 2012.

How are Contact Lens Users Characterized?[1]

- Four variables identify almost 9 of 10 contact lens users likely to be using contact lenses on any given day in the United States
  - » age
  - » socioeconomic status
  - » age-gender interaction
  - » socioeconomic status-education interaction

[1]Mark W. Swanson. A Cross-Sectional Analysis of U.S. Contact Lens User Demographics. Optom and Vis 2012 :(89, 6). 839–848.

Multi-Step Care Process

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

Contact Lens Complications[1]

- 80% are due to deficient compliance with wear/maintenance care
- User's perception of own behavior is essential to minimizing and/or preventing complications

[1]Ky W., Scherick K., Stenson S. CLAO Vol. 24(4): pp. 216-219. 1998.

Medical Noncompliance

- General[1]
  - » noncompliance rate of 25%
  - » patients forget as much as 50% of what they heard within minutes of leaving a medical visit
- Contact Lens
  - » noncompliance ranges from 50% to 79%[2,3]

[1]DiMatteo, MR. Med Care. 42: pp. 200-209. 2004.
[2]De Oliveira PR, Temporini-Nastari ER, Ruiz Alves M, Kara-Jose N. Eye Contact Lens. Vol. 29(3): pp.164-7. 2003
[3]Davidson, Si, Akingbehin T. Trans Ophthalmol soc UK; Vol. 100: pp. 286-290. 1980.

Factors Affecting Contact Lens Compliance[1]

- Complexity of treatment
- Frequency and duration
- Cost of regimen/treatment
- Nature of the Condition
  - » higher incidence of noncompliance in conditions that are asymptomatic, prophylactic, or suppressive in nature

[1]Donshik PC, Ehlers WH, Anderson LD, Suchecki JK. Eye Contact Lens. Vol. 33(6): pp. 430-4. 2007.

Behaviors Impacting Noncompliance[1]

- Contact lens replacement frequency
- Steps in lens care and hygiene
- Lens storage case replacement

[1]S. Hickson-Curran, et al. "Patient attitudes and behavior regarding hygiene and replacement of soft contact lenses and storage cases" [Contact Lens Anterior Eye (2011), doi:10.1016/j.clae.2010.12.005].

Lens Replacement Frequency[1]

- 2-Week Replacement Schedule
  - » 45% within 2 weeks
  - » 89% within 4 weeks
- Monthly Replacement Schedule
  - » 37% within 4 weeks
  - » 23% ≥ 8 weeks

[1]S. Hickson-Curran, et al. Cont Lens Anterior Eye. 35(2):92-3. 2012.

Lens Care and Hygiene[1]

- Median frequency for cleaning lens storage case
  - » 2-3 times per week
- 33% reported cleaning monthly or less often

[1]S. Hickson-Curran, et al. Cont Lens Anterior Eye. 35(2):92-3. 2012.

Lens Storage Case Replacement

- Median lens case replacement was every 4-6 months[1]
  - » at least every 3 months[2]
- 48% reported annual replacement or less often[1]

[1]S. Hickson-Curran, et al. Cont Lens Anterior Eye. 35(2):92-3. 2012.
[2]American Optometric Association website (http://www.aoa.org)

Contact Lens Compliance Study Findings[1]

- 54% considered themselves poor wearers
  - » inadequate cleaning of lenses or case (44%)
  - » noncompliance with medical orientation (15%)

- Contact lens care procedures
  - » 79% failing in implementation of procedures
  - » 30% poorly prepared for cleaning and maintenance awareness
    - lack of knowledge

[1]De Oliveira PR, Temporini-Nastari ER, Ruiz Alves M, Kara-Jose N. Eye Contact Lens; Vol. 29(3): pp. 164-7. 2003

Noncompliance

- Habitual wearers: avg. 2.6 years of wear
  - » 74% were noncompliant[1]
    - 20% did not understand chemical disinfection
    - 8% did not understand purpose of rinsing
    - 18% did not comprehend function of daily cleaner
    - 22% did not wash their hands before handling their lenses
    - reinforcement at follow up visits improved this behavior
- 91% of patients failed in following at least one procedure regarding the use of a multipurpose solution, despite the ease of use[2]

[1]Collins MJ, Carney LG. Clin Exp Optom; Vol. 9: pp.174-177. 1986.
[2]Turner FD, Stein JM, Sager DP, et al. CLAO J; Vol. 19: pp. 108-113. 1993.

Compliance Related Problems[1]

- 49% wore 2-week replacement (2WR) and 51% wore 1-month replacement (1MR) lenses

- Mean replacement time
  - » 2.6 x higher for 2WR
  - » 1.5 x higher for 1MR wearers
  - » median values of 31 and 37 days

[1]Dumbleton KA, Woods CA, Jones LW, Fonn D; Cont Lens Anterior Eye. Vol. 34(5): pp. 216-22. 2011.

Compliance Related Problems (Continued)[1]

- 23% reported signs/symptoms of complications
  - » 26% noncompliant vs.18% compliant
  - » 29% for never rubbing or rinsing versus 17% for rubbing/rinsing

- Two thirds did comply with the recommended replacement
  - » 2WR wearers stretched the replacement interval more than 1MR wearers

[1]Dumbleton KA, Woods CA, Jones LW, Fonn D; Cont Lens Anterior Eye. Vol. 34(5): pp. 216-22. 2011.

FDA's Strategies to Enhance CL Safety

- Labeling
  - » patient
  - » professional
- Standards
- Guidance

- Education
  - » patient
    - publications
    - website
  - » professional
    - website
    - publications
    - safety alerts

Patient & Professional Labeling[1]

- Add additional warnings and precautions
  - » “topping off” or reuse
  - » avoiding water exposure
  - » providing a discard date after opening
  - » updated directions for lens case care

[1]Guidance for Industry and Food and Drug Administration Staff - Contact Lens Care Products Labeling Document issued on: August 15, 2010. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm223663.htm

Plain Language Communication (Example)

Soaking and Storing Your Lenses

Instruction for Use:

Use only fresh multi-purpose (contact lens disinfecting) solution each time you soak (store) your lenses.

WARNING:

Do not reuse or “top off” old solution left sitting in your lens case since solution reuse reduces effective lens disinfection and could lead to severe infection, vision loss or blindness.

“Topping-Off” is the addition of fresh solution to solution that has been sitting in your case.

Note: *We recommend that the re-use or “topping off” warning be printed on the product carton and bottle label as well as the package insert.*

Publications for Patients & Professionals

- **FDA Consumer Publications**
  - » Kids & Contact Lenses - Sept. 2012
- **MedScape/WebMD Interviews**
  - » Decorative Contact Lenses: Truly Frightening - Oct. 2012
  - » Contact Lenses: The Risks You Need to Know - Oct. 2012
  - » Why Contact Lens Adverse Events Matter - Nov. 2012
- **FDA and YOU, Issue #10-Spring/Summer 2006**
  - » Contact Lens Solution Linked to Serious Eye Infection
- **FDA Consumer Health Information, May 29, 2007**
  - » Recall: Complete MoisturePlus CL Solution

Publications for Patients & Professionals (Continued)

- **FDA and YOU, Issue #10 - Spring/Summer**
  - » 2006 Contact Lens Solution Linked to Serious Eye Infection
- **Recall: Complete MoisturePlus CL Solution**
  - » FDA Consumer Health Information, May 29, 2007
- **Maturity Health Matters, Issue #6 - Summer 2007**
  - » Advanced Medical Optics Voluntarily Recalls Complete MoisturePlus Multipurpose CL Solution
- **FDA News Release, June 16, 2009**
  - » FDA Taking Steps to Improve CL Safety
- **FDA website/ For Consumers, June, 2009**
  - » Ensuring Safe Use of CL Solution

Peer Reviewed Publications: Eye and Contact Lens (November 2012 Issue)

- "Material Properties That Predict Preservative Uptake for Silicone Hydrogel Contact Lenses."
  Green JA, Phillips KS, Hitchins VM, Lucas AD, Shoff ME, Hutter JC, Rorer EM, Eydelman MB.

- "Impact of Contact Lens Materials on Multipurpose Contact Lens Solution Disinfection Activity Against *Fusarium solani*."
  Clavet CR, Chaput MP, Silverman MD, Striplin M, Shoff ME, Lucas AD, Hitchins VM, Eydelman MB.

- "The Effects of Contact Lens Materials on a Multipurpose Contact Lens Solution Disinfection Activity Against *Staphylococcus aureus*."
  Shoff ME, Lucas AD, Brown JN, Hitchins VM, Eydelman MB.

- "Strategies to Optimize Conditions for Testing Multipurpose Contact Lens Solution Efficacy Against *Acanthamoeba*."
  Shoff M, Eydelman MB.

- "Proposed Silicone Hydrogel Contact Lens Grouping System for Lens Care Product Compatibility Testing."
  Hutter JC, Green JA, Eydelman MB.

- "Preclinical Research to Aid in the Development of Test Methods for Contact Lenses and Their Care Products."
  Eydelman MB, Kiang T, Tarver ME, Alexander KY, Hutter JC.

- "The Food and Drug Administration's Role in Establishing and Maintaining Safeguards for Contact Lenses and Contact Lens Care Products."
  Eydelman MB, Tarver ME, Kiang T, Alexander KY, Hutter JC.

