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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Desai et al.

Serial No. 08/340,763

10/Declaration

Filed: November 16, 1994

Group Art Unit: 1502

Examiner: S. Howard

For: PRESERVED OPHTHALMIC DRUG COMPOSITIONS CONTAINING POLYMERIC QUATERNARY AMMONIUM COMPOUNDS

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Suketu D. Desai, Ph.D., hereby say and declare as follows:

1. I received my B.S. in Pharmacy from the University of Bombay in Bombay, India in 1984, my M.S. in Pharmacology from the University of Bombay in 1986, and my Ph.D. in Pharmaceutical Sciences from the University of Arizona, Tucson, Arizona, in 1992. Since 1992, I have worked in the field of ophthalmic product research and development.

2. I have been employed by Alcon Laboratories, Inc. since 1992. My current position at Alcon is Sr. Scientist II in the Drug Delivery Group. I am responsible for designing, synthesizing, and characterizing ophthalmic formulations, including formulations that are required to pass compendia preservative efficacy standards.

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3. As a result of my educational and work-related experiences, I am generally knowledgeable in the field of pharmaceutical formulation science, particularly as related to ophthalmic formulations.

4. I am one of the inventors of the subject matter claimed in U.S. Patent Application Serial No. 08/340,763 filed on November 16, 1994, and understand that this Application sets forth claims to ophthalmic compositions comprising a therapeutically effective amount of one or more acidic ophthalmic agents, a preservative-effective amount of a combination of an antimicrobial polymeric quaternary ammonium compound and boric acid, and an ophthalmically acceptable vehicle.

5. I am familiar with the Office Action dated September 26, 1995, in which claims 1-19 and 25 of the pending application were rejected under 35 USC §103 as unpatentable over Chandrasekaran (WO 89/06964) in combination with Chowhan (U.S. Patent No. 5,342,620). I believe that this rejection is based in part on a misunderstanding concerning the nature of the invention and the cited art.

6. As part of my responsibilities at Alcon, I have designed, conducted and reviewed studies to compare the preservative efficacy of Polyquad® (a polymeric quaternary ammonium preservative, also known as "polyquaternium 1") to that of the following conventional ophthalmic preservatives: benzalkonium chloride (a quaternary ammonium compound, but not a polymeric quaternary ammonium compound), benzyldimethyldodecylammonium bromide (a quaternary ammonium compound, but not a polymeric quaternary ammonium compound), sorbic acid, and thimerosal. These studies evaluated the preservative efficacy of combinations of boric acid and the identified preservatives in acidic ophthalmic drug formulations. I am familiar with the results of these studies.

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7. Briefly, the formulations identified in Table 1 below were subjected to a preservative efficacy screen based on the United States Pharmacopeia and European Pharmacopeia (Ph.Eur.) preservative efficacy standards for ophthalmic products. These standards are given in the specification at page 8, lines 5-21. The preservative efficacy screen involved inoculating the formulations identified in Table 1 to known levels of the gram-positive bacteria, Staphylococcus aureus (S. aureus); the gram-negative bacteria, Pseudomonas aeruginosa (P. aeruginosa); and the mold, Aspergillus niger, (A. niger). These inoculated formulations were then sampled at specified intervals of 6 hr, 24 hr, and 7 days to determine whether the antimicrobial preservative system present in the formulation was capable of killing or inhibiting the growth of organisms purposely introduced into the formulation. The magnitude of antimicrobial activity of the formulation determined compliance with the USP and Ph.Eur. preservative efficacy standards for ophthalmic products. The results of these screening tests are presented in Table 2 below.

Table 1: Formulation Ingredients

Formulation Preservative	A Benzalkonium Chloride	B Benzyldimethyl-dodecylammonium bromide	C Polyquaternium 1	D Sorbic Acid	E Thimerosal
	Composition (% w/w)				
Sodium Diclofenac	0.1	0.1	0.1	0.1	0.1
Vitamin E TPGS	3	3	4	3	3
Preservative	0.01	0.0125	0.001	0.2	0.005
Boric Acid	1.2	1.2	1.2	1.2	1.2
HPMC	0.1	0.1	---	---	---
EDTA	0.1	---	---	---	0.1
Mannitol	4	1	3.5	1.2	3.5
HCl/NaOH	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4	q.s. to pH 7.4
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%

Vitamin E TPGS: Vitamin E Tocopheryl Polyethylene Glycol 1000 Succinate
HPMC: Hydroxypropyl methyl cellulose
EDTA: edetic acid or its disodium salt

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Table 2: Preservative Efficacy Results For Formulations of Table 1

	Preservative Efficacy Screen Results		
FORMULATION of Example 1	**USP**	**Ph. Eur. A**	**Ph. Eur. B**
A (Benzalkonium chloride)	Fail	Fail	Fail
B (Benzyldimethyldodecyl-ammonium bromide)	Fail	Fail	Fail
C (Polyquaternium 1)	Pass	Pass	Pass
D (Sorbic Acid)	Fail	Fail	Fail
E (Thimerosal)	Pass	Fail	Fail

8. The results shown in Table 2 above demonstrate the disparity between the preservative efficacy of polquaternium 1, a polymeric quaternary ammonium antimicrobial compound, and other, conventional, preservatives of the type disclosed or suggested by the WO 89/06964 and the Chowhan references. In fact, the results show that, among the combinations tested, only the combination of polyquaternium 1 and boric acid was able to effectively preserve the indicated formulation of an acidic ophthalmic drug such that the preservative efficacy standards of the U.S. and Ph.Eur. were met. (These preservative efficacy standards are listed in the Specification at p. 8, lines 5 - 21.) Moreover, only one of the formulations containing conventional ophthalmic preservatives was able to pass even the U.S. preservative efficacy standards (the formulation containing thimerosal). This disparity in results is not suggested by either the WO 89/06964 or the Chowhan references, alone or in combination.

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9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine, imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Suketu D. Desai, Ph.D. Date: 2/26/96

Attorney Docket No. 1436

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