



U.S. Food and Drug Administration



# Lens – Solution Interactions: Impact on Biocompatibility

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# Disclaimer

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- This presentation should NOT be considered as Agency's guidance as described under current Good Guidance Practices
- The information presented here is only for scientific discussion at the symposium

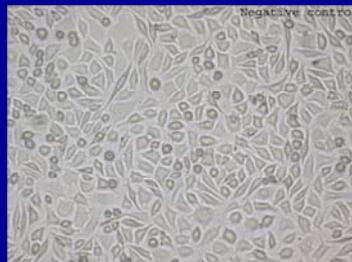
# Presentation Overview

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- General overview of biocompatibility testing of contact lenses and lens care products
- Lens-solution interactions: Background
- Biocompatibility testing strategy to address lens-solution interactions
- FDA efforts and update on ANSI/ISO standard activities



# Toxicity Testing: *Contact Lens*



# Testing on Contact Lens

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- Reclassification of daily wear contact lenses from class III to class II products (March 4, 1994)
- Extended wear contact lenses – class III
- FDA's May 1994 *Premarket Notification (510 (k)) guidance document for daily wear contact lenses*

# FDA's 1994 Guidance Document for Contact Lenses

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- Toxicity Testing Guidance for contact lenses and packaging containers
- Toxicity studies for contact lenses recommended in the guidance are based on ISO 10993 standards
- MSDS for each chemical constituent incorporated in the finished lens

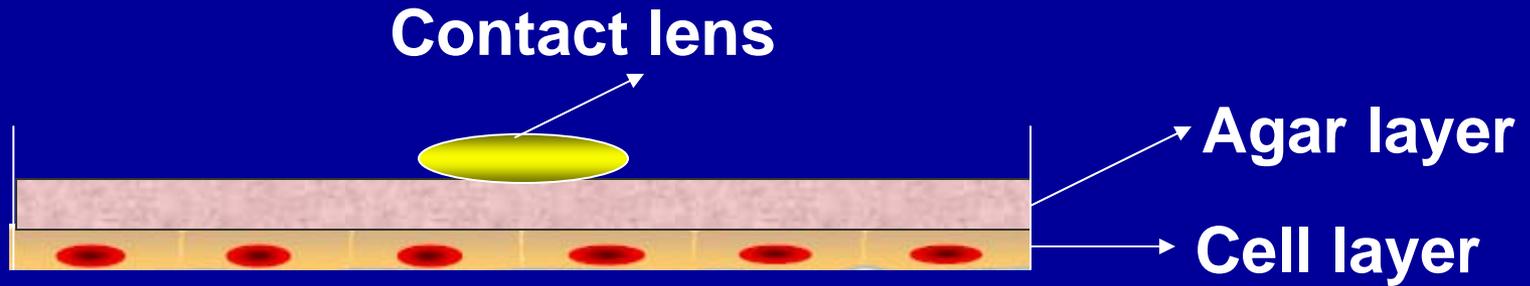
# Minimum Recommended Toxicity Tests for Class II Contact Lenses

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- Cytotoxicity Test
- Systemic Toxicity Test
- Ocular Irritation Test

# Cytotoxicity Testing on Contact Lens

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



- **Direct Contact Test (preferred test)**



# Systemic Toxicity Test



- **ISO 10993 -11**
- Polar and non-polar extract
- 5 mice / extract; 5 mice / blank vehicle
- Single dose
  - Polar extract – 50 ml/kg, i.v.
  - Non-polar extract – 50 ml/kg, i.p.
- Mice observed immediately and 4, 24, 48, and 72 hrs after injection
- Test fails if :
  - $\geq 2$  mice dead or abnormal behavior (e.g. convulsion)
  - $> 2$  gm weight loss in  $\geq 3$  mice

# Ocular Irritation Test



- **ISO 10993 -10**
- Polar and non-polar extracts
- Three rabbits per extract
- One eye with test extract, other eye with control extract
- 0.1 ml instillation (single dose) in conjunctival sac
- Observation: 1, 24, 48, and 72 hr after instillation
- Scoring according to Draize scoring criteria