Contact Lens Website Updates[1]

- Specifically provides directions related to using contact lens care products
- Repeats “Top Tips” from the home page
- Specific directions for care of the CL case
- Adds other caveats
  - » warns against using water & saliva
  - » replace your contact lens case every 3 months
- Includes a lens care instructional video
- Provides a link to FDA to report adverse events

[1]http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/default.htm

ISO Standards[1]

- ISO 9394: 2012, Ophthalmic optics - Contact lenses and contact lens care products - Determination of biocompatibility by ocular study with rabbit eyes
- ISO 11980: Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations
- ISO 11981: Ophthalmic optics - Contact lenses and contact lens care products - Determination of physical compatibility of contact lens care products with contact lenses

[1]http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm

ISO Standards (Continued)

- ISO 11986: Ophthalmic optics - Contact lenses and contact lens care products - Guidelines for determination of preservation uptake and release
- ISO 13212 Ophthalmic optics - Contact lens care products - Guidelines for determination of shelf-life
- ISO 14534 Ophthalmic optics - Contact lenses and contact lens care products - Fundamental requirements
- ISO 14729 Ophthalmic optics - Contact lens care products - Microbiological requirements and test methods for products and regimens for hygienic management of contact lenses

[1]http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm

ISO Standards (Continued)

- ISO 14730: Ophthalmic optics - Contact lens care products - Antimicrobial preservative efficacy testing and guidance on determining discard date
- ISO 18369-2: Ophthalmic optics - Contact lenses - Part 2: Tolerances
- ISO 18369-3: Ophthalmic optics - Contact lenses - Part 3: Measurement methods
- ISO 18369-4: Ophthalmic optics - Contact lenses - Part 4: Physicochemical properties of contact lens materials

[1]http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm

Guidance

- Contact Lens/Care Products Guidance
  - » 1994 Daily Wear Contact Lenses
  - » 1997 Contact Lens Care Products

Interactions of Contact Lens Materials with Multipurpose Care Product Solutions

Joseph C. Hutter, Ph.D.
FDA/CDRH/ODE/DOED/CLRD

May 13, 2014

Pre-Market Review of Contact Lens and Care Products: Chemistry

- Lenses
  - » tolerances (factory, storage, use), solution compatibility, manufacturing - residuals, purity, USAN† designation, physical properties (water, RI*, modulus, Dk**, %T***)
- Care products
  - » disinfection efficacy, purity, pH, osmolality, preservative concentration, effectiveness - cleaning, lubrication, compatibility with lenses

†USAN-United States Adopted Name Council; *RI-refractive index; **Dk-oxygen permeability; ***Transmission

Solution Compatibility Testing

- Purpose
  - » assess the effect of a contact lens solution on contact lens parameters and solution compatibility under the recommended care regimen
- Method
  - » lenses subjected to recommended cleaning/disinfection regimen 30 times (30-cycle test)
- Parameters
  - » physical
  - » optical

FDA Soft Contact Lens (SCL) Grouping System*

- Group 1: non-ionic hydrogels < 50 wt% water
- Group 2: non-ionic hydrogels > 50 wt% water
- Group 3: ionic hydrogels < 50 wt% water
- Group 4: ionic hydrogels > 50 wt% water

*for Poly(2-hydroxyethyl methacrylate) Materials

Silicone Hydrogel Lenses

- 1999: Balafilcon A (Bausch & Lomb)
  - » group 3 lens
- 2008: Additional silicone hydrogel lens materials introduced into US market:

lotrafilcon A	lotrafilcon B
senofilcon A	galyfilcon A
comfilcon A	enfilcon A

- 2014: 13 silicone hydrogel lenses cleared

Emergence of Silicone Hydrogel/Care Product Solution Incompatibilities

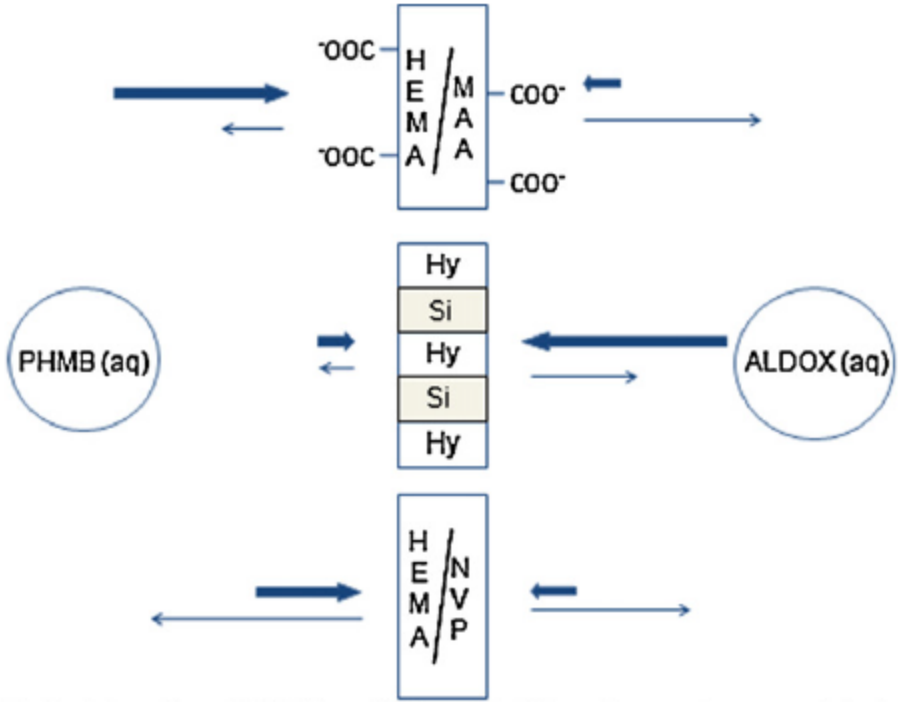
- Dimensional tolerance specification issues
  - » balafilcon A incompatible with AMO Ultracare H_2O_2
  - » galyfilcon A incompatible with Solocare Plus - polyhexamethylene biguanide (PHMB)
- 2008: Ophthalmic Advisory Panel recommended testing 3 representative silicone hydrogel lenses

Revision of the FDA Grouping System

- 2007: Addition of Group 5 to account for high oxygen permeability (silicone hydrogel) lenses
  - » editorial - FDA Group 5: Is a Single Grouping Sufficient to Describe SiHy Performance? [1]
- 2008: Ophthalmic Advisory Panel recommends revision of grouping system
- 2008 - 2012: FDA research results in the development of a new grouping strategy[2]

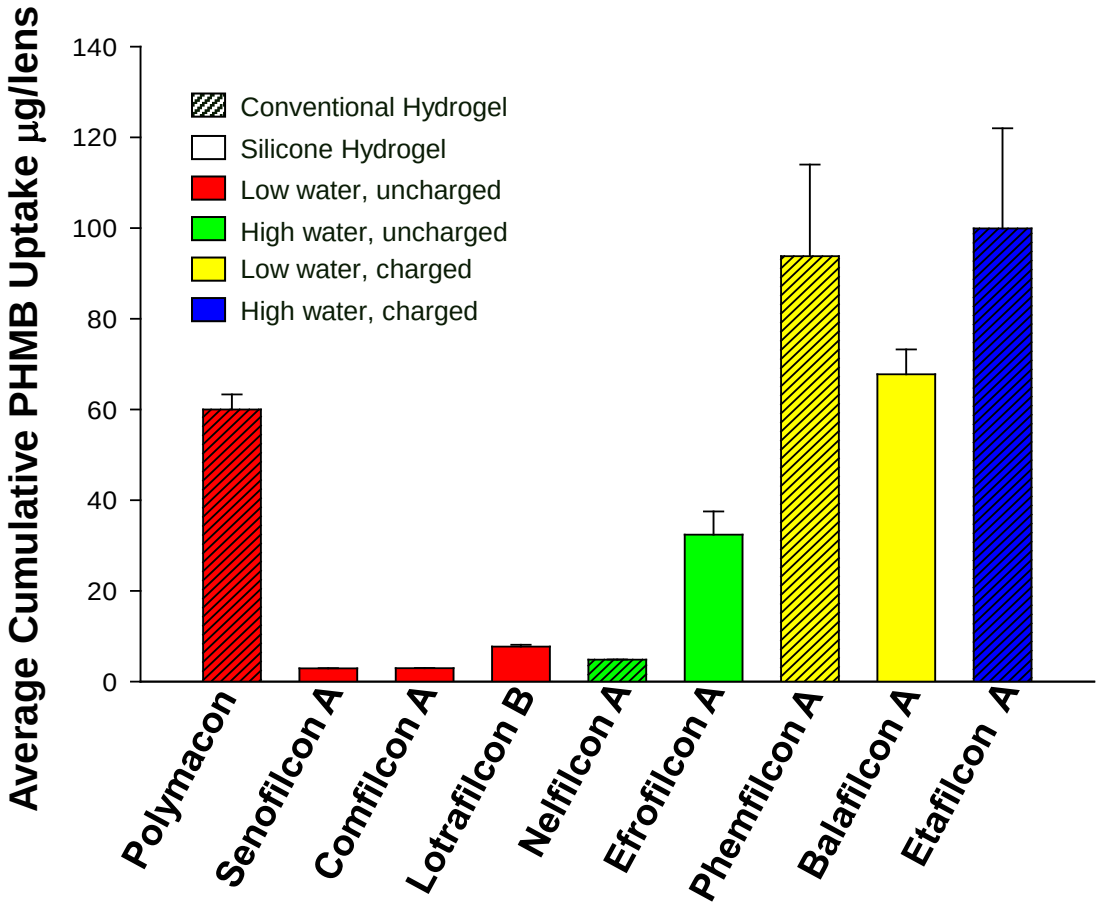
[1] http://www.siliconehydrogels.org/editorials/nov_07.asp
[2] http://journals.lww.com/claojournal/toc/2012/11000

Preservative Uptake and Release for Silicone Hydrogel Lenses[1]



[1]Powell CH, Lally JM, Hoong LD, Huth SW. Cont Lens Anterior Eye. Vol. 33(1): pp. 9-18. 2010.

FDA Research: PHMB Uptake Favored by Lenses with an Ionic Charge or with a High Water Content



[1]Adapted from Green JA et al. Eye & Contact Lens 2012 38(6):350-357

Rationale for a New Grouping Strategy[1]

- Water content & ionic charge predict preservative uptake/release of some components
- Surface treatments (ST) (e.g., plasma polymerized coatings) may limit diffusion of larger molecules into the bulk material
- ST may favor adsorption of some components over others relative to non-ST surfaces
- Silicone phases have high affinities for some care product components (e.g., Aldox, some surfactants)
- Semi-interpenetrating polymer networks will limit the effect of cross-links to retain swelling in certain ranges of osmotic pressure, affecting tolerances

[1]Hutter et al. Eye and Contact Lens Vol. 38(6): pp. 358-362. 2012.

