Ophthalmic Devices Panel of the Medical Devices Advisory Committee
Contact Person: Karen Warbutrton
CDRH (HFZ-460)
9200 Corporate Ave.
Rockville, MD, 20850

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I am a researcher and have been a member of this industry for the last 27 years. I have been involved in the research and development of contact lens care products for a number of companies in this industry, and I have developed numerous products marketed in this field. I am current retired but maintain a consulting practice. I developed the original lens classification system, I have participated as an expert to the Japanese MHLW from the US on lens classification, and I am currently an expert at ISO WG9/SC172 and project leader for revision of ISO 11986. I am providing these comments as an individual professional, and not at the behest of any entity or company in this field. My travel expenses to the June 10 panel meeting were supplied by Alcon Laboratories. I have participated in development of industry comments by the Contact Lens Institute as a participant from Alcon Laboratories.

I would like to provide to the Ophthalmic Panel with the following comments which represent my professional and technical assessment of some of the issues facing the care of contact lenses today.

Prior to the two incidents in 2006 and 2007 resulting in recalls of products in this field, there was a perception that there were few differences in the technologies used in the products in the marketplace. Our development efforts and the reception in the marketplace of new products reflected these perceptions regardless of the data developed and published in the peer reviewed and non-peer reviewed literature. The events of 2006 and 2007 have made us re-think all of our pre-conceptions based on the data before us.

We have long known that the patients who use the soft contact lens and must care for them are likely not to use the procedures recommended by either the practitioner or are provided in the labeling. Collins and Carney[1] in 1986 were among the first to report on non-compliance and were able to connect compliance to some signs observed in patients. Since that time more than 30 articles, posters and presentations have featured compliance or lack of compliance in patients. Even with reports of 40-100% of patients failing in some aspect of compliance, a rather constant rate of infections in patients has been observed. Since Poggio and coworkers[2] published their findings in 1989, three additional epidemiology studies over the period from 1989 to 2005[3.4.5] have shown an essentially unchanged infection rate with daily wear at approximately 4 per 10,000 wearers and approximately 20 per 10,000 for extended wear. The evaluations reported on the events of 2006 and 2007 provide a glimpse of the actions and activities either that are or are not clearly related to the infections reported from *Fusarium* or *Acanthamoeba*. The primary conclusions from these incidents are that the infections were more highly related to specific product formulations.

The current understanding of the more recent *Acanthamoeba* continues to raise questions relative to the overall implications for this rare infection. It was predicted based on work by Schaumberg that the rate of *Acanthamoeba* in the United States based on the 1985-1987 outbreak that the conservative rate of this keratitis was 1-2 per million patients.[6] The current data collected in the 2005-2007 outbreak collected by CDC is currently incomplete and does not allow us to understand if there are changes in the incidence beyond the implication of a single product, nor does it allow the scientific community to respond to any potential issues based on reasoned scientific approaches. As background, the rate of *Acanthamoeba* infections in the UK is about a factor of 10 higher than has been reported in the US. These differences are most often considered to be related to the water quality and water storage modes used in the UK.[7]

Chang[8] in reporting the information from the CDC evaluation related to investigation of *Fusarium* keratitis found that reuse of lens solutions or "topping off" was the only variable with odds ratios above 3 and a 95% confidence interval which did not include 1.0 other than the solution, ReNu with MoistureLoc. More interestingly patients who suffered infections were less likely than controls to never clean their lenses by rubbing (OR 0.4, 95%CI 0.2-0.9). Other areas of care often considered did not provide links to the *Fusarium* infection events. These included, rinses lenses, washing hands or cleaning and replacing lens cases. All these are known to be areas of non-compliance to lens care regimes.

Joslin and co-workers[9] reported that a single product formulation was the single strongest risk factor in the outbreak of *Acanthamoeba* infections in the Chicago area and a single hygiene factor was significantly related in an unconditional logistical multivariate regression. In univariate analysis "reuse of solution" was statistically significant (OR 3.19, 95% CI 1.10-9.27, p=0.033) and rubbing less than 10 times per month showed the next highest odds ratio (OR 2.54, 95% CI 0.1-10.95), however the chi-square p= 0.20.

