IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC., ALLERGAN SALES, LLC, Plaintiffs, v. ALCON, INC., ALCON LABORATORIES, INC., and ALCON RESEARCH, LTD., Defendants.	Civil Action No. 04-968-GMS **REDACTED VERSION**

DECLARATION OF VALENTINO STELLA, PhD

I, Valentino Stella, declare as follows:

1. I am currently a University Distinguished Professor of Pharmaceutical Chemistry at the University of Kansas where I teach courses in pharmacokinetics and drug stability. I have an undergraduate degree in pharmacy from the Victorian College of Pharmacy in Melbourne, Australia and practiced as a pharmacist for one year prior to entering graduate school in 1968. I have a doctorate in Analytical Pharmaceutical Chemistry and Pharmaceutics from the University of Kansas that I received in 1971. I then was an Assistant Professor at the University of Illinois Medical Center in Chicago before returning to the University of Kansas. During my time at the University of Kansas, I was the Director for the Center of Drug Delivery Research from 1989 to 1999. I have also been a consultant to the pharmaceutical industry, both to innovator and to generic companies, since 1972. For a detailed list of my experience and publications, see my CV attached hereto as Ex. 1.

2. I have been retained by plaintiffs in this litigation as a consultant. My consulting rate for this litigation is $375 an hour.

3. I am submitting this declaration on behalf of plaintiffs in opposition to Alcon's motion for summary judgment of invalidity of United States Patent No. 6,641,834 (the "'834 patent"). I have been asked to render my opinion as to whether the specification and originally-filed claims of the parent application to that patent disclose to one of ordinary skill in the art that the inventors were in possession of the claims of the '834 patent as issued. I have also been asked to give my opinion on the meaning of the term "about" in that patent to one of ordinary skill.

4. In forming my opinions, I reviewed Alcon's brief in support of its summary judgment motion along with the attached exhibits, the file history of the '834 patent, and the prior art cited and listed in that file history. I present my opinions below.

BACKGROUND

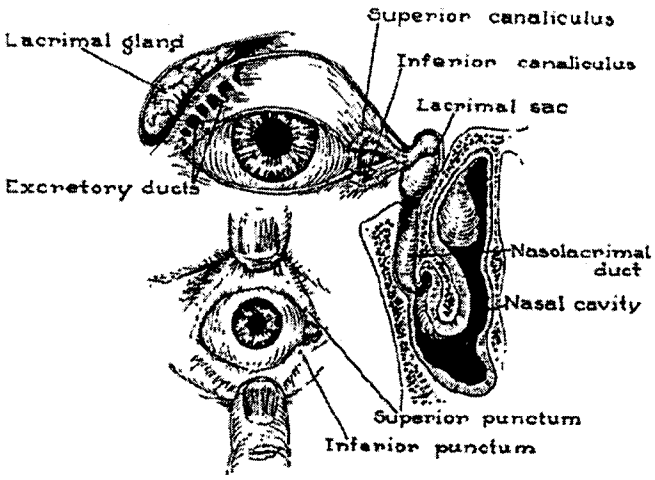
5. To appropriately understand the inventions of the patents in suit, it is necessary to understand some background information.

6. The goal of any formulator when creating a pharmaceutical product is to maximize efficacy while minimizing toxicity. However, this presents several challenges because efficacy is affected by many factors, such as the unique biological characteristics of the application site, in this case, the eye, the form of the drug[1](e.g., ionized or un-ionized), and the solubility of the drug, amongst many other things.

7. The patent at issue states that it is directed, in particular, to therapeutic formulations useful in ophthalmic preparations. '834 Patent, Col. 1, ll. 15-19. The human eye presents unique problems for the formulation of any ophthalmic pharmaceutical product. The most convenient and patient accepted method of delivery is simple eye drops. But

[1] In the formulation context, the word "drug" actually refers to the active ingredient in the pharmaceutical product rather than the entire formulation. Formulation means all of the ingredients that are in the pharmaceutical product.

because the human eye maintains a small volume of liquid on its outer surface, about 10 microliters, eye-drops (about 25 microliters) drain off rather quickly through the eye's drainage ducts. (See figure below.)



General Ophthalmology by Vaughan, Cook, and Asbury-Lange Medical Publications, Los Altos, Calif

Fig 24-2—Lacrimal drainage system of the eye, showing the lacrimal glands and the drainage system into the nasal cavity.