Silicone Hydrophilic Material Groups[1]

Group	Description
5-A	No Water Specification, Ionic*
5-B	High Water Content (≥50%), Nonionic
5-Cm	Low Water Content (<50%), Nonionic*, ST
5-C	Low Water Content (<50%), Nonionic*, Non-ST, Hydrophilic Monomer
5-Cr	Low Water Content (<50%), Nonionic*, Non-ST, Semi-interpenetrating network

*Being ionic in pH = 6.0-8.0

[1]Hutter et al. Eye and Contact Lens Vol. 38(6): pp. 358-362. 2012.

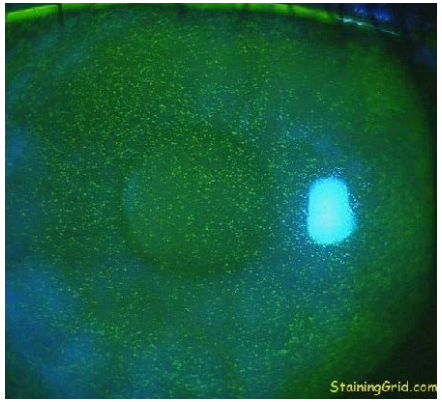
Question for the Panel

Do you believe that FDA's proposed grouping scheme for silicone hydrogel lenses is adequate to mitigate concerns regarding dimensional tolerance and compatibility? If not, what recommendations for modifications would you make?

Implication of the Silicone Hydrogel Grouping System for Clinical Testing

On-Eye Performance of Silicone Hydrogel Lenses

- Clinical performance differs from poly(HEMA)
  - » corneal swelling
  - » limbal/bulbar injection
  - » deposits
  - » punctate corneal staining[1]
    - preservative uptake/release PHMB



[1]Jones L, MacDougall N, et al. Optom Vis Sci. Vol. 79(12): pp. 753-761. 2002.

Contact Lens Care Product Guidance: Clinical Recommendations[1]

Lens material	Test	Control
Group 1 - < 50 wt% water, non-ionic	20	10
Group 4 - > 50 wt% water, ionic	20	10

[1]http://www.fda.gov/cdrh/ode/contlens.pdf

Proposed Clinical Test Matrix for Silicone Hydrogel Lenses

Lens Material	Test Group	Control Group
Silicone hydrogels:		
5-A No water specification, ionic (pH 6-8)	30	15
5-B High water > 50 wt%, non-ionic	30	15
5-C Low water < 50 wt% non-ionic, no surface treatment	30	15
5-Cm Low water, < 50 wt%, non-ionic, surface treated	30	15
5-Cr Low water, < 50 wt% , non-ionic, semi-interpenetrating network polymer	30	15
4 - Conventional: poly(2-hydroxyethyl methacrylate), high water > 50 wt%, ionic	30	15

Question for Panel Discussion

Do you believe that the proposed clinical test matrix for silicone hydrogel lenses is sufficient to address clinical performance issues? If not, what additional testing would you recommend?

Preservative Uptake and Lens Solution Incompatibilities

J. Angelo Green, Ph.D.
FDA/CDRH/ODE/DOED/CLRD
May 13, 2014

Preservative Uptake and Release Standard (ISO 11986: 1999)

- Preservative uptake (and release) is assessed for new solutions according to ISO 11986
- Uptake measured at different time points until a concentration plateau is obtained
- There are no acceptance criteria established in the standard
- Compromised disinfection efficacy caused by preservative uptake by the lens material is not evaluated

Preservative Uptake and Disinfection Efficacy[1]

- Reduction in disinfection efficacy, resulting from lens preservative uptake, has been implicated in cases of *Fusarium* keratitis after the use of a preserved care system, especially where solutions were reused or "topped off" rather than fully replaced each day

Reuse of Disinfectant Solutions: Biocidal Activity Against *Fusarium solani*			
No. of reuses	Alexidine level (ppm)[a]	MoistureLoc efficacy	Renu MultiPlus efficacy
1	4.1	Pass	Pass
2	1.8	Pass	Pass
3	1.3	Fail	Fail
4	1.2	Fail	Fail
[a]MoistureLoc only			

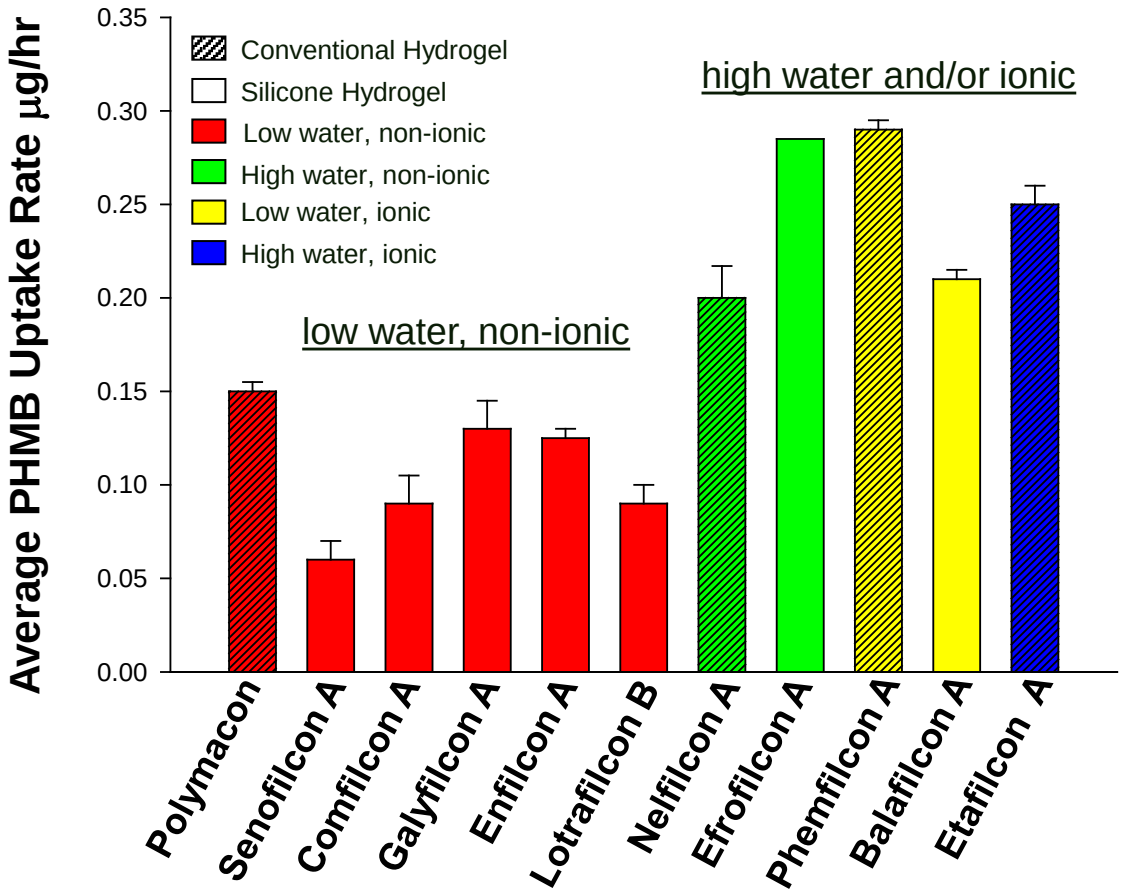
[1]Adapted from Levy B et al., Eye & Contact Lens. Vol. 32(6): pp. 256-261. 2006.

Preservative Uptake and Disinfection Efficacy

- Decreases in preservative concentration during lens storage reduce disinfection efficacy[1,2,3,4]
- Lens material properties determine extent of preservative uptake and may predict effects on solution disinfection efficacy[5]

[1]Rosenthal RA, et al. Eye & Contact Lens. Vol. 32: pp. 262-266. 2006.
[2]Warburton K, et al. ASM Meeting, May 2007.
[3]Shoff et al., Eye & Contact Lens. Vol. 38(6): pp. 368-373. 2012.
[4]Clavet et al., Eye & Contact Lens. Vol. 38(6): pp. 379-384. 2012.
[5]Green JA et al., Eye & Contact Lens Vol. 38(6): pp. 350-357. 2012.

Preservative Uptake of Hydrophilic Preservatives is Influenced by Water and Ionic Content of the Material[1]

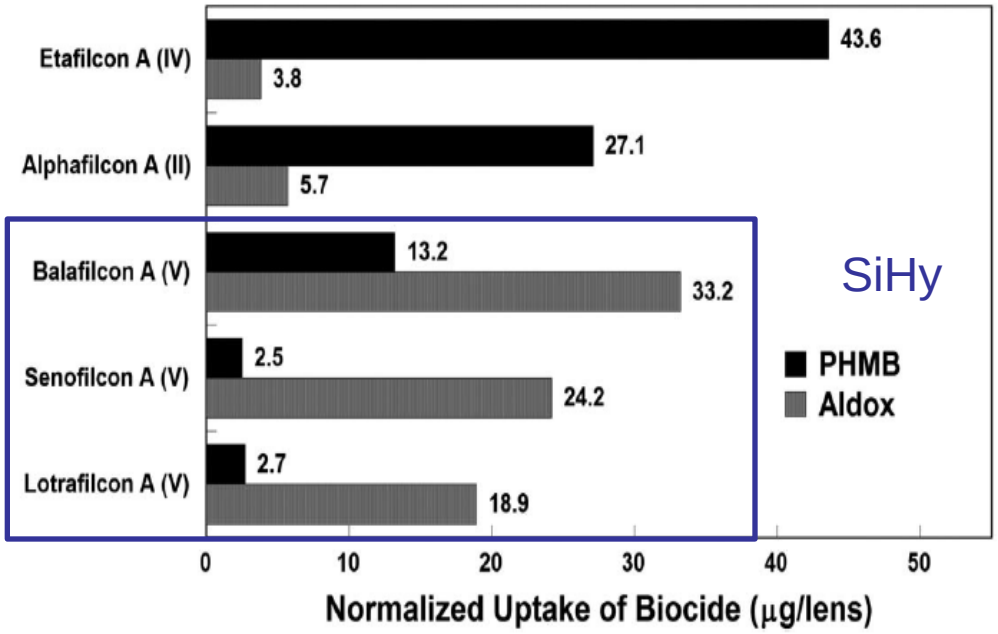


[1]Adapted from Green JA et al. Eye & Contact Lens 2012 38(6):350-357

Hydrophobicity of the Lens Material Influences Preservative Uptake[1]