The critical questions that arise from these events of infective keratitis relate to what areas contribute to these associations and what can be achieved to provide pre-market protocols and post market observations that effectively minimize any recurrence of these incidents. Our ability to change the patients' habits has proven to be limited and our willingness to provide increased patient instruction has not proven effective.

The base of current pre-clinical testing evolved based on results obtained in products developed during the 1980's and early 1990's. All of these products performed on the market without evidence of increases in infection reported. Products recently developed and linked to the current outbreaks show key similarities. They included ingredients not previously used and marketed for soft contact lens care. This suggests that the use of the new ingredients provide a different environment that we had anticipated in earlier development efforts.

The current testing process for microbiology is found in the ISO procedure (CEN/ISO 14729). It is designed to test the efficacy of a product candidate to kill or remove four different types of organisms, two gram-negative bacteria, a gram-positive bacteria, a yeast and a mold. These organisms were chosen to provide a common reference for all products. The primary criteria ("stand alone") demonstrates only effect of the solution on the organisms. Products not meeting the initial criteria have been subjected to a second test. In this second or regimen test, products

are asked to treat different representative types of lenses with organisms using the regimen suggested in the label. This test was carried out at higher inoculums than were expected under normal exposure, and the resulting effect was not sterility but less than 10 organisms per lens and solution.

Although it has not been incorporated into the "official" ISO test procedures, the initial products, which have been tested to delete the rub step, were subjected to additional testing in the United States and the general approach was incorporated into ANSI Z80.18 procedures. The products were asked to perform in the primary testing under ISO 14729 in the presence of artificial lens soilant. These products were asked to demonstrate that the additional insult did not deactivate the product. The product was also asked to demonstrate that the proposed regimen would reduce the 10^5 to 10^6 inoculums of each organism could reduce the level of organism to less than 10 in the presence of an organic soil. This modification should be considered for addition to the current test ISO 14929 protocols since it would provide assurance that a product is not significantly affected by deposits and soil from lens wear.

These test procedures, however, do not appear to effectively anticipate the effect of the lens in absorbing the biocides and decreasing the effectiveness of the system. This becomes important when considering the effect of re-use of solutions or "topping off" which may have been a factor in the recent infection outbreaks. A review of the literature reports between 13 and 48% top off their solutions at least some of the time. To upgrade current testing procedures, a review of the recent literature shows four papers which have evaluated the effect of uptake of biocides by lenses. Rosenthal (1997)[10], Dannelly[11], Rosenthal (2006)[12] and Warburton[13] looked at the effect on microbial efficacy of the uptake of biocides in lenses. Using these approaches as a model, the Contact Lens Institute in cooperation with FDA is evaluating a method to evaluate the effect of lenses and lens cases during the disinfection process. It is currently being evaluated as a draft standard at both ANSI and ISO. The critical ongoing step will be the inter-laboratory validation of the technique. I believe that this will be a step forward in understanding the impact of the lens and a key non-compliance behavior.

The option to remove the rubbing step from a care regimen has provided significant discussion in the field. These directions are recognized as being in opposition to the general directions provided by many eye care professionals. However, these directions of use apparently popular with consumers while not accepted in the practitioner's office do not appear to have changed the primary compliance of patients. In fact neither manufacturer's labeling nor practitioner training have affected the rate of compliance. The number of patients who do not rub lenses overall appears continue to be around 50% of patients in studies by Chang,[8] Joslin[9], Turner[14], Morgan[15], Stone[16], and Efron[17] with numbers ranging from 40 to 58%. It should be noted that Chang[8] found that patients who never clean lenses were less likely to have a Fusarium infection. Since the enhanced testing for this option may increase the overall margin in biocidal efficacy anticipating a known question of compliance, concern about cleaning of lenses becomes more of an issue in overall maintenance of lenses. The current requirements for measurement of micelle formation and or the demonstration of quantitative reduction of deposits are sufficient for testing of product effectiveness.

A lot of discussion has appeared with the outbreak of *Acanthamoeba* infections in Chicago and some other isolated reports. Currently the global standards do not require testing of this organism with the rationale outlined in the appendix to that standard. Critical to these efforts is a realistic understanding of the overall change in the incidence of this disease. All we currently know is the information reported in the CDC report and the scattered information from various centers. As I indicated before the rate in the US has been estimated at 1-2 per million patients. Given 10 times the rate is reported in the UK[7], we need to understand any changes to the US rate. The CDC and studies on the Chicago outbreak indicates that one product was significantly more associated with the incidents.