Fig. 24-2 is from Eric W. Martin, Dispensing of Medication, Mack Publishing Co. (1971), page 881.

8. Therefore, to maximize efficacy, it is desirable to design a formulation whereby the most amount of drug can be absorbed in the least amount of time possible. Conventional wisdom is that at most 5% of the drug that is placed on the eye in the form of eye-drops is actually absorbed. The remainder, which can be 95% or greater, drains through the nasal lacrimal duct into the nasal cavity. Because the nasal cavity contains a large number of blood vessels, the drug not absorbed by the eye and draining into the nasal cavity is usually rapidly and well absorbed into the blood stream. This absorbed drug has no ophthalmic benefit efficacy and can only lead to systemic toxicity (possible adverse side

effects). Thus, the solution to maximizing the efficacy cannot be to simply increase the dosage because that will most certainly increase the toxicity.

9. In the present case, brimonidine tartrate, the drug in Alphagan®, Alphagan® P and Alcon's proposed product, can lead to adverse side effects as indicated on the FDA approved labeling. Therefore, the goal is to use as little of the drug as possible while maintaining efficacy.

Form of the Drug – Ionized vs. Unionized

10. Weakly basic drugs containing only one ionizeable group, like brimonidine tartrate, can exist in two states: (1) the protonated or charged form that has an overall net positive charge; and (2) the neutral or unionized form. In solution, there is usually a mix of the two states. Of these two states, the neutral or un-ionized form passes most readily across membrane lipid bilayers of the cornea of the eye, as is disclosed in the '834 patent. '834 Patent Col. 6, ll. 8-17.

11. The cornea is made up of layers, the outmost layer being the epithelium. To pass through the epithelium, the drug must pass through the lipid membranes of the epithelial cells that separate the outermost area of the eye where the tears are. There are other layers of the cornea which are water-like. Drugs in the ionized state cannot readily pass through lipid membranes; however, un-ionized drugs can. In solution, neither the ionized or un-ionized form exist exclusively, rather there is an equilibrium between the two with the un-ionized form acting as a source for the ionized form.

12. The ratio of the ionized to un-ionized form of a weakly basic drug will be determined by its dissociation constant, Ka, which is usually characterized as pKa, the negative logarithm of Ka, and the concentration of hydrogen ion [H^+] in solution which is

usually characterized as pH, the negative logarithm of $[H^+]$. As you approach the point at which the pH is equal to the pKa for a weakly basic drug, the concentration of the un-ionized form becomes close to the concentration of the ionized form. For example, when the pH of the solution is equal to the pKa the ratio of un-ionized to ionized drug is 1:1. That is, 50% of the drug is in the ionized form and 50% of the drug is in the un-ionized form..

13. At pH values well below the pKa, the drug is present largely in the ionized form while at pH values well above the pKa, the drug is present largely in the un-ionized form. Therefore, at pH values lower than the pKa where the ionized form dominates, the concentration of the un-ionized form will increase as the pH increases and approaches the pKa of the drug. Because the un-ionized form is absorbed more quickly by the tissues described above and the concentration of un-ionized drug is dependent on the pH, increasing the pH can effect how much drug is readily absorbable by the cornea.

14. However, as you approach the pKa of a weakly basic drug like brimonidine tartrate, the solubility of the drug decreases dramatically. (The solubility of a drug is simply the ability of that drug to dissolve in solution.) This is the case because the least soluble form of the drug in aqueous vehicles is the un-ionized form. This means that as one approaches the pKa of the drug, the possibility that brimonidine tartrate will precipitate out of solution increases.

15. With this background, I offer my opinions below:

A. United States Patent 6,641,834 Discloses to One of Ordinary Skill in the Art That the Inventors Were in Possession of the Claimed Invention

16. It is my understanding that Alcon claims that the '834 patent does not disclose to one of ordinary skill in the art the "therapeutically effective" concentration limitations of "up to about 0.15%" "about 0.15%" or "0.15%" brimonidine. I have read the patent and its originally filed claims and I disagree completely. It is my opinion that one of skill in the art would immediately recognize that the inventors of the '834 patent had possession of the claimed inventions because the issued claims are supported by the specification and the originally filed claims.