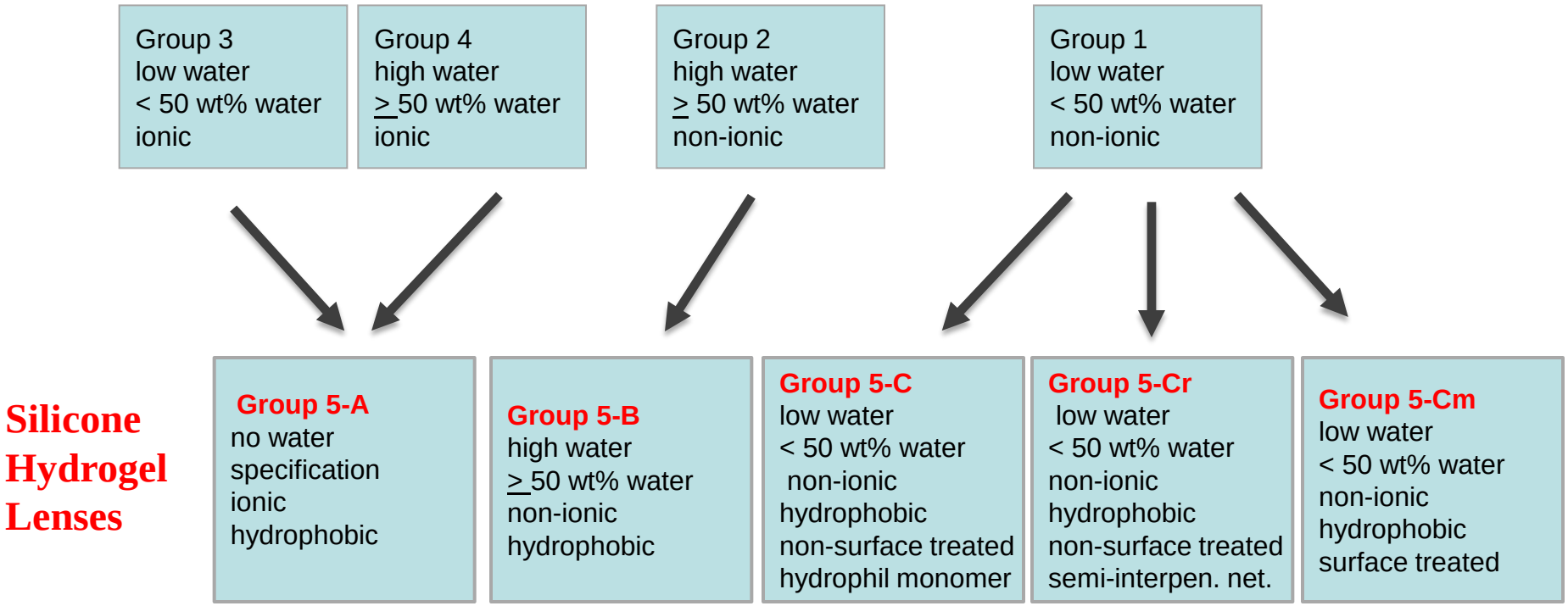
Biocide/ Preservative	Hydrophobicity Rating*
PHMB	2
Aldox	5

*Rating scale 1 to 5 (ranks from low- to high-based on formula weight of the largest aliphatic moiety with additional consideration of overall mass-to-charge ratio)



[1]Adapted from Jones and Powell, Eye & Contact Lens. Vol. 39(1): pp. 29-36. 2013.

Proposed Silicone Hydrogel Grouping System Captures Material Properties that Predict Preservative Uptake[1]

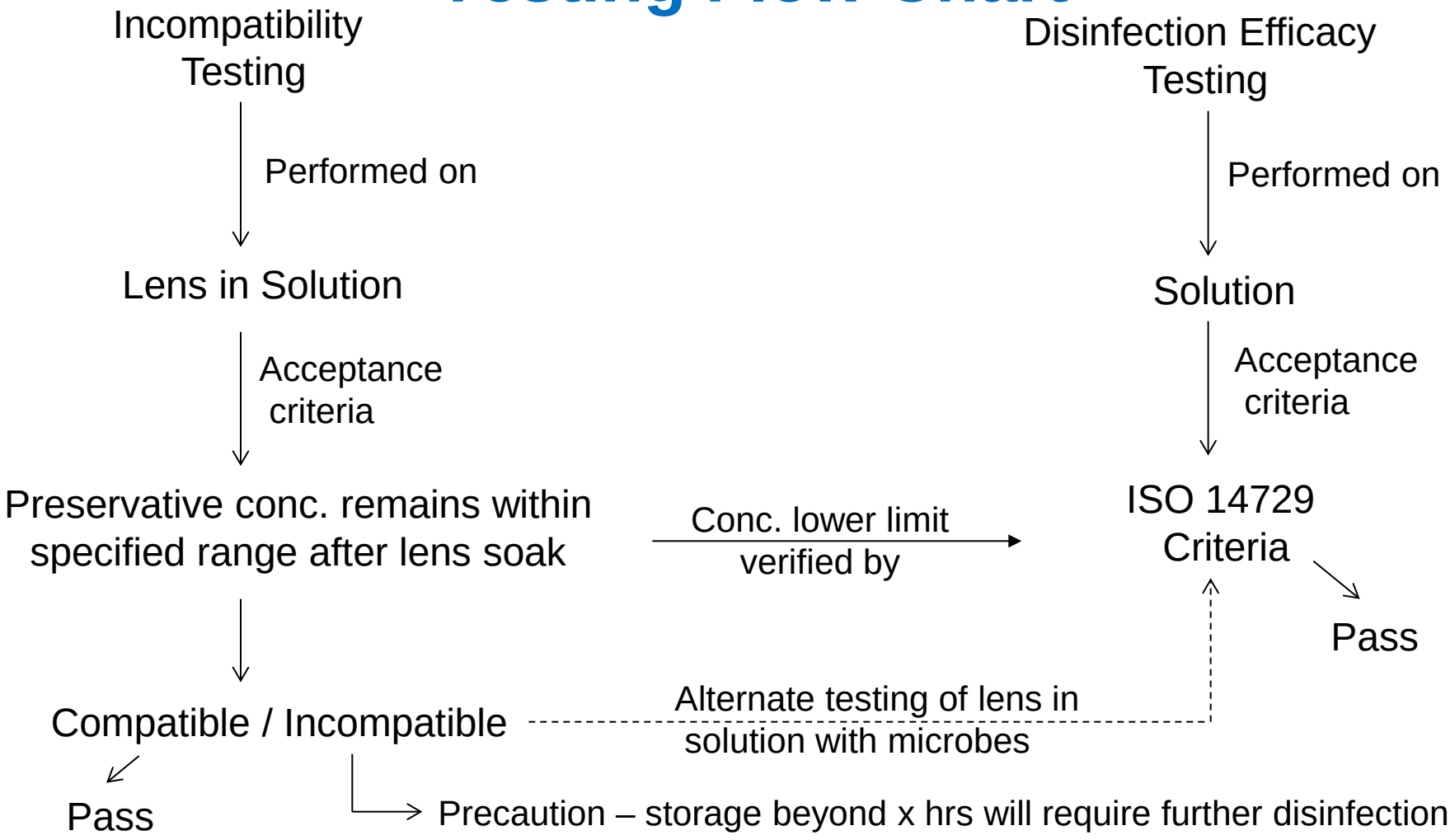


[1]Adapted from Hutter et al. Eye & Contact Lens. Vol. 38(6): pp. 358-362. 2012.

Proposed Revision to 510(k) Guidance for Preservative Uptake

- Introduce preservative uptake method similar to Section 4.2 of ISO 11986 with the following modifications:
  - » one conventional (Group 4) and five silicone hydrogel lenses (one each from Groups 5A, 5B, 5C, 5Cr, 5Cm) should be tested
  - » one lens per well should be submerged in 3 ml of test solution in a lens case (currently, there is no volume or container specified)
- Proposed acceptance criterion: Preservative concentration in lens case solution should remain within manufacturer specifications after recommended soak time

Preservative Uptake Incompatibility Testing Flow Chart



Question for Panel Discussion

As a modification to our care product guidance, new care product solutions will be screened for lens preservative uptake incompatibilities using representative lenses per FDA's proposed contact lens grouping system. The preservative concentration of the solution in the lens case should remain within the manufacturer's specifications after the recommended lens soak time. Incompatible lenses will be listed in the labeling. Please discuss the following:

a. Should our acceptance criterion account for patient non-compliance (e.g., longer soak times than recommended, solution reuse, etc.)?
b. How should the incompatible lenses be listed in the labeling (e.g., bold text, a unified table, etc.)?
c. Other recommendations?

