

# Meta-analysis of the ocular biocompatibility of a new multipurpose lens care system

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**Background:** The purpose of this paper is to evaluate the biocompatibility of a novel multipurpose solution (MPS) with a dual disinfectant system containing polyaminopropyl biguanide and polyquaternium-1 (Biotrue®) by analysis of biomicroscopy signs and adverse events in six large clinical trials.

**Methods:** Data from six consecutive, prospective clinical trials conducted from February 2008 to March 2010 were combined for meta-analysis. Subjects used the new MPS daily for periods of 2 weeks to 6 months. Slit-lamp signs were graded at each follow-up visit using an ordinal scale (0, one; 1, trace; 2, mild; 3, moderate; 4, severe). Analysis for biocompatibility included tracking of greater than grade 2 slit-lamp findings and number of adverse events.

**Results:** A total of 1,567 subjects (3,134 eyes) and 81 clinical investigators participated in the six studies, with 1,499 subjects completing the studies. Based on subject days in the studies, there were 72,904 exposures to the MPS and 7,212 biomicroscopy examinations. The completion rate for the studies was 96.3%. Per observation incidence of any finding greater than grade 2 at the follow-up visits were: corneal staining 0.08%, limbal injection 0.04%, bulbar injection 0.04%, tarsal conjunctiva abnormality 0.09%, and neovascularization 0.01%. There were no other slit-lamp signs greater than grade 2 and no statistically significant difference between hydrogels and silicone hydrogels for any finding. There were no reports of adverse events during the trials.

**Conclusion:** Analysis of over 72,000 daily exposures and 7,212 eye examinations showed that the novel MPS exhibited excellent biocompatibility in subjects using daily wear hydrogel or silicone hydrogel lenses.

**Keywords:** contact lens, solutions, disinfection, meta-analysis, silicone, hydrogel

## Introduction

Biocompatibility is generally defined as “the property of being biologically compatible by not producing a toxic, injurious or immunological response in living tissue”.<sup>1</sup> This general definition is surprisingly suitable for assessment of the biocompatibility of a multipurpose soft contact lens disinfection solution (MPS); it takes into account the solution’s balance of chemical activity that should be effective against microorganisms while nontoxic to human tissue<sup>2-5</sup> and the unique capability of the corneal immune system to respond to stimuli by influx of inflammatory cells that form corneal infiltrates.<sup>6,7</sup>

There are contradictory reports in the literature with regards to in vitro measures of the biocompatibility of MPS systems.<sup>8-11</sup> When cell viability was assessed by quantifying cellular adenosine triphosphate content, resazurin reduction, and lactate dehydrogenase release in transformed human corneal epithelial cells and primary bovine corneal

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epithelial cells, Opti-Free Express® and Opti-Free RepleniSH® (Alcon, Fort Worth, TX, USA) significantly reduced cell viability compared with the control after 2 hours of exposure in both the transformed and primary corneal epithelial cells, whereas ReNu MultiPlus® (Bausch & Lomb Incorporated, Rochester, NY, USA) and Aquify® (CIBA Vision Incorporated, Duluth, GA, USA) had a minimal effect on cell viability in human corneal epithelial cells compared with Opti-Free Express and Opti-Free RepleniSH after 2 hours of exposure at 100% solution.<sup>8</sup> Somewhat different results were obtained when the cytotoxicity of various MPS/lens combinations was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cellular viability assay.<sup>9</sup> A significant reduction in cell viability was found for all lenses soaked in Opti-Free Express, most significantly for lotrafilcon A lenses soaked in Opti-Free Express compared with balafilcon A, lotrafilcon B, and comfilcon A lenses. Lenses soaked in ReNu and Solo (CIBA Vision Incorporated) also showed reduced cell viability in this study.<sup>9</sup>

