Contact Lens Solutions – New Regulatory Issues

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Disclaimer

- This presentation should NOT be considered Agency guidance as described under current Good Guidance Practices
- The information is intended for thoughtful discussion at this symposium on contact lens care product testing
- It is not intended to be used for establishing substantial equivalency to a currently marketed product
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Medical Devices

Promote & Protect the Public’s Health
The Total Product Lifecycle

Ensuring the Health of the Public Throughout the Total Product Life Cycle -- It's Everybody's Business
Continued Safe Use

Contact Lenses  Care Products

Challenges

Consumers
CDRH MATRIX
Structure of the Matrix

9 Product-Specific Networks

4 Diagonal Networks

CDRH Offices

Liaisons

Liaisons
CDRH Matrix
9 Product Networks

- Cardiac Electrophysiology and Monitoring
- Cardiothoracic and Peripheral Vascular
- Gastroenterology, Urology and Renal
- General Surgery, Physical Medicine, Ob/Gyn
- Infection Control, Dental, General Hospital, Infusion Pumps
- Ophthalmics and ENT
- Orthopedics
- Neurology, Anesthesia, Respiratory
- Plastic and Reconstructive Surgery and Breast Implants
CDRH Matrix
4 Diagonal Networks

- Radiological Products
- Diagnostics
- Science
- Regulatory Affairs and Special Interests
Class II Ophthalmic Devices

- Fundus Cameras
- Ophthalmoscopes
- Slitlamp Biomicroscopes
- Tonometers
- Microkeratomes (laser)
- Phacoemulsification Devices
- Contact Lenses (daily wear)
- Contact Lens Care Products
Medical Device Regulations

1. How do you make it?
   The quality system regulation

2. What are the directions for use?

3. Why monitor adverse events?
Device Advice is CDRH’s self-service site for medical device and radiation emitting product information. It is an interactive system for obtaining regulatory information concerning medical devices.

Medical Device Regulations

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Radiation Emitting Products

Does Your Product Emit Radiation?

http://www.fda.gov/cdrh/devadvice/
1. How do you make it?
The quality system regulation
Please note: as of October 1, 2002, FDA charges fees for review of Premarket Notification 510(k)s and Premarket Approvals.

Good Manufacturing Practices (GMP) / Quality System (QS) Regulation

- Introduction
- Flexibility of the GMP
- Applicability of the GMP
- GMP Exemptions
- Types of Establishments Exempt from GMP
- Types of Establishments Subject to the GMP
- Additional Quality System Information

Introduction

The current Good Manufacturing Practice (GMP) requirements set forth in the Quality System (QS) regulation are promulgated under section 520 of the Food, Drug, and Cosmetic (FD&C) Act. They require that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed under a quality system to meet these specifications; that devices be manufactured under a quality system; that finished devices meet these specifications; that devices be correctly installed, checked, and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed. Thus, the QS regulation helps assure that medical devices are safe and effective for their intended use. The Food and Drug Administration (FDA) monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with the GMP requirements in the QS regulation.

The QS Regulation is contained in Title 21 Part 820 of the Code of Federal Regulations. This regulation covers quality management and organization, device design, buildings, equipment, purchase and handling of components, production and process controls, packaging and labeling control, device evaluation, distribution, installation, complaint handling, servicing, and records. The preamble describes the public comments received during the development of the QS regulation and describes the FDA Commissioner's resolution of the comments. Thus, the preamble contains valuable insight into the meaning and intent of the QS regulation.

http://www.fda.gov/cdrh/devadvice/32.html
Design Goal

Do you want people to fit the product?

or

Do you want the product to fit the people?
Rub / No Rub

- Can you get people’s habits to fit the products?

  or

- Do you develop products that fit their habits?
Design Control Guidance for Medical Device Manufacturers

Design controls may be applied to any product development process. The simple example shown in Figure 1 illustrates the influence of design controls on a design process.

Figure 1 – Application of Design Controls to Waterfall Design Process (figure used with permission of Medical Devices Bureau, Health Canada)

Design Controls

- Developmental testing
  - Firm includes in design control
  - Acanthamoeba testing

- “stressed MPS”
  - Simulated evaporation to address misuse
  - Safety margins via “topping off tests”
New contact lenses and care products are more chemically complex with greater potential for interactions.

Will a care product’s margin of safety overcome “misuse”? 
Factors that could affect disinfection efficacy

- Uptake of preservative by lens (raises toxicity and micro. effectiveness concerns)
- Uptake of care product’s preservative by lens case
- Increased adherence of microorganisms to lenses (due to lens chemistry or lens-solution interactions)
Factors that could affect disinfection efficacy

- **Interference from lens deposits**
  (protein/lipid/other)

- **Decomposition of preservative at high temperature**

- **Decomposition of preservative over time**
Factors that could affect disinfection efficacy

- Decreased availability of preservative due to interaction with other solution ingredients

- User non-compliance: repeated use of lens case solution, no rubbing/rinsing, no cleaning of cases/biofilm
2. What are the labeling directions for use, Rx or OTC?
Medical Device Labeling

- 21 CFR parts
  - 801 – General Device Labeling
  - 812 – Investigational Device Exemptions
  - 820 - Good Manufacturing Practices

http://www.fda.gov/cdrh/devadvice/33.html
Medical Device Labeling

- **Label**
  - On the immediate container

  *vs.*

- **Labeling**
  - Includes the label
  - Accompanies the device it is held for sale after shipment or delivery
Labeling Considerations