Variables that may Impact Care Product Disinfection Efficacy from a Microbiological Perspective

Jeffrey Brocious, M.S.
FDA/CDRH/ODE/DOED/CLRD

May 13, 2014

Current Disinfection Test Methods

- CL Lens Care Guidance - May 1997
  - » predates ISO 14729
- Disinfection efficacy tests:
  - » 5 challenge organisms
    - *S. aureus, P. aeruginosa, S. marcescens, C. albicans,* and *F. solani*
  - » stand alone test
    - primary criteria: 3 log bacterial kill, 1 log fungal kill
    - secondary criteria: average sum of all bacteria = 5 log kill, fungal stasis
  - » regimen test
    - all organisms ≤ 10 colony forming units (CFUs)

Current Disinfection Test Methods

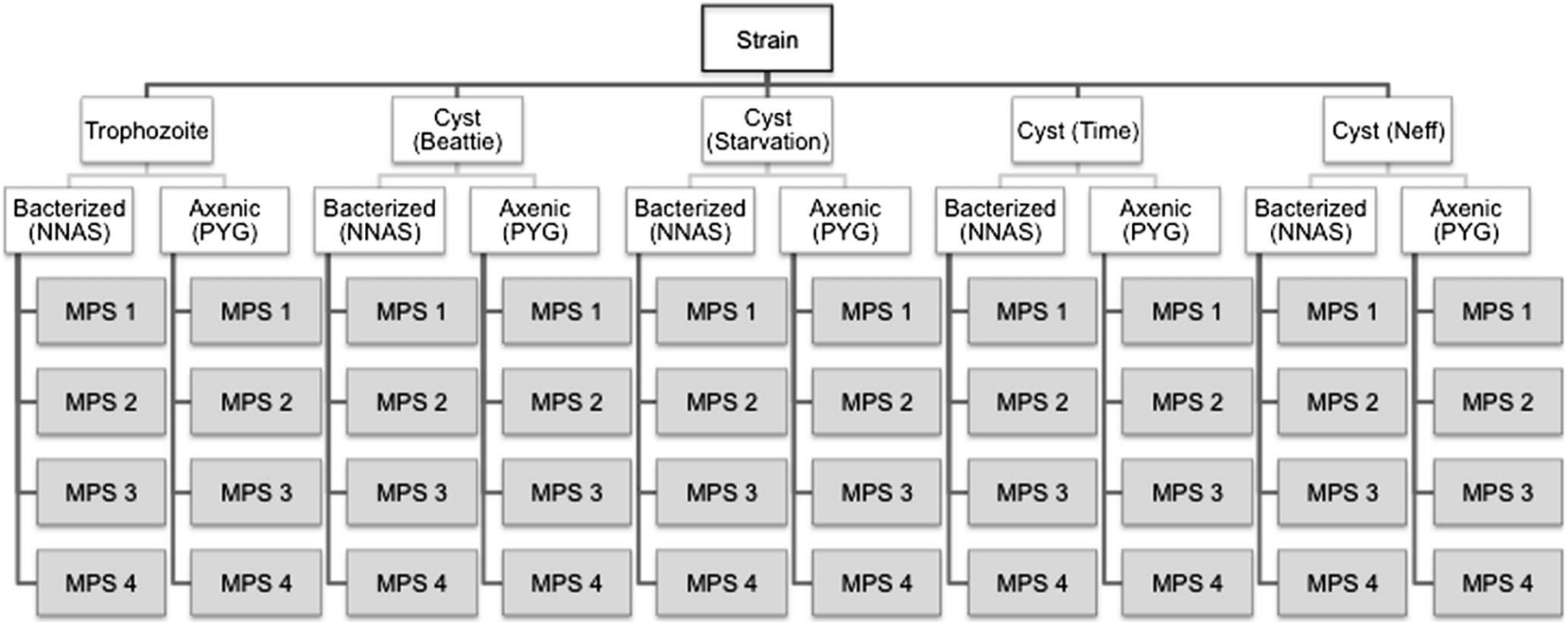
- ISO 14729 and 1997 FDA CL Care Product Guidance do not include the evaluation of the following:
  - » soil[1]
  - » lens material
  - » extended soaking times
  - » evaluation of *Acanthamoeba*

[1]T Schunk RS Schweisfurth. Contactologia. Vol. 11; pp.84-89. 1989.

2009 CL Care Product Microbiology Workshop

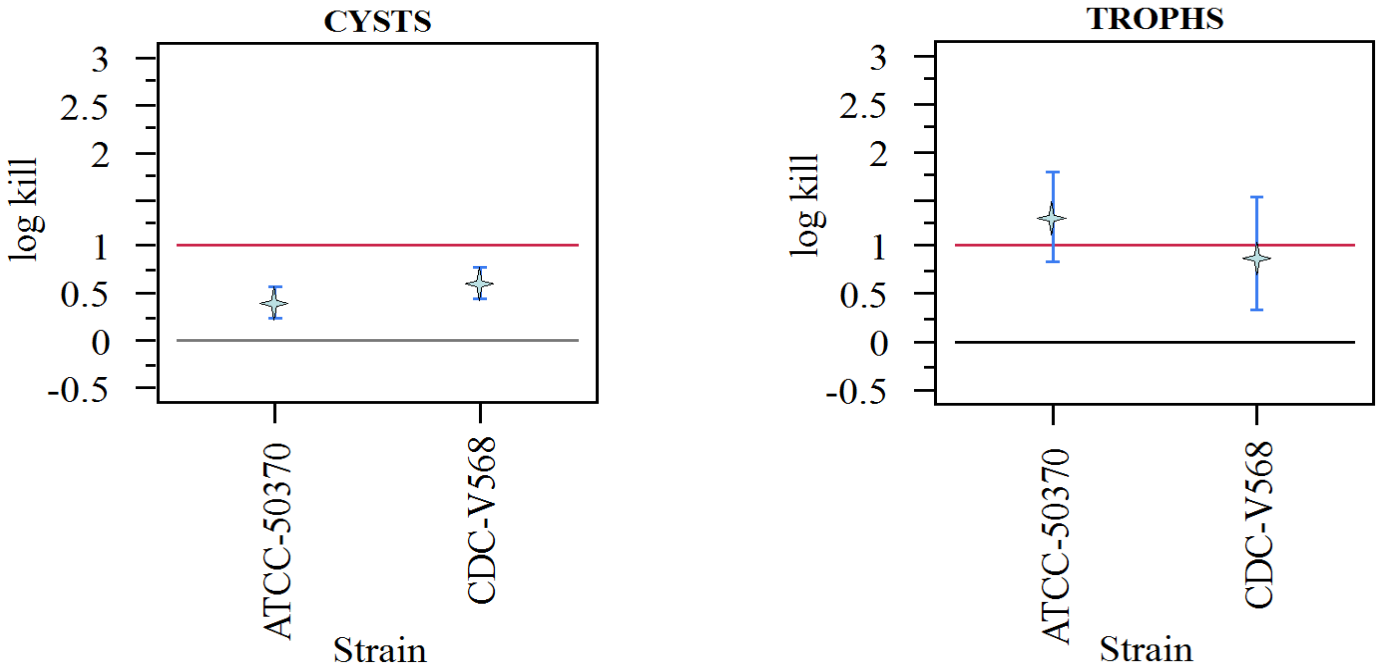
- Parameters for evaluating disinfection efficacy:
  - » strain
  - » life cycle
  - » growth method
  - » encystment technique

FDA Research: Methods to Determine Solution Efficacy Against *Acanthamoeba*[1]



[1]ME Shoff, MB Eydelman. Eye & Contact Lens Vol. 38(6); 363-367. 2012.

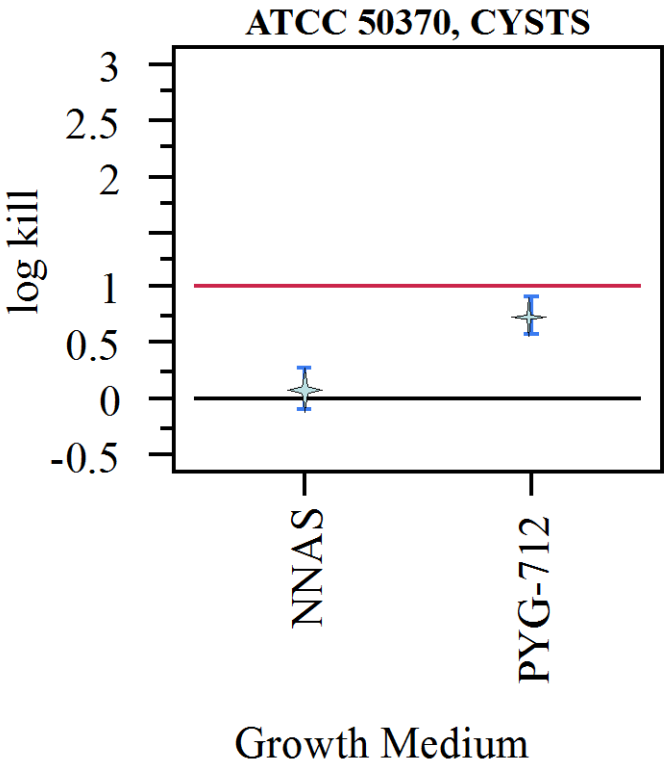
Impact of Strain & Life Stage on Solution[1]

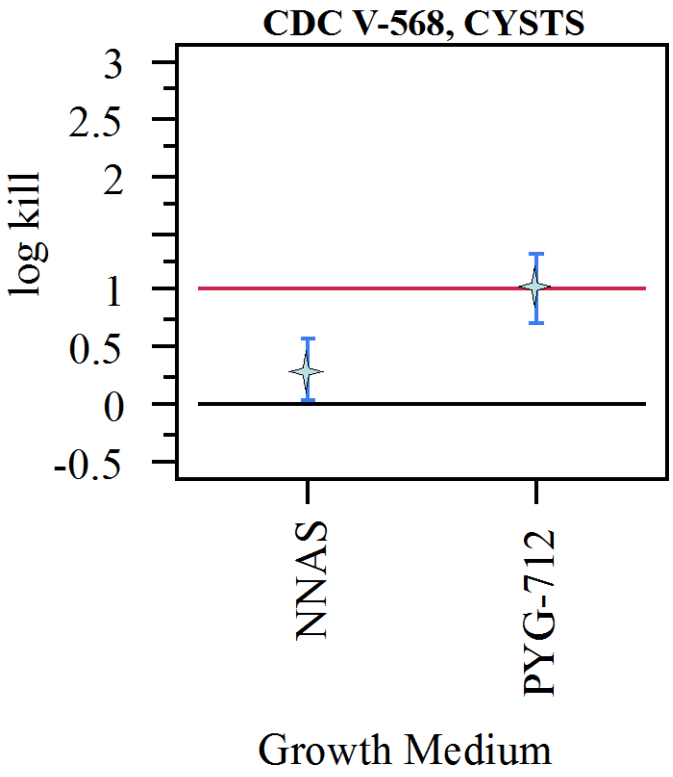


- Average log kill for cysts vs. trophs ($p<0.0001$)
- Average log kill of amoeba strain for cysts and trophs (cysts, $p=0.1254$, trophs, $p=0.2940$)

[1]ME Shoff, MB Eydelman. Strategies to Optimize Conditions for Testing Multipurpose Contact Lens Solution Efficacy Against *Acanthamoeba,* Eye & Contact Lens 2012, 38(6) 363-367.