The expression of membrane-associated mucins, a measure of surface barrier protection around corneal epithelial cells, has also been used to evaluate the biocompatibility of MPS.<sup>10</sup> Results from testing indicated that MPS containing boric acid downregulated the expression of membrane-associated mucins in cultured human corneal epithelial cells. Conversely, Lehmann et al<sup>11</sup> investigated the effect of treating cells with boric acid using two cytotoxicity assays as well as the impact of boric acid on corneal epithelial barrier function using human corneal epithelial cells *in vitro*. In addition, Biotrue® MPS (Bausch & Lomb Incorporated) was tested for ocular compatibility. Their findings contradicted those of Imayasu et al<sup>10</sup> and showed that boric acid passed both cytotoxicity assays and did not disrupt corneal tight junction integrity. Biotrue MPS also passed two different cytotoxicity tests alone (agar diffusion assay) and in combination with contact lenses (direct contact assay).

For an MPS solution, either ineffective disinfection or low biocompatibility can be associated with the development of corneal infiltrates, making corneal infiltrates a bell-wether clinical performance measure for MPS products.<sup>12,13</sup> Recently, asymptomatic and symptomatic corneal infiltrates have been reported in association with certain MPS systems to a varying degree when used with daily wear silicone hydrogel contact lenses.<sup>14,15</sup>

When new lens care products are introduced for wide clinical use, the biocompatibility of the product contributes directly to the patient's wearing experience; it impacts comfort on insertion, comfort during wear, and their long-term success

with the product in terms of ocular health. Excellent comfort and vision and low rates of ocular complications during contact lens wear are the clinical measures of a positive patient experience with an effective and biocompatible MPS product.

Advances in the formulation of MPS solutions could take many forms. A new solution could offer more robust antimicrobial efficacy, it could be designed to maintain the pre-lens tear film or to keep lenses clean. The approach taken in the development of a new disinfection system by Bausch & Lomb Incorporated has been reported to optimize and balance each of these performance features through a biomimetic design.<sup>16</sup> By incorporating two disinfecting agents, the solution has demonstrated excellent disinfection performance against many clinical isolates for pathogenic species and standard test organisms.<sup>17</sup> The borate-buffering system potentiates the preservative efficacy of the MPS and does not cause *in vivo* or *in vitro* cytotoxicity as measured by the viability and junctional integrity of human corneal epithelial cells.<sup>5,8,11,18</sup> Hyaluronan, a conditioning agent, is recognized as a long-lasting wetting agent that can interact with the surface of contact lenses.<sup>19,20</sup> The formulation's hyaluronan component acts as the lubricating moiety. An *in vitro* investigation has demonstrated that it is adsorbed on the lens material and released slowly over a period of 20 hours.<sup>21</sup> This novel MPS formulation also stabilizes lysozyme in its native state (preventing lysozyme from denaturing) to a significantly greater degree than a number of other MPS.<sup>22</sup> This holistic approach to MPS formulation was achieved by consideration of all the functions of a contact lens disinfection solution at the formulation stage, ie, disinfection, lubrication, maintenance of clean lens surface, and biocompatibility, and should result in an MPS with excellent on-eye performance.

Regardless of the specific formulation features, it is essential for any new product to demonstrate acceptable biocompatibility both *in vitro* and *in vivo*. For this novel MPS solution, excellent results from a single clinical trial have been published.<sup>23</sup> The purpose of this analysis is to report the combined safety results from six consecutive prospective clinical trials as a measure of the clinical biocompatibility of this new multipurpose lens care solution (Biotrue) with daily wear hydrogel and silicone hydrogel soft contact lenses.

## Materials and methods

Biomicroscopy and adverse event results from six consecutive, prospective clinical studies conducted between February 2008 and March 2010 were combined for meta-analysis. Results from all participating subjects at all visits while using the MPS are included. Subjects used the new MPS daily to clean and

disinfect their daily wear hydrogel or silicone hydrogel soft contact lenses. Lens care regimens with and without instructions to rub the lens surface were used. Eighty-one unique clinical investigators participated in these studies. The size, duration, and design of the six studies are shown in Table 1.

