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June 5, 2008

Karen F. Warburton
Executive Secretary
Ophthalmic Devices Panel
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

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**Re: Ophthalmic Device Panel
One Hundred and Eleventh Meeting**

Dear Ms. Warburton:

Bausch & Lomb is submitting the following comments for consideration by FDA and the Ophthalmic Device Panel. As announced in the published CDRH Advisory Committee notice, the purpose of the June 10, 2008 meeting of the Ophthalmic Devices Panel is to discuss and make recommendation on contact lens care product topics such as:

- Preclinical Testing;
- Clinical Performance Measures; and
- Labeling for contact lenses and lens care products.

Bausch & Lomb shares a common objective with FDA to continue to support the development and manufacture of products that are safe and effective. A science-based review of the topics that have been outlined for the panel discussion is essential to achieve a realistic balance between safety and risk. We fully support the agency in this initiative and look forward to actively participating in any consideration of revising existing guidance for these class II medical devices.

Prior to the Ophthalmic Devices Panel Announcement, FDA provided to industry representatives a draft document containing initial concepts regarding possible contact lens care product testing which may be a subject of the panel's discussions. Bausch & Lomb believes that the draft paper contains important concepts that should be considered, though it is apparent from the initial version that there are still significant details yet to be defined with the proposed concepts. The panel discussion is a good first step to defining the issues and process that should be considered before these draft concepts are incorporated into device review guidance.

As the agency and members of the Ophthalmic Device Panel consider the outlined topics, it is crucial to incorporate a full analysis of the existing scientific literature and postmarket experience, which reflects important information on preclinical testing methodologies and clinical outcomes. This information is particularly important to balancing the regulatory review with appropriate science for the development of future guidance for lens care products.

This letter is intended to provide certain considerations on the identified topics that Bausch & Lomb would like to have the agency and panel consider as part of the discussion on contact lens care products. Further commentary, as to this topic and as to other topics may be provided following the June 10th Panel Discussion and we would welcome further discussion with the agency on these issues.

Preclinical Testing

As the agency and members of the panel are aware, it is important that new test methods, such as those mentioned in the draft document, be defined, validated, standardized, and implemented in a manner that ensures uniform application within the industry. Some examples of testing suggested by FDA that require this development include: a) the effect of preservative uptake by lenses; b) activity against *Acanthamoeba sp.*; and c) the characterization of film deposition in a lens case. These are either being evaluated or are under active development by standards and or industry groups of which FDA is a participant in some manner. We believe that this process of developing standard testing methods and criteria should continue so that reliable, validated and standardized data is obtained to allow for an objective science based FDA review.

Clinical Performance Measures

The proposed grouping of Silicone Hydrogel lens materials is based on the current knowledge of existing technology. However, as technology evolves there may be other logical methods of grouping lens materials for testing purposes.

Corneal Staining

Evaluating clinical signs such as corneal staining as part of a clinical study is not new and is currently included in all clinical studies as recommended by current FDA guidance. It is important that in considering changes to existing test methods the agency and panel consider the depth of scientific literature and postmarket experience.

In the current FDA guidance, a key element of the clinical investigation plan is to evaluate performance during a time period that realistically tests the performance of the device and allows identification and risk assessment of any associated adverse device effects. Thus, FDA has recognized in existing guidance that clinical signs such as superficial punctate staining (grade 1 and 2) is not a safety concern. While the draft concept paper appears to conclude or presume that "maximum" staining can be observed at a two-hour time period and that the presence of staining shortly after lens insertion is an indication of an "immediate toxic reaction," it does not consider that other combinations of active agents may impact ocular tissues at varying time intervals.

Regarding the evaluation of corneal staining, it is important to note that there is no established scientific link between superficial micropunctate corneal staining and corneal infection. In addition, a recent study conducted to assess the relationship between transient corneal staining after wearing contact lenses soaked in different multipurpose solutions and an inflammatory response indicative of a compromised epithelial tissue demonstrated that there was no difference in acute inflammatory response associated with the transient contact lens solution-induced staining.

For these reasons, Bausch & Lomb encourages the FDA and panel members to review the full breadth of available scientific literature and postmarket experience of currently marketed products to assure that any conclusions are balanced with relevant scientific knowledge and to continue the current recommendation to use a follow-up period that permits demonstration of performance of the device over an appropriate length of time to identify risks without limiting or mandating specific time intervals for follow-up evaluations.

Although not an exhaustive compilation, attached for your consideration are references for some of the more relevant publications of clinical studies and the evaluation of corneal physiology.

Labeling

It is well established that clear labeling is an important part of the special controls established for these class II devices. Bausch & Lomb concurs with FDA that clear labeling is important for the proper safe use of lens care solutions and as such the product labeling regarding usage needs to be clear and cautionary and should not have the affect of confusing OTC consumers. To that end, labeling-related guidance should consider both existing and future products. The "grandfathering" of existing product labeling has the potential to create consumer confusion, and should be avoided.

In conclusion, Bausch & Lomb is supportive of FDA's initiative to evolve the testing and review of new lens care solutions. We invite the agency's questions and concerns regarding the best scientific methods and meaningful data to ensure the safety and efficacy of lens care products.

Sincerely,

A handwritten signature in blue ink, appearing to read "Michael A. Santalucia". The signature is fluid and cursive, with a long horizontal flourish extending to the right.