Impact of Growth Method on Solution[1]



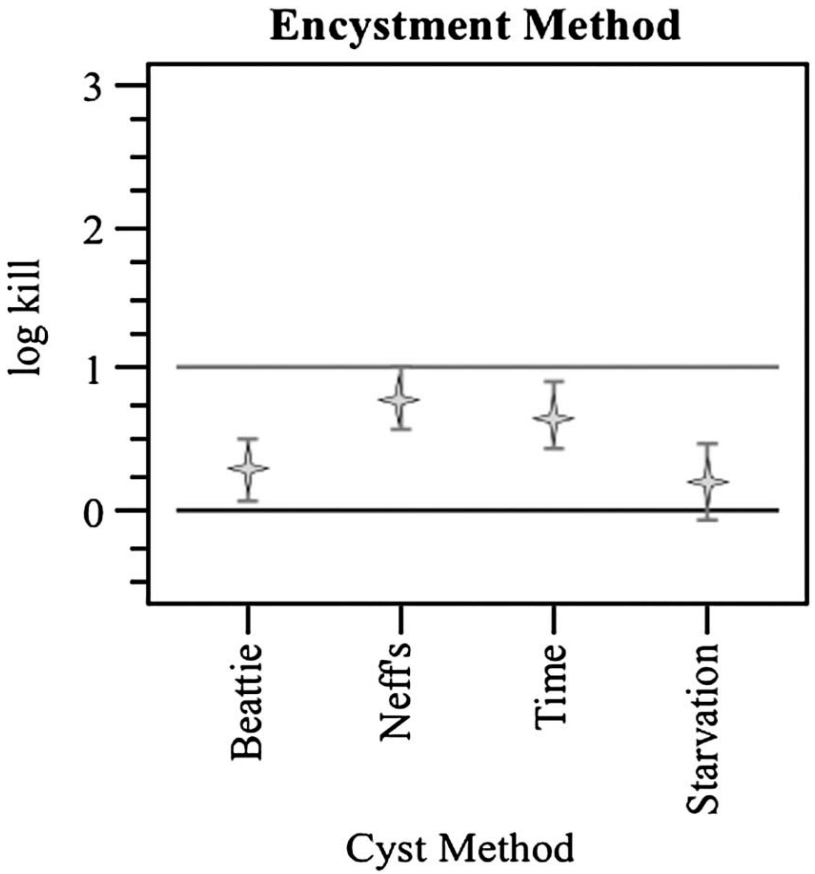


- Average log kill of cysts for each growth method ($p<0.0001$)

[1]ME Shoff, MB Eydelman. Eye & Contact Lens Vol. 38(6); 363-367. 2012.

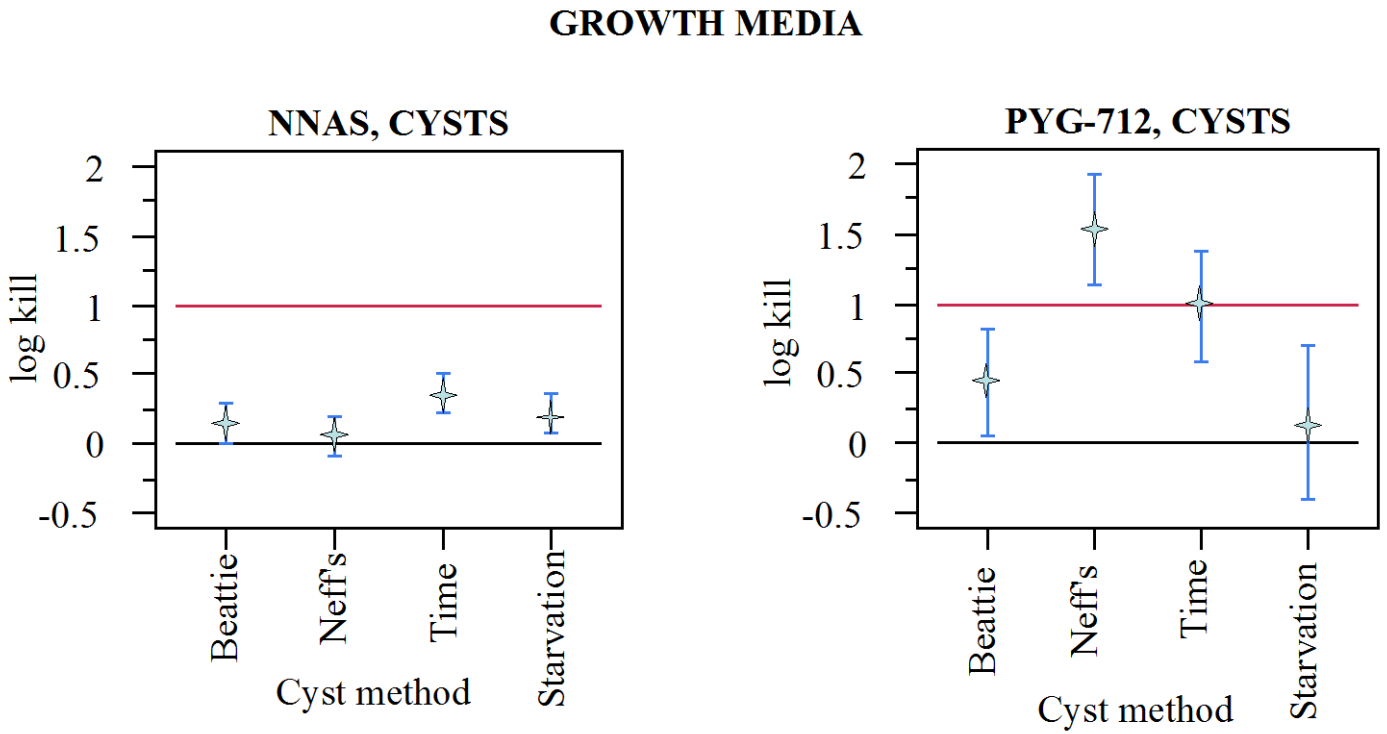
Impact of Encystment Method on Solution[1]

- Average cyst log kill for both strains for all encystment methods (P=0.0013)



[1]ME Shoff, MB Eydelman. Eye & Contact Lens Vol. 38(6); 363-367. 2012.

Impact of Encystment Method on Solution (Continued)[1]



- Average cyst log kill by growth method for all encystment methods ($p<0.0001$)

[1]ME Shoff, MB Eydelman. Eye & Contact Lens Vol. 38(6); 363-367. 2012.

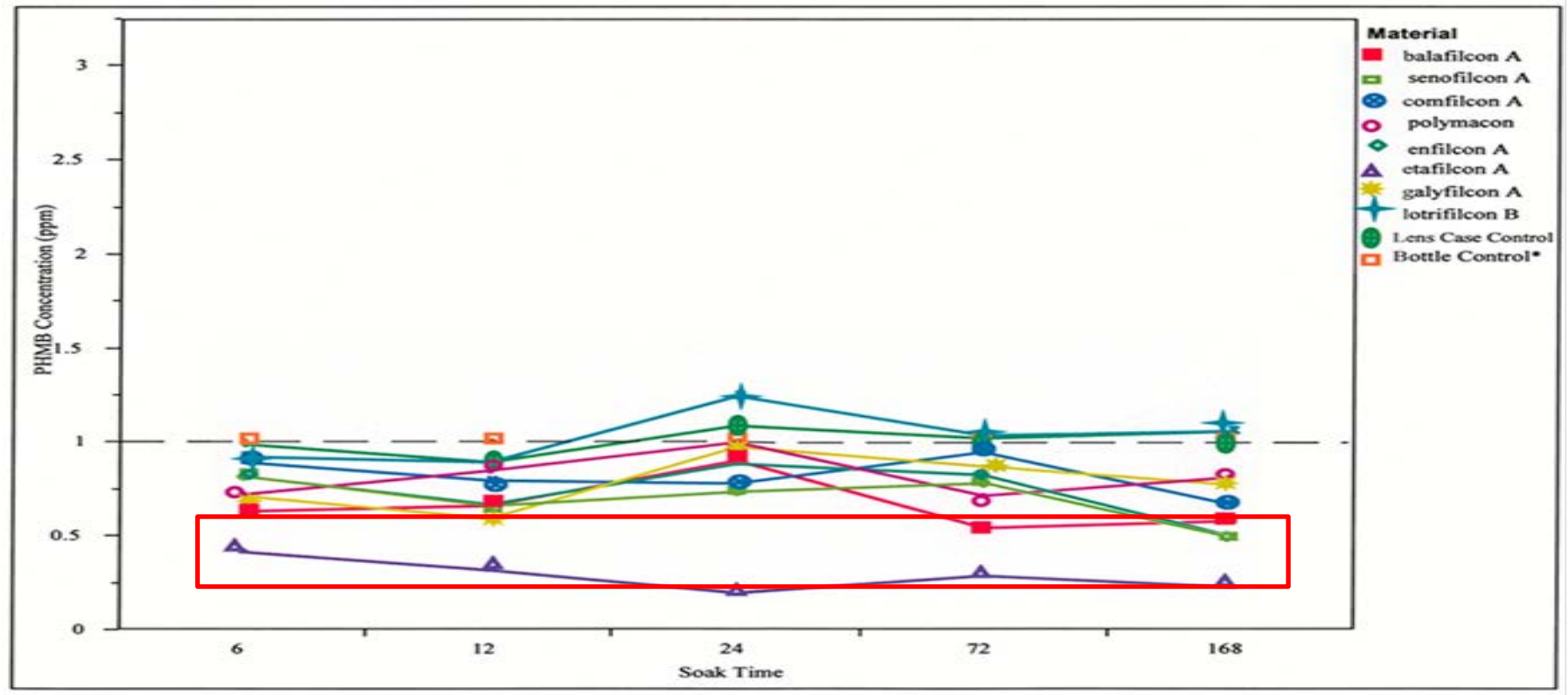
FDA Recommendations

- The following factors should be incorporated into a protocol when testing for disinfection efficacy:
  - » at least 2 strains of *Acanthamoeba*
  - » organism grown bacterized
  - » encysting using starvation method or Beattie method