17. In my opinion, the person of ordinary skill of art would be someone with a Bachelor's or PharmD Degree in Pharmacy, Pharmaceutical Sciences or related science disciplines, three to five years of formulation experience, who is supervised by a PhD or someone with substantially longer formulation experience. The person would likely be a member of a formulation development team that may include analytical chemists and related development scientists.

18. The specification of the '834 patent repeatedly states that the invention of the patent is directed to "therapeutically effective concentrations." See, e.g., '834 Patent, Col 1, ll. 1-6, l. 19; and Col. 3, ll. 11-14, and teaches that "[f]urthermore, solubilized alpha-2-adrenergic agonist compounds provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-andrenergic agonists." '834 Patent, Col. 1, ll. 48-52. From these repeated disclosures, a person of ordinary skill would understand that the formulations disclosed in the patent were understood by the inventors to be therapeutically effective formulations.

19. In addition, the originally filed claims also show that the inventors were in possession of "therapeutically effective" formulations. The original provisional application filed on July 14, 2000, that ultimately resulted in the issuance of the '834 patent included four independent claims (1, 24, 28, and 40). Each independent claim referred to an amount of drug effective to provide a therapeutic benefit to a patient. For example, claims 1, 24 and 40 include the following limitation:

> An alpha-2-adrengergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

From this disclosure, a person of ordinary skill would understand that the formulations disclosed in the patent were understood by the inventors to be therapeutically effective formulations.

20. The specification sets forth that a manner in which to achieve these goals is to increase the concentration of the un-ionized form of the drug. At column 2 of the patent, the inventors state:

> In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

'834 Patent, Col. 2, ll. 48-52.

21. That the inventors possessed the idea of increasing the un-ionized form of the drug is also clear from the originally filed claims which were directed to substantially un-ionized drug as follows:

WHAT IS CLAIMED IS:

1. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component; and

a liquid carrier component.

7. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized.

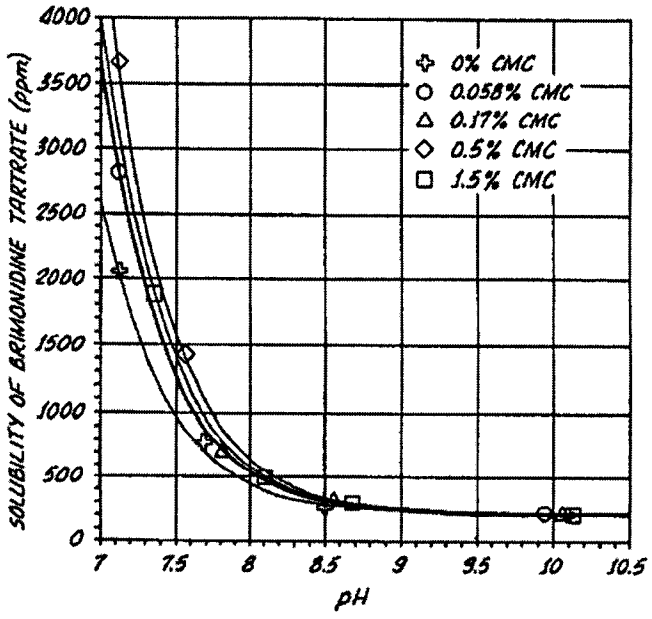
8. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized in a biological environment to which the composition is administered.

22. As can be seen, the original claim 1 was directed to "therapeutic[ally] benefi[cial]," solubilized alpha-2-adregeneric agonists, of which brimonidine tartrate is one. Dependent claims 7 and 8 required that the alpha-2-adregeneric agonist be "substantially un-ionized." As discussed above, the concentration of the un-ionized form increases as the pH of the solution approaches the pKa of the drug. The pKa of brimonidine tartrate is 7.78. '834 Patent, Col. 13, l.16. One of skill in the art reading these originally filed claims would understand that the inventors recognized that as the pH increases and approaches a point that is near the pKa of brimonidine tartrate, the concentration of the un-ionized form of brimonidine tartrate increase. Therefore, one of skill in the art would also immediately recognize and understand that the inventors were claiming compositions where a substantial