Subjects were healthy contact lens wearers who were of legal age and who habitually wore one of the following spherical lens types in both eyes: balafilcon A (PureVision<sup>®</sup>, Bausch & Lomb), galyfilcon A (Acuvue Advance<sup>®</sup>, Johnson & Johnson, Jacksonville, FL, USA), senofilcon A (Acuvue Oasys<sup>®</sup>, Johnson & Johnson) lotrafilcon B (O2 Optix<sup>®</sup>, Alcon) lotrafilcon A (Night and Day<sup>®</sup>, Alcon), or any US Food and Drug Administration group IV hydrogel soft lenses. All subjects were correctable to at least 0.3 logMAR (logarithm of the minimum angle of resolution) acuity in each eye and had clear central corneas with no corneal infiltrates or other biomicroscopy findings greater than grade 2. Subjects who had worn gas permeable contact lenses within the last 30 days or polymethylmethacrylate lenses within the last 3 months were excluded. Enrolled subjects had also habitually used a lens care product for cleaning, disinfecting, and storage of lenses. Subjects were excluded if they were pregnant, breast-feeding, or planning to become pregnant, had recently worn rigid lenses, or had participated in any clinical study within the 2 weeks prior to the study. Patients were also excluded if they had ocular astigmatism >1.00 DC in either eye, anisometropia >1.00 D, aphakia, amblyopia, or a history of corneal surgery.

In each clinical trial, ocular biomicroscopy was performed without soft contact lenses in place at each study visit. After white light observation, sodium fluorescein was instilled for evaluation of corneal staining through a Wratten gel barrier filter (Kodak #12) viewed under the biomicroscope's cobalt illumination. Corneal staining, tarsal conjunctival abnormalities, bulbar and limbal injection, corneal infiltrates, epithelial edema, neovascularization, and microcysts were graded on an ordinal system of 0–4 (annotated as 0, none; 1, trace; 2, mild; 3, moderate; 4, severe) with text descriptors for each variable and grade. Integer grades were assigned for each sign. All notations of signs greater than grade 2 were summarized with regard to clinical management of the signs, including temporary cessation of lens wear, pharmaceutical management, and other methods as applicable. An adverse event was defined as a sight-threatening condition, which may include, but was not limited to, the following: corneal ulcers, anterior uveitis (iritis), other ocular infections or inflammations, incident corneal scarring (central 4 mm), incident corneal neovascularization (central 4 mm), and/or permanent loss of vision. Other standard clinical tests, such as visual acuity

and evaluation of contact lens fit and surfaces, were also performed but are not the subject of this analysis.

All statistical analyses were carried out in SAS version 9.1.3 (SAS Institute Inc, Cary, NC, USA). Data were presented as counts and percentages for categorical variables. A generalized linear regression model was used to account for the correlations among repeated measurements from the same subjects for comparisons of biomicroscopy findings between the hydrogel and silicone hydrogel lenses.<sup>24</sup> In this model, biomicroscopy findings with grades 0, 1, and 2 were classified as minimal, and findings with grade 3 and 4 were classified as clinically relevant because they are of a level typically requiring clinical management in terms of temporary interruption of lens wear or use of topical medications. This binary classification of slit-lamp findings was used as the dependent variable in the model and assumed to have a binomial distribution with a logit link. Lens material type (hydrogel or silicone hydrogel) was treated as the predictor variable, adjusting for study and site. Two-tailed tests were used for all analyses, with *P*-values less than 0.05 deemed to be statistically significant.