FDA Research: Real World Testing

- Soak times
- Lens materials
  - » high water, charged
    - etafilcon A – conventional hydrogel
  - » low water, charged
    - balafilcon A – silicone hydrogel
  - » low water, uncharged
    - galyfilcon A – silicone hydrogel
    - senofilcon A – silicone hydrogel
    - comfilcon A – silicone hydrogel
    - enfilcon A – silicone hydrogel
    - lotrafilcon B – silicone hydrogel
    - polymacon – conventional hydrogel

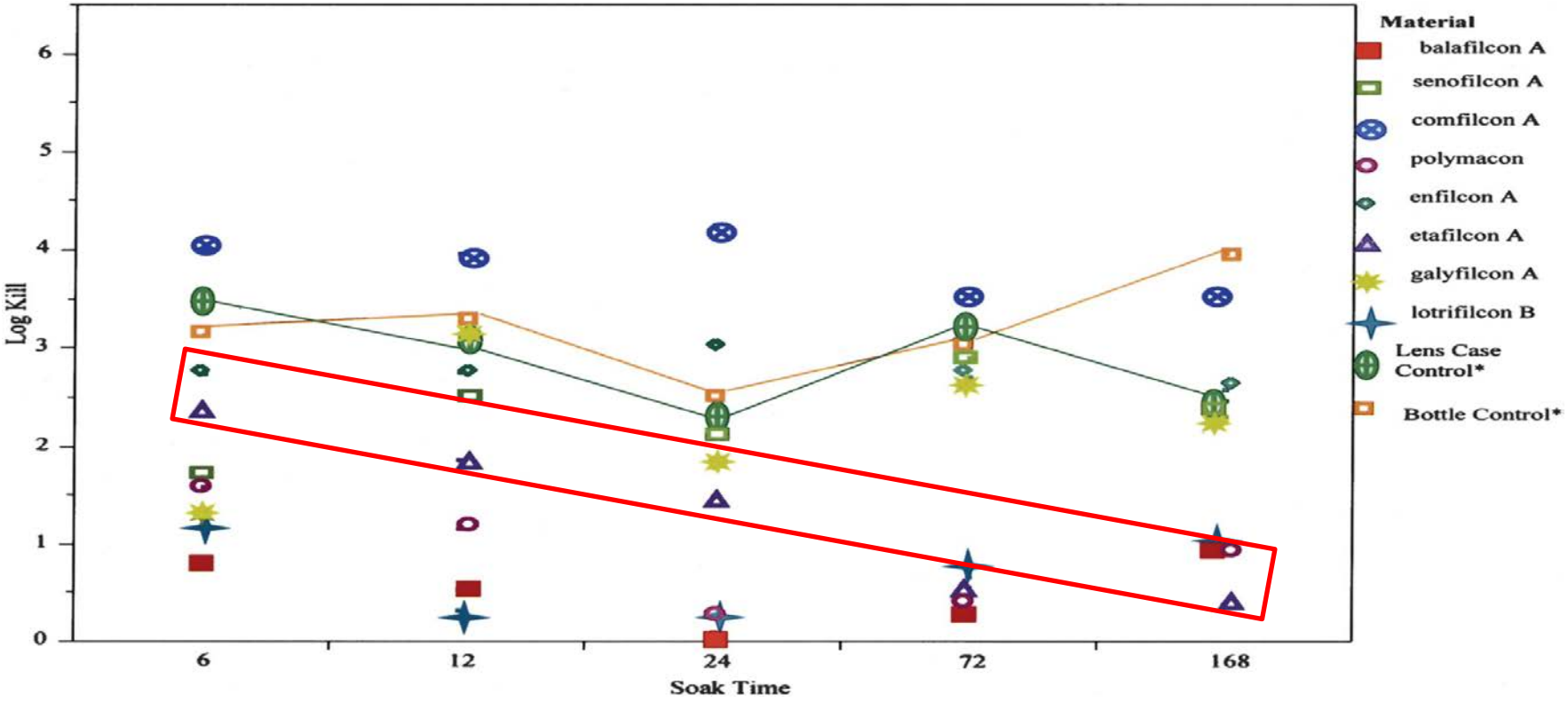
Impact of Lens Material on Uptake of Polyhexamethylene biguanide (PHMB)[1]



- Concentration of PHMB versus soak time (etafilcon A, comfilcon A, balafilcon A, polymacon $p<0.0001$)

[1]ME Shoff, AD Lucas, JN Brown, VM Hitchins, MB Eydelman, Eye & Contact Lens. Vol. 38(6). pp. 368-373. 2012.

Impact of Lens Material on Log Kill of *Staphyloccus aureus*[1]



- Log kill of *S. aureus* over time

[1]ME Shoff, AD Lucas, JN Brown, VM Hitchins, MB Eydelman, Eye & Contact Lens. Vol. 38(6). pp. 368-373. 2012.

Impact of Lens Material on Log Kill of *Fusarium solani*[1]

Lens Material	Hours After Depleted Solution Inoculation With *F. solani*	Log Reduction[a] of *F. solani* by Depleted Solutions After Variable Lens Soaking Periods				
		6 Hours	12 Hours	24 Hours	72 Hours	7 Days
Etafilcon A	6	0.35	0.16	0.01	−0.02	−0.07
	24	0.90	0.51	−0.13	0.06	−0.12
Polymacon	6	0.39	0.13	−0.07	0.11	−0.12
	24	0.98	0.88	0.56	0.27	−0.01
Balafilcon A	6	0.35	0.12	−0.10	−0.05	−0.11
	24	0.73	0.53	0.37	0.08	0.01
Lotrafilcon B	6	0.53	0.51	0.13	0.80	−0.07
	24	1.2	1.06	1.2	1.13	0.27
Enfilcon A	6	0.61	1.73	0.88	0.53	0.49
	24	1.57	3.10	1.77	1.67	0.98
Comfilcon A	6	1.07	2.37	1.37	1.20	1.23
	24	2.37	4.20	2.53	2.77	2.17
Galyfilcon A	6	0.67	1.53	1.03	0.55	0.52
	24	1.17	2.43	2.20	1.67	0.93
Senofilcon A	6	0.75	0.20	1.10	0.95	1.06
	24	1.13	0.97	2.37	2.00	1.33
Lens Case Control (solution in case no lens)	6	1.14	1.00	1.38	1.60	1.01
	24	1.60	1.70	2.23	2.48	1.45
Bottle control[b]	6	1.75	2.35	1.60	1.70	1.25
	24	1.85	3.30	2.55	2.85	1.75

- Log kill of *F. solani* challenged with PHMB over time

[1]CR Clavet et al. Eye & Contact Lens. Vol. 38(6): pp. 379-384. 2012.

Impact of Lens Material on Uptake of Polyquaternium-1 and Myristamidopropyl Dimethylamine[1]

Lens Material	Log Kill	*P*-value	OD Reading
Control Set 1	2.56	N/A	0.437
Balafilcon A	3.57	0.0029	0.463
Comfilcon A	3.28	0.0029	0.475
Lotrafilcon A	3.12	0.0006	0.484
Control Set 2	2.14	N/A	0.384
Senofilcon A	2.85	0.0015	0.397
Enfilcon A	2.71	0.0104	0.334
Etafilcon A	2.41	0.0435	0.389
Galyfilcon A	2.93	<0.0001	0.403

- Log kill of *S. aureus* at 6 hours of soaking
- NA = not available; OD = optical density

[1] adapted from ME Shoff et. al. Eye & Contact Lens. Vol. 38(6): pp. 374-378. 2012.

Question for Panel Discussion

Current microbiological test methods (e.g., ISO 14729) do not take into account “real-world” solution testing parameters in which the lens stored in a case is considered. Please discuss whether you believe the following factors should be incorporated into current preclinical testing:

a. soil
b. longer soak times
c. lens uptake
d. any other factors

The Impact of Using Tap Water as a Rinsing Agent in the Care of Rigid Gas Permeable Lenses

Marc Robboy, O.D.
FDA/CDRH/ODE/DOED/CLRD
May 13, 2014

The Use of Tap Water Rinse in the RGP Lens Care Regimen

- Tap water rinse has been included in the care of rigid contact lenses dating back to the 1950's
- Mechanical action from rinsing breaks up debris and removes deposits prior to chemical disinfection with conditioner solution
- Absence of standardized pre-clinical testing methodology against *Acanthamoeba*

Early Association of *Acanthamoeba* Keratitis and Contact Lens Wear

- The first case of *Acanthamoeba* keratitis in the US was reported in 1973 in a South Texas patient with ocular trauma.[1]
- "Three patients who used daily-wear soft contact lenses sterilized with saline made from distilled water and salt tablets, developed *Acanthamoeba* keratitis…"[2]

[1]Visvesvara GS. In: Lennette EH, Balows A, Hausler, WJ Jr, Truant JP, eds. Manual of Clinical Microbiology, 3rd edition: pp. 704-8. 1980.
[2]Moore MB, McCulley JP, Luckenbach M, et al. Vol. 100(3): pp. 396-403. 1985.