Michael A. Santalucia

REFERENCES

1. Mowrey-McKee M, Sills A, Wright A. CIBA Vision Corporation. Comparative cytotoxicity potential of soft contact lens care regimens. *CLAO J* 2002;28:160–164.

Conclusions: The USP direct contact with cycled lenses test and three modifications of the USP elution test we developed were useful in determining the rank order of in vitro biological reactivity of six contact lens disinfection solutions. Results were consistent across tests for the noncytotoxic solutions AOSep Disinfectant, SOLOCare, COMPLETE Comfort PLUS, and for the cytotoxic solution OPTI-FREE Express with Aldox. ReNu MultiPlus and ReNu MPS yielded mixed results, with noncytotoxicity for all tests except the quantification of viable cells method.

2. Howarth-Winter J, Simon M, Kolli H, et al. Cytotoxicity evaluation of soft contact lens care solutions on human conjunctival fibroblasts. *Ophthalmologica* 2004;218:385–389.

Conclusions: This in vitro study demonstrates that the examined soft contact lens care solutions induce changes in mitochondria of human conjunctival cell only at higher doses as observed by the MTT test. However, this damage to the mitochondria did not lead to cell death as shown by the cell analysis system.

3. Tchao R, McCanna DJ, Miller MJ. Comparison of contact lens multipurpose solutions by in vitro sodium fluorescein permeability assay. *CLAO J* 2002;28:151–156.

Conclusions: The sodium fluorescein permeability assay can be effectively used to compare the effect of various contact lens-care products have on an epithelium in cell culture. This assay can be incorporated into a developmental program that requires a rapid and sensitive assay for comparing the potential toxicity of novel lens care formulations.

4. Merchea M, Reindel W, Snyder C, White M, China P, LaFrance M, Fullard R. Inflammatory mediators associated with transient, contact lens solution-induced corneal staining. *The Association of Research in Vision and Ophthalmology 2008 Annual Meeting*.

Conclusions:

- Transient corneal staining is not accompanied by objective clinical signs such as limbal/bulbar injection indicative of an active inflammatory response.

- Transient solution induced corneal staining based on a particular lens material – solution combination is not associated with subjective comfort scores as has been previously reported in uncontrolled studies.
 - There is no difference in ocular inflammation based on the measurement of 27 inflammatory markers (cytokines) in tears of eyes with transient solution induced corneal staining.
 - Multi-purpose solutions are not related to a significant up-regulation of inflammatory markers.
 - Future study of chronic tear cytokine profiles in contact lens wearers is warranted.
5. Ward K. Superficial Punctate Fluorescein Staining of the Ocular Surface. *Optometry and Vision Science* 2008;85: 8-14.

Conclusions: This review highlights major challenges in attempting to extrapolate from the clear importance of gross corneal staining down to the meaning of observation of superficial punctate staining, and should promote greater circumspection in interpreting this phenomenon. The literature reflects that superficial punctate corneal staining does not reflect corneal injury or toxicity. More work is required to elucidate the various mechanisms underlying superficial punctate staining, and to provide clinicians with a rational interpretation algorithm for this observation.

6. Fleiszig, SMJ. The pathogenesis of contact lens-related keratitis. *Optom Vis Sci* 83:12, E866-E873, December 2006.

Conclusions: Our interest in exploring tear fluid as a defense originally ignited when we found that cytotoxic *P. aeruginosa* could damage an intact cornea on rat eyeballs, but only once they had been removed from their in vivo environment. This suggested that corneal epithelial cells were inherently susceptible to bacteria, even when grown in their normal environment on the eye, but that in vivo factors were protective. We have since shown that tear fluid plays an important role in defense against infection. Yet, contact lenses are likely to alter biochemistry of tear fluid at the most critical location: between the lens and the cornea. This could potentially trigger a chain of events that leaves the cornea susceptible to infection in some contact lens wearers.

The corneal surface is probably the most exposed of all our mucosal surfaces to a daily barrage of potential pathogens. It is also the least able to afford an infection, because even a small scar at the center of the cornea can cause

loss of vision. Because transparency is critical for vision, the healthy cornea lacks various features used by other tissues in defense against infection, including blood vessels and various immune factors. How the cornea maintains its broad-spectrum resistance to infection with pathogens that easily infect other sites that have much better access to defense strategies is not at all well understood. The fact that so many *P. aeruginosa* isolates can grow effectively in human tear fluid, but cannot infect the healthy cornea, suggests that there is much more to this fascinating story than bacteriostatic activity of tear fluid but that tear fluid is involved.

Research to define biochemical changes that occur as a result of lens wear could provide new directions for preventing infection in contact lens wearers. Modifications to lens materials/design/or modes of wear could be aimed specifically at reducing disruption to, or to replacing, identified critical tear factors. Beyond contact lenses, research in this area has the potential to lead to biocompatible new approaches to prevent a wide range of infectious diseases of the eye and other sites.

7. Barrett RP, Mowrey-McKee M, Zhang Y, Hazlett LD. Punctate fluorescein corneal staining observed using polyhexamethylene biguanide containing disinfecting solution not indicative of corneal surface damage. Invest Ophthalmol Vis Sci. 2005;46: E-Abstract 5732.

Conclusions: We conclude that corneal staining with fluorescein following contact lens disinfection with PHMB is not indicative of damage to the surface of the cornea and that the staining is an artifact that disappears within hours.