If we are to expect the products available in the market to be effective against all forms of this organism, we have some technical hurdles to overcome. The fact that this protozoa exists in a trophozoite form and a resistant cyst form, designed to protect the organism, provides technical difficulties. Cysts can be formed by a number of different insults including starvation, osmotic stress, and in effective chemical attack. Each of these modes may give different cyst forms which have different susceptibility to effective disinfection. Development of a method to overcome these obstacles is on the agenda for the experts of ISO Working Group 9 meeting in Paris next month. A recent publication by Kilvington[18] indicates that the product implicated by the CDC and Chicago evaluations is more likely to cause the formation of “immature cysts” which remain viable to return to the trophozoite form. The difference in these observations for the suspect product and products not linked to these events may provide an approach to future testing.

Lens cases have been the source of many pictures--images of a several year old, never cleaned, lens cases. The care and cleaning of lens cases has never been good and the replacement has been even worse. In my experience marketing a product providing a new case with every bottle produced the highest level of complaints asking: Please no more cases--I have a drawer full. The contamination of cases is widely reported in compliance studies with as high as 82% of cases contaminated with organisms. Gray[19] reported that 81% of cases returned in a study including both hydrogen peroxide and multi-purpose solutions. 24% of these cases had contamination with fungi and 7% with protozoa. The use of tap water with cases is rampant with 42-72% of patients using tap water to clean cases. While there was little correlation of the recent outbreaks, case cleanliness is a concern. Re-emphasis on cleaning instructions, elimination the use of tap water, potentially boiling lens cases periodically, and better availability of new cases may be critical.

While we continue to focus on mechanisms to approach sterility during our care regimes, we forget where the organisms come from that contaminate our lenses. It is obvious we need to minimize the association of organisms with lenses and cases, but can we truly eliminate exposure of patients to organisms? In the early 1990’s, Mowrey-McKee,[20, 21] and Hart [22] published a series of three papers discussing the contamination of lenses by handling. Their initial observation was that lenses coming from the eye and removed using sterile technique were nearly sterile and had low levels of organism associated with them. Handling, however, for worn lenses by patients produced lenses contaminated with a mean level of approximately 2,000 organisms. In these studies 11% of lenses showed fungal contamination. Stone[16] in a

small study in 2007 found that patients handling lenses contaminated their lenses with a mean of 2,000 to 10,000 organisms depending on hand washing. These observations are critical in understanding infection when we work to minimize the exposure by our care systems only to re-inoculate during the re-insertion process.

Do we provide ourselves with false hope on the effectiveness of our regimens. Houlsby[23] in the 1980 and Rosenthal [24]recently have looked at the possible effectiveness of product regimen steps. Both show dramatic reductions of organisms and apparent effectiveness of systems. With most of these steps we are removing and not necessarily killing or inactivating the organisms. But, these studies are carried out with the hands in sterile gloves. Today we have no information about removal in cleaning steps in the presence of a source of re-inoculation.

The labeling of the multi-purpose solutions currently has been emphasizing the directions for use (e.g., No Rub) prominently on the box and bottle while providing alternative both with and without a rub step in the patient directions for use on the side or back and in the insert.. It seems appropriate to not to provide information on the indications for use (such as “no rub” or other use directions) on the primary front panel of the carton or on the front section of the bottle label allowing practitioners to provide clear options to patients. Providing options based on demonstrated advancements in the science behind these systems are important if we are to have the opportunity to move technology forward for contact lens care products. Over the last 25 years, we have moved forward from individual products for each step of care often using a heat disinfecting unit to a single bottle for cleaning, rinsing, disinfection and storage at room temperature. The very effective enzyme cleaning process either as liquid or the earlier tablets has been largely abandoned by current care regimens.

We know that the potential or risk for infection must have two components. First is the exposure to microorganisms. Since exposure to organisms is routine and is primarily dependent to the flora associated with the individual environment, the second component becomes important. Wilcox and Holden[25] quote, in a review in Bioscience Reports, comments associated with Klotz[26]. “It is generally accepted that bacteria do not infect an intact corneal surface.” Fleiszig[27] has provided a body of research indicating the importance of corneal damage in the infection process for pseudomonas.