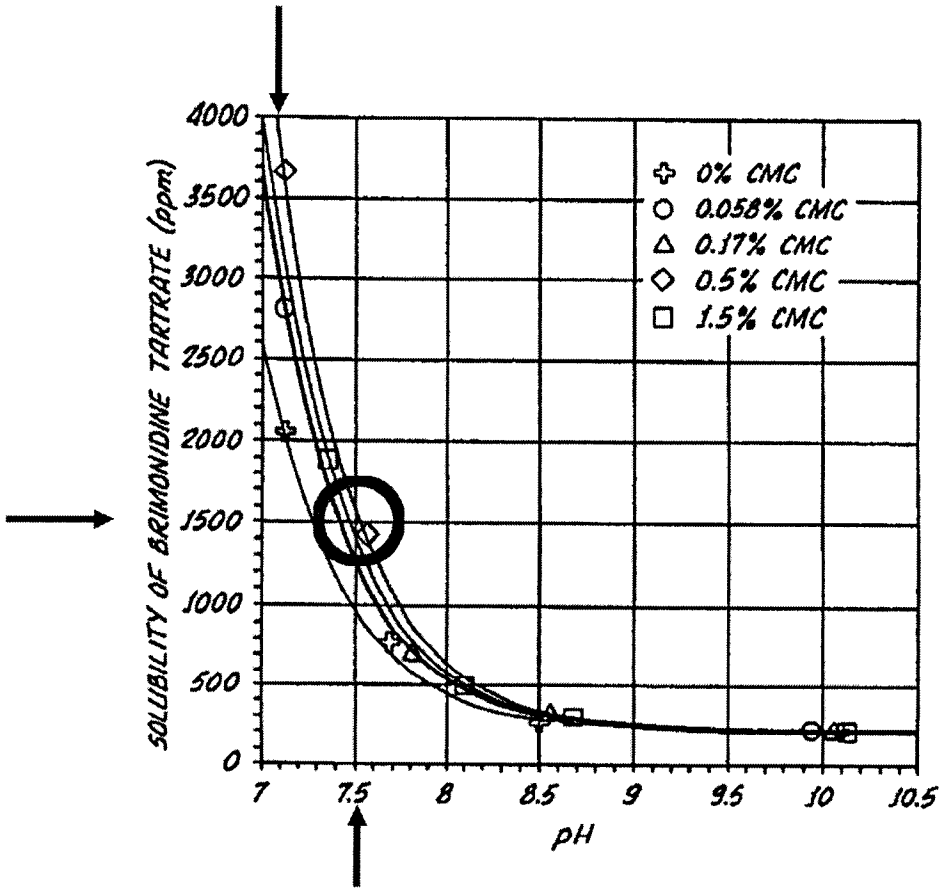
portion of the brimonidine tartrate would be un-ionized, i.e., near the pKa of brimonidine tartrate.

23. The patent then clearly discloses that the preferred concentration in the formulation that will achieve this goal of increasing the un-ionized form of the drug is about 0.15 (w/v) %. Column 11 of the patent specifies pH of 7.5 as the most preferred pH for the carrier as follows: "The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5." '834 patent, Col. 11, ll. 3-6. (A "carrier" is the pH-controlled aqueous solution isotonic with tear fluids into which the brimonidine is dissolved.) Formulating a brimonidine tartrate solution at a pH of 7.5 will result in a substantial amount of un-ionized drug and much more un-ionized drug as compared to a formulation with a pH of around 6.5.

24. Figure 1 of the '834 patent is a solubility vs. pH plot.



25. As can readily be seen, at the patent's most preferred pH, 7.5, the concentration limit of brimonidine formulations represented by the graph is about 1500 ppm, or 0.15% (w/v). I have demonstrated this below.



26. The 0.15 % amount is also clearly expressed in Table IV of the '834 patent. Table IV of the '834 patent contains the data that was used to generate the curves in Figure 1.