# Additional Recommended Tests for Contact Lenses

- Required if
  - a lens material is manufactured using a new monomer
  - UV-absorber incorporated in the lens
    - *Not required if the same UV absorber cleared/approved previously for same class of lenses using the same method of incorporation into the lens marketed by the manufacturer*
- Two additional tests:
  - **Sensitization test**
  - **Three week ocular irritation study in rabbits**

# Sensitization Test

- **ISO 10993 -10**
- Both polar and non-polar extracts
- Test:
  - Guinea Pig Maximization Test

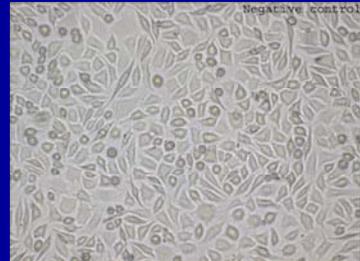


# 22-Day Rabbit Ocular Irritation Study



- ***ISO 9394: Ophthalmic Optics – Contact lenses and contact lens care products – Determination of Biocompatibility by ocular study using rabbit eyes***
- **6 – 8 rabbits**
- **One eye – Test lens; Contralateral eye – control lens**
- **Same lens care regimens for both test and control lenses**
- **Lenses worn daily for a minimum of 7 hrs from Day 1 – day 21, minimum of 4 hrs on day 22**
- **Daily obs, macroscopic scoring each day, Slit lamp exam before treatment and on days 8, 15, 22**
- **Termination on day 22**
- **Histopathology of the eye**
- **Corneal metabolism**

# Toxicity Testing: *Contact Lens Care Products*



# Contact Lens Care Products

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- Reclassification of Contact lens care products from class III to Class II
- Contact Lens Cases and Accessories (e.g. Mechanical Cleaning Aids and Accessory Cleaning Pads) regulated as Class II
- *FDA's 1997 Premarket Notification (510(k)) Guidance for Contact Lens Care Products*

# Class II Contact Lens Care Products

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- Saline Solutions
- Cleaners (Daily Cleaners and Periodic Cleaners)
- Chemical Disinfecting Products for Contact Lenses (including Conditioning Solutions for Hydrophobic lenses)
- **Multi-purpose Solution**
- In-eye contact lens solutions (e.g. Lubricating and/or Rewetting drops)
- Heat Disinfection Units

# Biocompatibility Testing Matrix for Contact Lens Care Products (excluding heat disinfection system)

Test	Same active ingredients within marketed Concentration	Same active ingredients in higher concentration than marketed products	Same active ingredients in lower concentration than marketed products	New ingredients for ophthalmic use or different active ingredients
<b>Cytotoxicity</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
<b>Acute ocular irritation</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
<b>Acute oral toxicity</b>				<b>X</b>
<b>Sensitization</b>				<b>X</b>
<b>22-Day rabbit ocular irritation study</b>				<b>X</b>

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## **Lens – Solution Interactions:**

**Why** address lens-solution interactions

# Preclinical Testing of Contact Lens Care Solutions

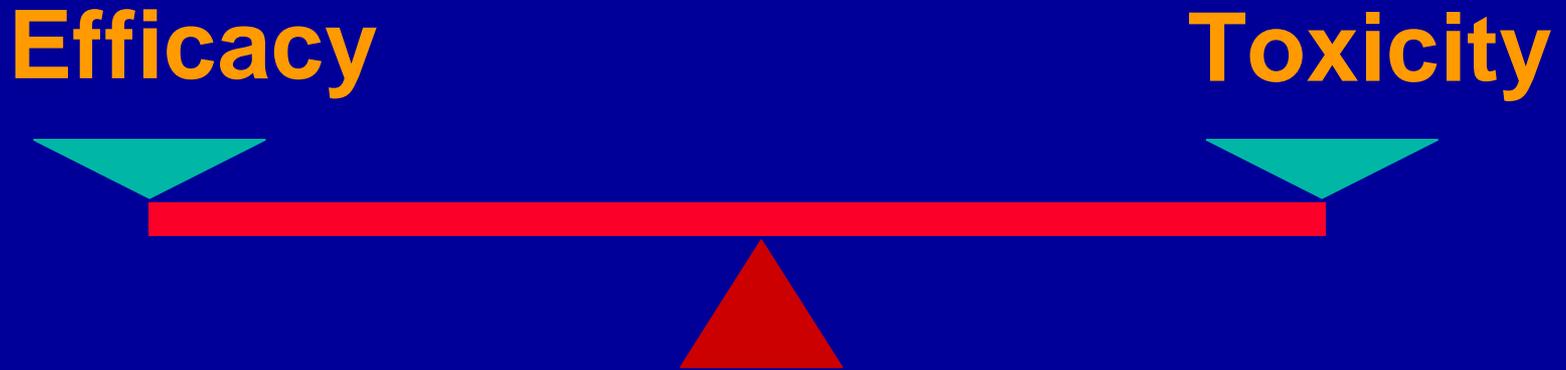
- FDA's *1997 Premarket Notification (510(k)) Guidance for Contact Lens Care Products*
- Post 1997: Silicone Hydrogel Lenses (1999)
- **Testing for Consideration**
  - Preclinical and Clinical Study Designs to address potential lens-solution interaction and its impact on product safety

