Author's response to reviews

Title: Effectiveness of ophthalmic solution preservatives: a comparison of latanoprost with 0.02% benzalkonium chloride and travoprost with the sofZia preservative system

Authors:

Gerard Ryan Jr (jerry.ryan@pfizer.com)
Joel M Fain (joel.m.fain@pfizer.com)
Cherie Lovelace (cherie.lovelace@pfizer.com)
Karl M Gelotte (karl.m.gelotte@pfizer.com)

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Author's response to reviews: see over
Rachel Neilan, MSc
Executive Editor
BMC-series Journals
BioMed Central Floor 6
236 Gray's Inn Road
London, WC1X 8HL

Re: MS: 3212216384477830. Effectiveness of ophthalmic solution preservatives: a comparison of latanoprost with 0.02% benzalkonium chloride and travoprost with the sofZia preservative system Gerard Ryan Jr, Joel M Fain, Cherie Lovelace and Karl M Gelotte

Dear Ms. Neilan:

Thank you for your communication of February 14, 2011 regarding the above manuscript. We welcome the opportunity to revise our manuscript based on the reviewers’ comments and have provided a point by point response for each in italics below. Please contact us if further changes are required.

Sincerely yours,

Gerard Ryan, Jr.
Senior Scientist/Microbiologist
Parenteral Center of Emphasis
Pfizer Inc
Eastern Point Road
Groton, Connecticut 06340
Phone: (860) 441-1259
Fax: (860) 715-7738
E-mail: jerry.ryan@pfizer.com
Reviewer: Alan Robin

Page 2, line 1: I would add the word “laboratory” before the word “studies”.

We agree with the reviewer’s suggestion and have modified the sentence accordingly.

Page 2, line 4: I would just say: BAK is the most commonly…

This change has been made.

Page 2, line 7: I would substitute the word “employ” for “use”.

This change has been made.

Page 4, paragraph 1: Might I suggest that the authors expand both here and in the discussion about the probably and potential problems associated with eye drop tip-eye and adenexa touch as demonstrated with { Stone JL, Robin AL, Novack GD, Covert DW, Cagle GD. An Objective Evaluation of Eye-Drop Instillation in Glaucoma Patients. Archives of Ophthalmology, 2009;127:732-736.} and with { Hennessy AL, Katz J, Covert D, Protzko C, Robin AL. Videotaped Evaluation of Eyedrop Instillation in Glaucoma Patients with Visual Impairment or Moderate to Severe Visual Field Loss. Ophthalmology. 2010 June 24 epub ahead of print}. These work clearly find that eye drop bottle contamination is a likely problem and that this could possibly be a much more important issue than previously believed.

These studies are now mentioned in the introduction section (page 4, end of paragraph 1) and details have been provided in the discussion section per the below:

Added to the introduction:

“In more recent studies using video recordings to evaluate the performance of patients with ocular hypertension or glaucoma, only a third of patients were actually successful at instilling a single drop of medication without touching the eye or ocular adnexae [3,4].”

Added to the discussion:

“Recent studies in which patients were videotaped to assess their success at instillation of topical ocular hypotensive medications highlight the concerns about bottle contamination [3,4]. In the first of these studies, 92.8% of patients with a diagnosis of glaucoma or ocular hypertension who used 1 or more glaucoma medications for at least 6 months reported no problems administering their eye medications; yet less than a third of patients were successful at instilling a single drop with touching the bottle to the eye [3]. In a subsequent study in patients with visual impairment or moderate to severe visual field loss, only 39% were able to instill a single drop without touching the eye; age (<70 vs ≥70 years) was found to be a significant predictor for less successful instillation [4]. These studies demonstrate that bottle contamination is a more important issue than previously believed.”

Page 4, second paragraph: 5th line: The authors do NOT know why the sofZia system was developed. Might I suggest that the first part of the sentence be
deleted. Instead, perhaps the authors might say: An alternative preservative system has been developed...."

*We agree with Dr. Robin’s suggestion and have deleted the first part of the sentence.*

**ALSO.** Om the second to last line of this paragraph, Travatan Z has been developed by Alcon, not Allergan!!!

*We thank Dr. Robin for noting this oversight and have made the correction.*

Page 5, line 4: both products are approved in both the US and Japan.

*Japan has been added as suggested.*

Page 6, lines 1-3: Why were these and not other fungi and bacteria included? The authors should clearly give an explanation within the text of the manuscript.

*An explanation is provided as follows (with added text in bold):*

*Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 9027), Escherichia coli (ATCC 8739), Candida albicans (ATCC 10231) and Aspergillus brasiliensis (a subspecies of Aspergillus niger; ATCC 16404). These organisms were selected based on EP [11] and USP [12] test protocols.*

Page 7, lines 15-16: How did travoprost do against the other tested microorganisms?

*Results are now detailed as follows (page 7, line 19; revised text in bold):*

*When evaluated against EP-B criteria (table 2), travoprost still did not satisfy EP requirements due to its limited effectiveness against Staphylococcus aureus at 24 hours (table 3). There was the required 1 and 3 log reductions for Pseudomonas aeruginosa and Escherichia coli at 24 hours and 7 days, respectively. However, while travoprost marginally satisfied EP-B criteria for fungi at 14 days (1.0 and 1.9 log reductions for Candida albicans and Aspergillus brasiliensis, respectively), reductions were well below those achieved at 6 hours by latanoprost with 0.02% BAK.*

Also, in the discussion the authors should look at the relative frequency of these microorganisms causing trabeculectomy related blebitis and endophthalmitis to add a clinical perspective to this manuscript.

*In a PubMed search, we identified several references to bacterial causes and have added the following text to the first paragraph of the discussion section (page 8, paragraph 2). Unfortunately, we were unable to locate publications about fungal cases (blebitis or endophthalmitis) because they occur relatively infrequently:*

*“Staphylococcus infections are frequently associated with both primary and recurrent bleb infections following trabeculectomy [15] and endophthalmitis subsequent to postoperative*
procedures such as lens replacement [16]. Pseudomonas aeruginosa is also a common cause of endophthalmitis, occurring postoperatively or subsequent to corneal ulcers, and is often associated with poor visual outcomes [17].”

In the discussion, it might be worthwhile to state which pharmaceutical company sponsored which study?

*Reviewer applicable, we have included information on the sponsorship of the studies.*

**Reviewer: Masahiko Ayaki**

Abstract and text; I found sentences expressing the comparison between “latanoprost with BAK and travoprost with SofZia”. However, this study is a comparison between eyedrop product preserved with 0.02%BAK and product preserved with SofZia. BAK of lower concentration may be similar bactericidal effect to SofZia. The authors are encouraged to express “0.02%” everywhere to avoid misunderstanding.

*We agree with Dr. Ayaki’s comment to include the concentration of BAK and have done so whenever appropriate. However, since a lower concentration of BAK was not evaluated in this study, we cannot conclude that a lower concentration would be similar to that of SofZia.*

Page 8-11; The description of OSD may be too much. The presence of OSD in glaucoma patients is very important discussion but this paper does not examine OSD.

*We believe that the information on OSD will be relevant to the clinician reader and prefer for this content to remain in the paper.*

Tables 1 and 2 may be unnecessary since they are not their works and confusing for the readers.

*Since ophthalmologists will generally not be familiar with the microbial tests used in the study, we believe that these tables should remain in the paper.*