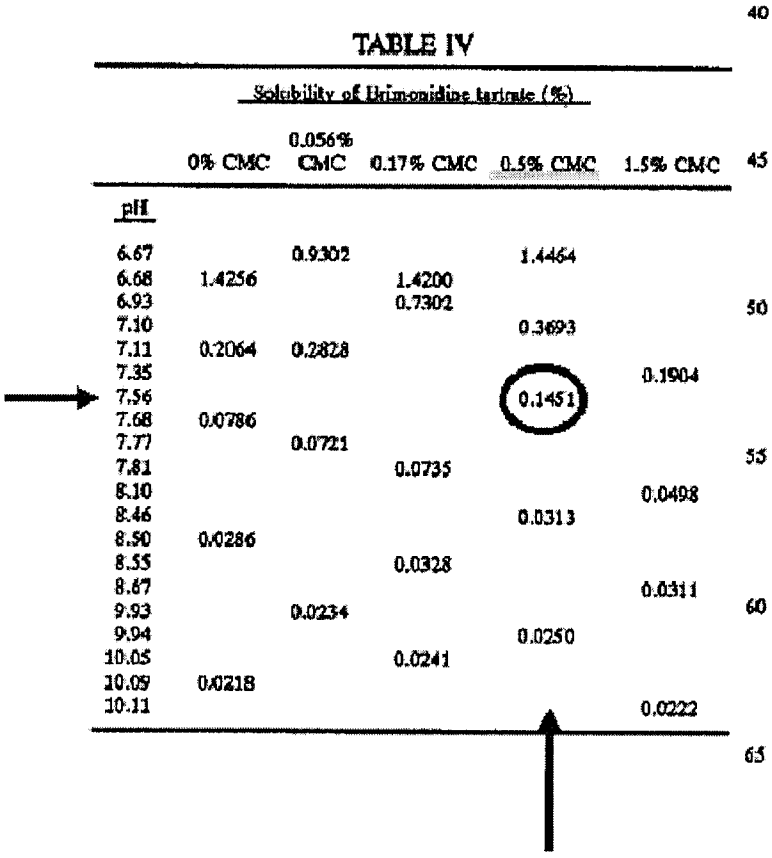


TABLE IV

Solubility of Brimonidine tartrate (%)

pH	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

27. The line in Figure 1 that showed the best solubility profile was a formulation containing 0.5% CMC (underlined in the figure above in yellow). For an eye drop dosage, the greater the solubility the less likely the drug is to precipitate out of solution. Therefore, greater solubility is preferred. One of skill in the art, knowing that the most soluble drug would be the preferred drug would be instantly drawn to the 0.5% CMC column. As mentioned above, the most desirable pH as stated in the patent is 7.5, therefore, tracking down the 0.5 % CMC column, the data point in the area of pH 7.5 is 0.1451 % brimonidine

tartrate – 0.1451% is about 0.15%. Therefore, one of skill in the art would again be directed to the "about 0.15 %" limitation by Table IV.

28. I also note that at the end of example 2, the only pH selected for discussion by the inventors was pH 7.5. '834 patent at col. 16, ll. 1 – 3. This discussion, which is based on Figure I, also demonstrates that the inventors believed that no more than about 1600 ppm brimonidine could be dissolved in solution at their preferred pH value, no matter how much solubility enhancing agent they used. In my opinion, 1600 ppm brimonidine is "about 0.15%".

29. Based on the above, it is my opinion that one of skill in the art would immediately recognize that the inventors of the '834 patent had possession of a therapeutically effective composition containing up to about 0.15% brimonidine tartrate as that claim limitation is clearly supported by the patent specification and the originally filed claims.

B. "About" Means "Approximately," But, if a Numerical Component of the Word is to be Given, it should be Construed to Mean Plus or Minus 10%

30. It has been explained to me that the "ordinary meaning" of the word "about" has been found by the Court handling patent appeals to mean "approximately," and this is consistent with how one of skill in the art would interpret the term. I see nothing in the patent specification that suggests to me that the meaning should be different than that. I have reviewed Alcon's arguments on the numerical limitations that should be read into this term, and I disagree.

31. One of ordinary skill in the art would never read Table IV as limiting the meaning of the word "about" in the fashion proposed by Alcon. To the extent a numerical limitation might be read into the claim, the numerical limitation that one of skill would use

would be those margins of error most commonly associated with formulations of drugs. It has been my experience that this margin of error is plus or minus 10%, based on the fact that specifications on most pharmaceutical products encompasses this range. *The United States Pharmacopeia*, 28th Rev., 2005. Thus, a 50mg tablet of a drug is typically required to contain between 45 and 55 mg to be within relevant legal limits.

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33. Nonetheless, I do not see anything in the patent making Alcon's "rounding" construction appropriate. Nor do I see anything in the patent necessarily requiring the 10% margin of error, though it would be the one most commonly employed by the person of ordinary skill if such a person were asked to put a number on it. And, in my experience, the word "about" is commonly used by those of skill in this art to mean "approximately."

I declare the above to be true and correct pursuant to the laws of the United States of America.

V Stella 5/16/05

Valentino Stella, PhD