# *Fusarium* Keratitis Outbreak



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

# Contact Lens Care Solution



- 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
  - Hydrophobicity
- Uptake of other chemical ingredients
- Adverse effect on corneal epithelium
- Compromised corneal surface – increased risk for infection

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**Lens – Solution Interactions:  
Biocompatibility testing Strategy for a  
new MPS to address lens-solution  
interactions**

# Testing Strategy: Points to be taken into consideration

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- 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

# Biocompatibility Testing Strategy for a Multi-purpose Solution (MPS)

- **Testing on MPS** (per FDA's 1997 guidance document)
- **Testing on MPS in conjunction with various groups of lenses**
  - Cytotoxicity Testing (*in vitro*)
  - Ocular irritation study (*in vivo*)
  - 22-Day rabbit ocular irritation study (*in vivo*)
- **MPS should include preservatives/any other chemically active ingredients at the upper end of their respective specifications for testing**

# Lens Groups to be Tested with MPS

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## 1. Conventional Hydrogels:

- i. Group IV* (e.g. etafilcon A)

## 2. Silicone Hydrogels:

- i. Surface modifications by plasma polymerization* (lotrafilcon B due to higher water content)
- ii. Plasma oxidation surface treatment* (balaflcon A)
- iii. Not surface treated* (galyfilcon A due to higher water content)
- iv. Comfilcon A*

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**Cytotoxicity Testing: On MPS alone and on MPS in combination with various lenses to address Lens-solution Interaction**

# Salient Features of Cytotoxicity Test Methods for evaluating MPS

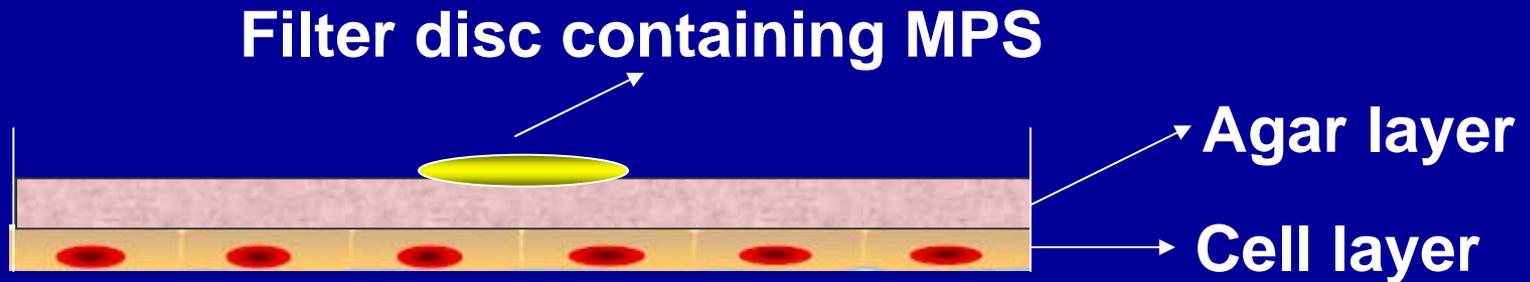
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- Standard ISO/USP test methods
- L-929 cell model
- Tests to evaluate direct exposure to MPS
- Test to evaluate indirect exposure to MPS through contact lenses
  - Conventional hydrogel (Gr IV)
  - Silicone hydrogels with different surface treatments