## Results

A total of 1,567 subjects participated in the prospective clinical trials described in Table 1. Of the 1,567 subjects who were enrolled, 1,499 completed the study. Data are shown for all visits that occurred after assignment to the test solution. Data from baseline visits were not included in the analysis because they did not reflect exposure to the new product. Details of the number of subjects assigned each test regimen (rub or no rub) and lens material group (hydrogel or silicone hydrogel) are shown in Table 2. A very high proportion of subjects completed the various studies, with an average completion rate of 96.3% across all studies.

There were no adverse events reported during these clinical trials. The biomicroscopy findings observed during the 7,212 ocular examinations are shown in Table 3 regardless of the assigned regimen (with or without rub). There were no instances where grade 3 or 4 epithelial edema, epithelial microcysts, or corneal infiltrates were observed, and only one instance where grade 1 corneal infiltrates were noted.

A generalized mixed-effects model compared differences in signs between wearers of hydrogel and silicone hydrogel lenses and showed no statistically significant difference in frequency of grade 3 or 4 for any signs tested, ie, corneal staining (*P* = 0.22), limbal injection (*P* = 0.59), bulbar injection (*P* = 0.58), and superior tarsal conjunctival signs (*P* = 0.69). Presence of epithelial edema, epithelial microcysts, and corneal infiltrates were not compared by lens

**Table 1** Study design and subject enrollment

Region	Design	Duration	Visits	Sites*	Study dates	Enrolled test subjects n (eyes)	Completed subjects n (eyes) %	Habitual lens material
Asia	Randomized, masked, controlled	2 weeks	Baseline 2 weeks	14	Feb – Mar 2008	181 (362)	172 (344) 95%	Silicone hydrogel: Balafilcon A Senofilcon A
USA	Open-label, single arm	2 weeks	Baseline 2 weeks	15	Jan – Feb 2009	300 (600)	293 (586) 98%	Lotrafilcon A and B Hydrogel and silicone hydrogel
USA	Open-label, single arm	2 weeks	Baseline 2 weeks	20	Feb – Mar 2010	392 (784)	385 (770) 98%	Hydrogel and silicone hydrogel
USA	Randomized, investigator-masked, controlled	1 month	Baseline 2 weeks 1 month	20	Nov 2009 – Jan 2010	156(312)	153 (306) 98%	Silicone hydrogel: Balafilcon A Galyfilcon A
USA	Randomized, controlled, investigator-masked	3 months	Baseline 2 weeks 1 month 2 months 3 months	24	Mar – Aug 2008	358 (716)	321 (642) 90%	Lotrafilcon A Lotrafilcon B Senofilcon A Hydrogel: Group IV Silicone hydrogel: Balafilcon A Galyfilcon A
USA	Open-label, single arm	3 months (Group I) 6 months (Group IV)	Baseline 2 weeks 1 month 2 months 3 months Group IV only: 4 months 5 months 6 months	9	Jul 2008 – Feb 2009	180 (360)	171 (342) 95%	Lotrafilcon A Lotrafilcon B Senofilcon A Hydrogel: Group IV Hydrogel: Group I and IV

**Note:** Only subjects who were in the test group are shown. \*#1 unique sites participated in the studies with some sites participating in more than one study.

**Table 2** Number of subjects per lens care regimen

Lens material group	Test regimen with rub subjects (eyes)	Test regimen with no rub subjects (eyes)
Silicone hydrogel	576 (1,152)	507 (1,014)
Hydrogel groups I and IV	329 (658)	148 (296)
Total	905 (1,810)	655 (1,310)

**Note:** All subjects that are included in slit-lamp finding analyses are included.

material group because they were never observed at levels above grade 2 in any subjects in any of the trials.

Only 18 eyes (0.58%) presented with grade 3 or 4 findings from 13 subjects (0.96%). Of these, five subjects had corneal fluorescein staining, four subjects had tarsal conjunctival findings, one subject had limbal and bulbar redness, one subject had bulbar redness, and one subject had corneal neovascularization. All signs were noted at one visit only.