As we have seen that lenses can take up the biologically active ingredients in the products and there are concerns the potential release by lenses of these biologicaly active ingredients. The current methods to measure contact lens uptake and release are based on CEN/ISO 11986 These methods have relied on endpoint evaluation of the plateau of uptake and the total release over time. Working Group 9 of TC172/SC7 of ISO is currently evaluating a revision of the uptake and release standard with the goal of understanding the kinetics of both the uptake and the release. This measurement is critical and we need to understand the maximum exposure of the eye to the release of biologically active materials. The use of this revised method provides an improved tool for care product evaluation.

In order to properly measure the potential impact of exposure to the biologically active ingredients in lens care products, we carry out a series of studies to evaluate the potential toxicity of ingredients. Currently, we use a number of different levels of studies, all of which are

critical in building a pre-clinical understanding of interaction with the ocular environment. These include both cell culture studies and animal testing. As reported by Hoffman[28], a broad exposure and availability of techniques and models are important to assure that products are not rejected by false positive endpoints (or missed by negative results). The importance of the scientific validation of any new technique cannot by under emphasized. Numerous cell based assays have been reported providing differences in both levels but rank order of the products tested. The difficulty in using either just animal or cell-based assays can be seen in attempts mandated by the European Commission to replace the Draize test in rabbits with a cell-based assay. To date this effort started in the 1990's has not been able to validate an acceptable assay to replace the primary ocular irritation or Draize test.

The careful use of a broad spectrum of the available techniques outlined in the international horizontal standard ISO 10993-1 through 10 provides approaches a good basis for preclinical testing of lens care systems. Cell testing, short term animal studies combined with the longer term lens wear study on rabbits provide an appropriate pre-clinical base (ISO 9394:1998). The full range of studies in most cases should be indicated for the evaluation of new products especially with new ingredients. Selection of specific assays needs to be justified.

Clinical studies are important in developing our understanding of the products in the use environment. These are needed using the broadest variety of lens types to provide the initial needed measure of safety in the real world. The levels required to see the incidence of the *Acanthamoeba* keratitis outbreak cannot be achieved in the pre-market clinical studies. The post-market reporting process is a critical mechanism in evaluating product performance, and the enhancements to the reporting systems such as the recently introduced Sightnet are an important step forward adding to the MDR reporting system.

The last area, I would comment on is the classification of soft contact lenses. I was involved in the development of the four classes of hydrophilic soft contact lenses based on conventional technologies that was proposed and adopted in the 1980's. I had the opportunity to re-evaluate this system in the 1990's when it was accepted in Japan. It was recognized soon after introduction that the inclusion of silicone domains into hydrogels does not fit into the classical four groups. The classical groups currently tested in our pre-clinical and clinical efforts are bracketed by low water, non-ionic group 1 lenses and high water, ionic group 4 lenses. I strongly support continued testing of these two groups as extremes in these conventional hydrogel technology approaches. The introduction of a new group of lenses with a significant inclusion of silicone based ingredients has required re-thinking our approach and we have included the materials into a class loosely designated as group 5. This group is in the process of being included in US and global standards.[29] Sub-grouping of the silicone hydrogels has been proposed and are necessary to adequately test the range of available technical approaches to these lens materials. There has not been acceptance of a clear classification criteria in the standards bodies for the subgroups. There are two basic approaches that have proposed to the classification. It is important that in classing these new materials we include both the properties of the bulk polymer as well as the surface treatment used to enhance surface properties. Both of the current two proposals give the same results when applied to the silicone hydrogels. There are four subgroups based on the first six silicone hydrogel materials. These groups are

the same whether the criteria proposed by Stone[30] or by placing the materials into the manufacturing technologies used. Each of these groups should be tested in order to have the general labeling for use with silicone hydrogel lenses or the specific technologies spelled out on the label.

I would leave this reference with what I believe is an outstanding discussion of the overall area focusing on compliance. The article, a Guest Editorial by Nathan Efron[17] entitled "The Truth about Compliance" that appeared in Contact Lens and Anterior Eye 1997; 20(3):79-86.

Respectfully Submitted,

Ralph P. Stone, Ph.D.
R.P. Stone Consulting, Inc.
6012 Laurel Valley Ct.
Fort Worth, Texas, 76132

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