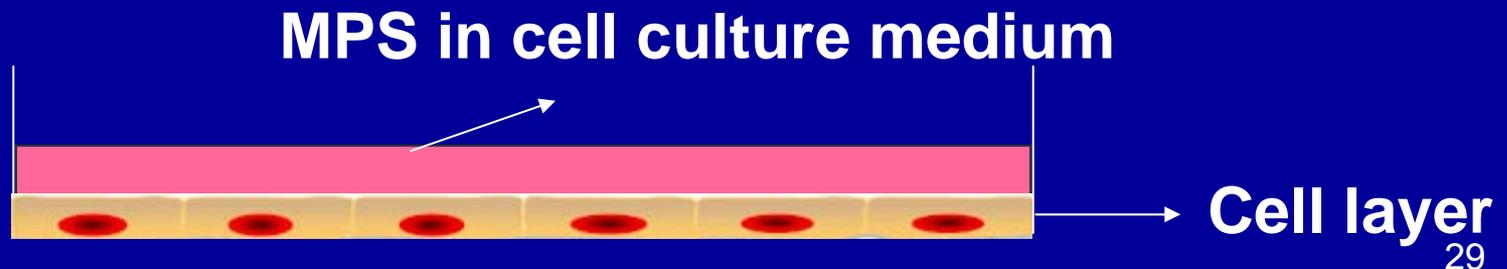
# Cytotoxicity Testing on MPS

(to evaluate direct exposure)

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



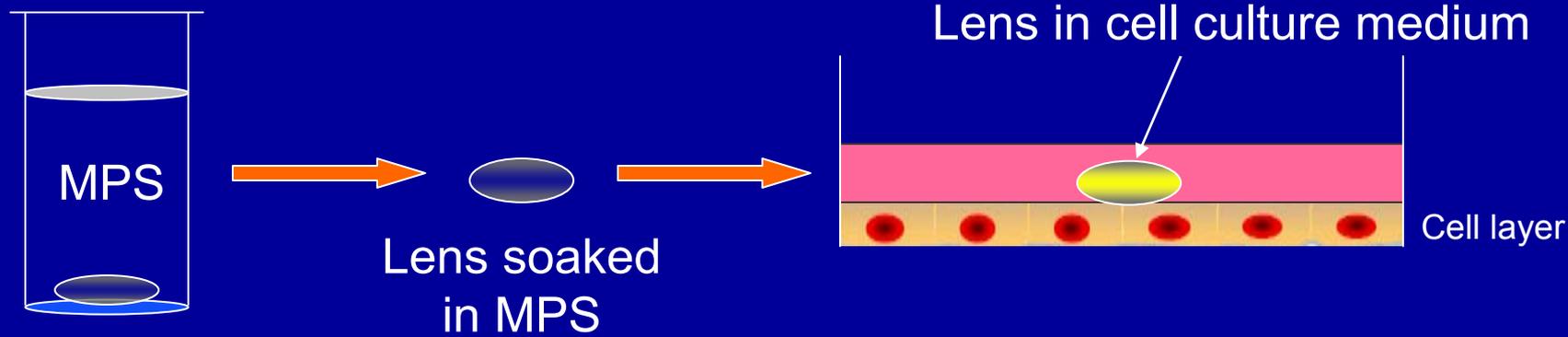
- **Modified Elution Assay (additional test)**



# Cytotoxicity Testing of MPS-soaked Lenses

(additional test to evaluate indirect exposure)