When the grade 3 or 4 findings were judged by the clinical investigators as to the likelihood that they were related to the lens care solution, six of 19 were considered not related to the product, two of 19 were unlikely related to product use, seven of 19 were likely related, and four of 19 were considered product-related. Three eyes with tarsal conjunctival abnormalities, one eye with neovascularization, and one eye with limbal and bulbar redness were judged as events that were unrelated to lens care product use. One eye with a tarsal conjunctiva abnormality and one eye with corneal staining were unlikely related to the product. These findings judged unrelated or unlikely related to the product were from four subjects and two subjects, respectively.

## Discussion

During the process of developing a novel disinfecting MPS, manufacturers must test these new products in laboratory experiments and clinical settings according to US Food and Drug Administration and other international regulatory

agency guidelines. The six prospective clinical trials reported here go beyond the scope of the clinical requirements outlined in any of the guidance documents in terms of breadth, and provide eye care practitioners with an extensive assessment of the biocompatibility characteristics of the product.

While single-use testing in a clinical research center has been used to assess time-point specific corneal fluorescence after only one exposure,<sup>25</sup> the repeated exposure under normal use conditions (lenses being worn again and again after cleaning, disinfection and storage in a contact lens storage case) relates much more closely to actual use conditions. Clinical observation after repeated use is very likely to be a more reliable predictor of long-term success with the products.<sup>14</sup>

Use of meta-analysis as a statistical tool can help researchers identify trends and significant associations by combining data from similar studies, even if the newly tested hypothesis was not the purpose of the original studies.<sup>26</sup> The meta-analysis presented in this paper included results from 7,212 biomicroscopy examinations. The breadth of these clinical evaluations demonstrates that the solution performed well when used by a wide variety of patients with a large number of hydrogel and silicone hydrogel contact lens materials. The incidence of biomicroscopy findings considered to be clinically relevant was negligible. Clinically relevant findings considered to be related to the product were found in only seven (0.45%) of the 1,560 subjects.

Corneal infiltrates with soft contact lens wear have been the focus of much attention over the past decade because they can be an indication of an immune response to contact lens wear.<sup>27</sup> A contact lens immune challenge can present as diffuse corneal infiltration of inflammatory cells and can be triggered by dead bacteria on the contact lens surface, by the solution components themselves or by deposits left on the lens surface as a result of poor cleaning efficacy or technique.

**Table 3** Graded slit-lamp findings.

	Corneal infiltrates n (%)	Corneal staining n (%)	Limbal injection n (%)	Bulbar injection n (%)	Tarsal abnormality n (%)	Neovascularization n (%)
Grade 0	7211 (99.99%)	5136 (71.21%)	6585 (91.31%)	6408 (88.85%)	6078 (84.28%)	7027 (97.43%)
Grade 1	1 (0.01%)	1894 (26.26%)	577 (8.00%)	740 (10.26%)	1059 (14.68%)	179 (2.48%)
Grade 2	0	176 (2.44%)	47 (0.65%)	61 (0.85%)	69 (0.96%)	5 (0.07%)
Grade 3	0	5 (0.07%)	3 (0.04%)	2 (0.03%)	4 (0.06%)	1 (0.01%)
Grade 4	0	1 (0.01%)	0	1 (0.01%)	2 (0.03%)	0

**Note:** Test regimen n=7,212 eye visits.

In the trials analyzed here, there were no clinically relevant corneal infiltrates in any study participants, indicating a robust disinfection capacity, good cleaning performance, and low irritation from the new disinfection MPS.

## Conclusion

With over 72,000 exposures to the dual disinfectant system and 7,212 eye examinations, this meta-analysis demonstrates that the novel MPS had excellent biocompatibility with eyes wearing either hydrogel or silicone hydrogel lenses on a daily basis.

## Disclosure

This study was presented as a poster at the annual meeting of the American Academy of Optometry, November 19, 2010, San Francisco, CA, USA. The authors are employees of Bausch & Lomb Incorporated.

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