- **Discard upon opening dates**
  - 21 CFR 800.1 does not mandate
  - EU marketing does mandate
3. Why monitor adverse events?
Post-Market Issue

- Medical errors and patient safety
- Device related vs. human factors
- Long term safety (device durability-latent toxic effects)
- After clinical trials, performance of device in community practice
Post-Market Issue

- Change of user setting (e.g. hospital -> home, doctor/laboratory-> patient)
- User related problems
- Unusual pattern of adverse events not requiring product recall
- Challenge mechanisms of surveillance
Adverse Event Reporting

Device failures / malfunction

Office of Surveillance and Biometrics

- Med Watch
  - Manufacturer and User Facility Device Experience Database (MAUDE) System

- Medical Product Safety Device Network (MedSun) programs – sentinel system

http://www.fda.gov/cdrh/mdr/mdr-general.html
MAUDE

- Voluntary reports from patients & practitioners

- Medical Device Reporting (MDR)
  - Mandatory reports from manufacturers

- Available on-line
  http://www.fda.gov/medwatch/getforms.htm
Recalls

Facility Inspections

Compliance Corrective Actions

http://www.fda.gov/cdrh/safety/041006-keratitis.html
Fusarium Keratitis

May 06  B&L MoistureLoc withdrawn

Acanthamoeba Keratitis

May 07  AMO Complete MoisturePlus withdrawn
June 2008 Advisory Panel

6 main questions posed by the FDA:

- Labeling directions and warnings
- Clinical study design
- Microbiology testing
- Acanthamoeba as a test organism
- Silicone hydrogel lens groupings
- Cytotoxicity testing
Panel Recommendations

- Agreed with the professional organizations - current products be used only with rubbing directions.

- “No rub” technologies should meet the same new “higher bar” level of biocidal effectiveness as “rub” products after new standardized test methods and performance criteria were developed.
Panel Recommendations

- **Revised warning statements**
  - topping off or reuse
  - avoiding water exposure
  - providing a discard date after opening

- **Solution-induced corneal staining and microbial keratitis - unclear**
  - Did not recommend an additional short-term visit in the study protocol at this time
Panel Recommendations

- A real world microbiology test, which challenges the care product with microbes in the lens case with the contact lens

- Add Acanthamoeba as a challenge organism. No detailed discussion of methodology or performance criteria
Panel Recommendations

- Endorsed a separate category for Si-Hy lenses include with conventional hydrogels in both clinical and cytotoxicity testing
FDA Response to Panel Recommendations

- Recommend manufacturers include only “rub” directions for use in labeling
- Convene workshop on Acanthamoeba and other microbiological test methods
- Develop standardized method for Acanthamoeba with standards organizations
FDA Response to Panel Recommendations

- Revise guidance documents
  - Include test methods that represent “real world”
  - Additional warnings and precautions
- Update contact lens website
- Biocompatibility of Lens/Solution
- Clinical study methodology
FDA’s Thinking

Preclinical and Clinical Studies

Designed to address

- Potential lens-solution interaction
- Impact on product safety
Chemistry

Considerations
Si-Hy Lens Grouping

### Group 5 Representative Silicone Hydrogels

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Surface Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>lotrafilcon B</td>
<td>Plasma polymerized surface</td>
</tr>
<tr>
<td>2.</td>
<td>balafilcon A</td>
<td>Plasma oxidized surface, macropores</td>
</tr>
<tr>
<td>3.</td>
<td>galyfilcon A</td>
<td>No surface treatment, semi-interpenetrating network of water soluble polymer</td>
</tr>
<tr>
<td>4.</td>
<td>comfilcon A</td>
<td>No surface treatment, co-polymerized with substantial VP</td>
</tr>
</tbody>
</table>

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

Considerations
Testing Considerations

- What chemical interactions determine disinfection effectiveness?
- What’s the effect of preservative uptake by lenses on disinfection efficacy?
- Will Si-Hy contact lenses be used?
- What are the cleaning directions?
‘Real World’ Considerations

Do test methods reflect ‘real world’ conditions?

- Do regimen test rub and rinse times (e.g., total up to 20 seconds) exceed typical consumer use?
- What are consumer deviations from directions for use (e.g. topping off)?
- How does improper care of lens case/hygiene (e.g. biofilm) factor in?
- Will organisms that cause clinical infection be more resistant than current test organisms?
‘Real World’ Considerations

- Are disinfection and preservative effectiveness tests done with product at low end of active ingredient specifications (worst case)?

- Will there be reduced effectiveness in marketed lots? (Temperature effects during storage or transport)
Biocompatibility
Considerations
**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)
  - 22-Day rabbit ocular irritation study (in vivo – new for ophthalmic use)
Test Proposal: Points to consider

- 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
Clinical Testing
Considerations
Si-Hy CL’s: Interactions with Care Products - Solution-related Corneal Staining

How best to assess and characterize the ocular response to preservative uptake & release?

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

# CL Care Products Clinical Considerations

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<thead>
<tr>
<th>Lens Mat’l</th>
<th>Test</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>lotrafilcon B</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>balafilcon A</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>galyfilcon A</td>
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<td>15</td>
</tr>
<tr>
<td>comfilcon A</td>
<td>30</td>
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</tr>
<tr>
<td><strong>Group IV</strong></td>
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<td>15</td>
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Labeling
Considerations
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

- Literature debate on digital rub component.

Continued Safe Use

Practitioners

Regulatory Authorities

Consumers

Industry
Enhanced Safety?

- Informed Eye Care Providers
- Educated Consumers
- Greater product safety margins
Thank You