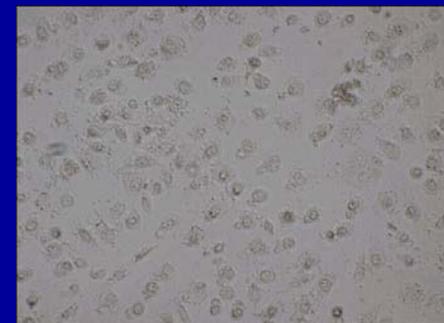
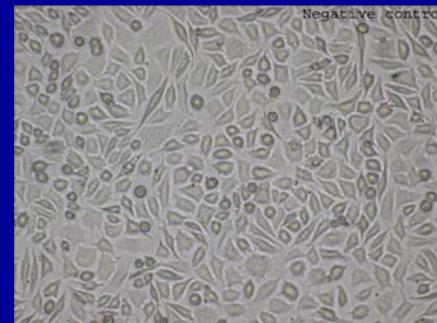
## Direct Contact Assay



- Conventional hydrogel lens
- Silicone hydrogel lens

Non-cytotoxic response

Severe cytotoxic response



# MPS: Cytotoxicity Testing Summary

- **Agar diffusion assay** (currently used)
- **Modified elution assay** (additional test)
- **Direct contact cytotoxicity assay on the following lenses soaked in MPS for 96 hrs** (additional tests)
  - Conventional hydrogel (Gr IV)
  - SiHy lenses with plasma oxidation surface treatment: balafilcon A
  - SiHy lenses with surface modification by plasma polymerization: lotrafilcon B
  - SiHy lenses with no surface treatment: galyfilcon A
  - SiHy lens: comfilcon A

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**Acute Ocular Irritation Test: On MPS  
alone and on MPS in combination with  
various lenses to address Lens-solution  
Interaction**

# MPS: Acute ocular Irritation Testing Strategy

- **Neat solution** (currently used)
- **Testing of polar and non-polar extracts of the following lenses soaked in MPS for 96 hrs** (additional tests)
  - Conventional hydrogel (Gr IV)
  - SiHy lenses with plasma oxidation surface treatment: balafilcon A
  - SiHy lenses with surface modification by plasma polymerization: lotrafilcon B
  - SiHy lenses with no surface treatment: galyfilcon A
  - SiHy lens: comfilcon A

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**22 day Rabbit Ocular Irritation Study  
(ISO 9394): Testing Strategy for MPS to  
address Lens-solution Interaction**

# MPS: 22-day Rabbit Ocular Irritation Testing Strategy

- **Testing the neat solution with conventional hydrogel lens** (currently used)
- **Testing with conventional as well as silicone hydrogel lenses** (additional tests)
  - Conventional hydrogel (Gr IV)
  - SiHy lenses with plasma oxidation surface treatment: balafilcon A
  - SiHy lenses with surface modification by plasma polymerization: lotrafilcon B
  - SiHy lenses with no surface treatment: galyfilcon A
  - SiHy lens: comfilcon A

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# **Acute Oral Toxicity: Testing Strategy for MPS to address Lens-solution Interaction**

# MPS: Acute Oral Toxicity Testing Strategy

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- **Testing on neat solution** (currently used)
- No additional tests

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# **Sensitization Test: Testing Strategy for MPS to address Lens-solution Interaction**

# MPS: Sensitization Testing Strategy

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- **Testing on neat solution** (currently used)
- No additional tests

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# FDA Efforts and ANSI/ISO Update

# Ongoing FDA Efforts and ISO TC 172 / SC7/ WG9 Activities

- Active participation in ANSI / ISO Standard Activities (ISO TC 172 / SC7/ WG 9 Contact lenses and Care Products)
- FDA's proposal on cytotoxicity testing of lens care solution to address potential lens-solution interactions
  - Presented at FDA Panel Meeting, June 10, 2008
  - Discussed at ANSI Z80 SC7 Meeting on March 31, 2008; ISO TC 172 / SC 7/ WG 9 meeting in Paris, July 2008;
  - Up for discussion at ISO TC 172 /SC 7/ WG9 Interim meeting in London, May 2011
- Proposed revision of ISO 9394 (3-wk rabbit ocular irritation study) to include testing of lens care product with representative conventional and silicone hydrogel lenses (during systematic review of the standard, August 2008)
  - ISO TC 172 / Sc7/ WG 9 project group for revision of the standard
  - N1180: ISO/CD 9394: currently out for voting and comments

# ACKNOWLEDGEMENT

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- Shelley Buchen

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*Thank You*