Early Association of *Acanthamoeba* Keratitis and Contact Lens Wear (Continued)[1]

- "Of 11 contact lens-wearing patients who presented with *Acanthamoeba* keratitis, 6 wore daily wear soft contact lenses, 2 wore extended-wear soft contact lenses, 1 wore a PMMA hard contact lens, 1 wore an RGP lens, and 1 wore a Saturn lens (combined hard and soft lens)."

[1]Moore MB, McCulley JP, Newton C, et al. Ophthalmol. Vol. 94(12): pp. 1654-61. 1985.

Acanthamoeba Keratitis Outbreak (2007)[1]

National Outbreak of *Acanthamoeba* Keratitis Associated with Use of a Contact Lens Solution, United States

Jennifer R. Verani, Suchita A. Lorick, Jonathan S. Yoder, Michael J. Beach, Christopher R. Braden, Jacquelin M. Roberts, Craig S. Conover, Sue Chen, Kateesha A. McConnell, Douglas C. Chang, Benjamin J. Park, Dan B. Jones, Govinda S. Visvesvara, and Sharon L. Roy, for the *Acanthamoeba* Keratitis Investigation Team[1]

An outbreak of *Acanthamoeba* keratitis, a rare, potentially blinding, corneal infection, was detected in the United States in 2007; cases had been increasing since 2004. A case–control study was conducted to investigate the outbreak. We interviewed 105 case-patients from 30 states and 184 controls matched geographically and by contact lens use. Available contact lenses, cases, solutions, and corneal specimens from case-patients were cultured and tested by molecular methods. In multivariate analyses, case-patients had significantly greater odds of having used Advanced Medical Optics Complete Moisture Plus (AMOCMP) solution (odds ratio 16.9, 95% confidence interval 4.8–59.5). AMOCMP manufacturing lot information was available for 22 case-patients, but none of the lots were identical. Three unopened bottles of AMOCMP tested negative for *Acanthamoeba* spp. Our findings suggest that the solution was not intrinsically contaminated and that its anti-*Acanthamoeba* efficacy was likely insufficient. Premarket standardized testing of contact lens solutions for activity against *Acanthamoeba* spp. is warranted.

Author affiliations: Centers for Disease Control and Prevention, Atlanta, Georgia, USA (J.R. Verani, S.A. Lorick, J.S. Yoder, M.J. Beach, C.R. Braden, J.M. Roberts, D.C. Chang, B.J. Park, G.S. Visvesvara, S.L. Roy); Illinois Department of Public Health, Chicago, Illinois, USA (C.S. Conover); California Department of Public Health, Sacramento, California, USA (S. Chen); Florida Department of Health, Tallahassee, Florida, USA (K.A. McConnell); and Baylor College of Medicine, Houston, Texas, USA (D.B. Jones)

[1]Verani JR. Emerg Infect Dis. Vol. 15: pp. 1236-1242. 2009.

Recommendations Against the Use of Water to Minimize *Acanthamoeba* Keratitis[1]

- Ophthalmic Advisory Panel (June, 2008)
- Consensus Statement by Ophthalmic Organizations (June, 2008)[1]
  - » *"Minimize contact with water while wearing lenses."*
  - » *"Contact lenses should not be rinsed or stored in water."*
  - » *"Rinse the lens case with fresh solution, not water..."*
- Revisions to FDA Consumer Website re: Contact Lens Care (June, 2009)
- Addendum to 510(k) FDA Contact Lens Care Labeling Guidance (August, 2010)

[1]http://www.businesswire.com/news/home/20080610005501/en/Leading-Ophthalmology-Organizations-Provide-FDA-Recommendations-Improve

Recommendations Against the Use of Water to Minimize *Acanthamoeba* Keratitis (Continued)[1]

- FDA Consumer Updates Website: Ensuring Safe Use of Contact Lens Solution

DON'T:

- Don't use contact lens solutions that have gone beyond the expiration or discard date.
- Don't "top-off" the solutions in your case. Always discard all of the leftover contact lens solution after each use. Never reuse any lens solution.
- Don't expose your contact lenses to any water: tap, bottled, distilled, lake, or ocean water. Never use non-sterile water (distilled water, tap water, or any homemade saline solution). Exposure of contact lenses to water has been associated with Acanthamoeba keratitis, a corneal infection that is resistant to treatment and cure.
- Don't put your lenses in your mouth to wet them. Saliva is not a sterile solution.
- Don't transfer contact lens solutions into smaller travel size containers. This can affect the sterility of the solution which can lead to an eye infection. Transferring solutions into smaller size containers may also leave consumers open to accidentally using a solution that is not intended for the eyes.

[1]http://www.fda.gov/forconsumers/consumerupdates/ucm164197.htm

Recommendations Against the Use of Water to Minimize *Acanthamoeba* Keratitis (Continued)[1]

- Addendum to 510(k) FDA Contact Lens Care Labeling Guidance
  - » *"Never use water… to disinfect your lenses."*
  - » *"Do not… rinse your lens case with water..."*
  - » *"Water can harbor microorganisms that can lead to severe infection, vision loss or blindness..."*
- The Guidance explicitly states that the scope of the care products labeling pertains to both RGP and hydrophilic lenses

[1]http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm223663.htm

The Use of Tap Water Rinse in the RGP Lens Care Regimen[1]

- 18 RGP cleaners and solutions were reviewed
  - » 15 (83%) recommended the use of non-sterile water to rinse the lenses and/ or the lens case
- Labeling for these devices was cleared prior to the 2008 FDA Ophthalmic Devices Panel Meeting

[1]Legarreta JE, Nau AC, Dhaliwal DK. Eye & Contact Lens. Vol. 39(2): pp. 158–161. 2013.

Incidence of *Acanthamoeba* Keratitis

- "*Acanthamoeba* Keratitis is a rare condition occurring at an estimated yearly rate of 1.2 per million in adults and 0.2 per 10,000 in contact lens wearers."[1]
- CDC to provide updated information

[1]Radford CF, Minassian DC, Dart JK. Br J Ophthalmol. Vol. 86: pp. 536–542. 2002.

Acanthamoeba Keratitis in RGP Wearers: Published Literature

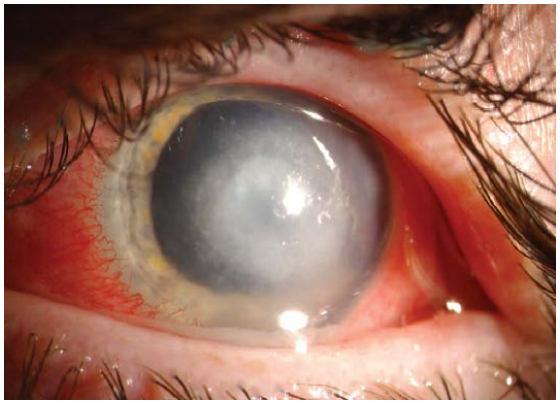
- 30% of the first 50 reported cases of microbial keratitis in overnight orthokeratology were attributed to *Acanthamoeba* keratitis[1]

- This was most likely due to the contact lenses being rinsed with tap water as part of the lens care regimen

[1]Watt K, Swarbrick HA. Eye Contact Lens. Vol. 31: pp. 201–208. 2005.

Acanthamoeba Keratitis in RGP Wearers: Published Literature (Continued)[1]

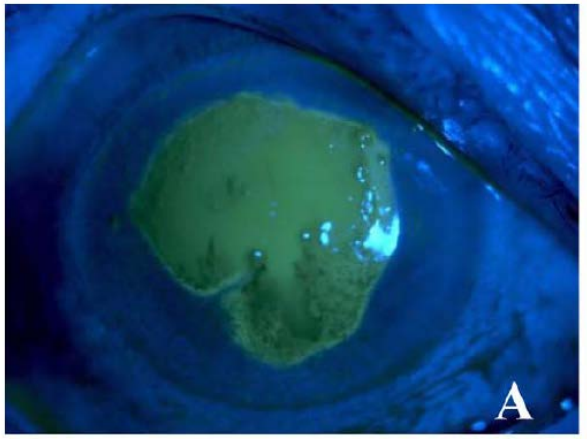
"A corneal ulcer in the left eye was noted and confirmed as *Acanthamoeba* infection... Vision deteriorated to light perception… Additional complications included secondary angle-closure glaucoma… the patient cleaned his lenses with the Boston Cleaning System, as instructed, but followed … with a routine rinse with tap water and storage in tap water in his lens case…"



[1]Robertson DM, McCulley JP, Cavanagh HD. Eye & Contact Lens. Vol. 33(3): pp. 121–123. 2007.

Acanthamoeba Keratitis in RGP Wearers: Published Literature (Continued)[1]

"A case of a 59-year-old Spanish patient who presented with severe ocular pain… corneal scrapings were positive for *Acanthamoeba* genotype T11… she admitted to use tap water to wash the lenses… this is the first case of severe keratitis due to *Acanthamoeba* genotype T11 in Spain."



[1]Lorenzo-Morales J, Morcillo-Laiz R, et al. Cont Lens Anterior Eye. Vol. 34(2): pp. 83-6. 2011.

Acanthamoeba Keratitis in RGP Wearers: Published Literature (Continued)[1]

"A 63-year-old woman presented to the cornea service…with a four- month history of nonresolving contact lens–associated keratitis in her left eye. The patient had been an RGP contact lens wearer for 25 years and used tap water to clean her contact lenses as instructed on the bottle of her contact lens solution. Cultures and smears were performed and were positive for *Acanthamoeba* keratitis… Ultimately, the patient underwent a penetrating keratoplasty… The final visual acuity was counting fingers at face."

[1]Legarreta JE, Nau AC, Dhaliwal DK. Eye & Contact Lens. Vol. 39(2): pp. 158–161. 2013.

Alternatives to Water for the Rinsing of RGP Lenses Prior to Disinfection

- Preserved saline rinse
- Unpreserved saline rinse

Question for Panel Discussion

Some RGP lens regimens still recommend the use of water. What alternatives would you recommend to replace water?