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TAB 13

DEFENDANTS' [PROPOSED] FINDINGS OF FACT AND CONCLUSIONS OF LAW

CONFIDENTIAL -FILED UNDER SEAL

FINDINGS OF FACT

A. Parties

1. Plaintiff Allergan, Inc. is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 2525 Dupont Drive, Irvine, California 92612. Plaintiff Allergan Sales, LLC is a limited liability company organized and existing under the laws of the State of Delaware and is a wholly-owned subsidiary of Allergan, Inc. Its principal place of business is at 2525 Dupont Drive, Irvine, California 92612. Plaintiffs collectively hereinafter will be referred to as "Allergan."

2. Defendant Alcon Laboratories, Inc. is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at 6201 South Freeway, Forth Worth, Texas. Defendant Alcon Research, Ltd. is a limited partnership organized and existing under the laws of the State of Texas and has its principal place of business at 6201 South Freeway, Fort Worth, Texas. Defendant Alcon, Inc. is a corporation organized and existing under the laws of Switzerland and has a principal place of business in Hunenberg, Switzerland, and is related to Alcon

Laboratories, Inc. and Alcon Research, Inc. Defendants collectively hereinafter will be referred to as "Alcon."

B. Background: The Litigation

3. This is a patent infringement action brought by Allergan under the Hatch-Waxman Act, codified at 35 U.S.C. §271(e)(2), with respect to Alcon's proposed 0.15% brimonidine tartrate composition for the treatment of glaucoma and elevated intraocular pressure.

4. The patents-in-suit are U.S. Patents Nos. 6,641,834 (issued November 4, 2003, the "'834 patent") and 6,673,337 (issued January 6, 2004, the "'337 patent"). Allergan is the record owner of both patents-in-suit. The '834 and '337 patents are directed to "Compositions containing alpha-2-adrenergic agonist components."

C. The Technology At Issue: Glaucoma

5. The glaucomas are a family of diseases that involve damage to the optic nerve, which transmits signals to the brain from the retina of the eye, where the visual image is formed. If left untreated, glaucoma can result in a loss of visual field (side vision), and may lead to visual disability and ultimately blindness in the affected eye. The main goal of glaucoma treatments is to prevent and/or minimize the rate of progression of nerve damage. Once glaucomatous damage occurs to the optic nerve, it cannot be reversed.

6. In the United States, the most common types of primary glaucoma are primary open-angle glaucoma and normal tension glaucoma. There is no "cure" for open-angle glaucoma. One risk factor associated with glaucoma is elevated pressure in

the eye, or elevated "intraocular pressure" or "IOP." Medical management of glaucoma is typically and primarily focused on the reduction of the elevated IOP, ideally to a target pressure that depends on the patient's age, baseline pressure, and degree of damage. Treatment of glaucoma, in this way, is similar to the treatment of systemic hypertension ("high blood pressure") or hypercholesterolemia ("high cholesterol") in which no specific benefits may be perceived by a patient and chronic, life-long therapy and observation is needed. IOP reduction is the primary and only proven treatment for all glaucomas.

D. The Technology at Issue: Alpha-2 Adrenergic Agonists; Brimonidine

7. The patents at issue in this case are concerned with the use of substances known as "alpha-2 adrenergic agonists." These chemical substances are defined by a property that they possess – namely, they trigger a response by a particular group of chemical receptors that are found in a wide variety of cells.

8. "Receptors" are proteins that may be found in the membrane of a cell. They are bound by specific signaling molecules that are on the outside of the cell, and that binding process triggers the receptor to initiate some biochemical response inside the cell.

9. The "adrenergic receptors" (or adrenoceptors) are one specific type of receptor. Once activated, these receptors set into motion a cascade of biological reactions that, among other things, may lead to the heart beating more rapidly and the pupils dilating. There are different classes of "adrenergic" receptors. The class of adrenergic receptors of interest here – alpha-2 adrenergic receptors – is typically found in pre-synaptic nerve terminals and, when they are activated, trigger a response by the cell.

10. An agonist often mimics the action of the naturally occurring substance that binds to that receptor. Thus, an "alpha-2 adrenergic agonist," or "alpha agonist" for short, is a substance that binds to the alpha-2 adrenergic receptor triggering the receptor to respond by inactivating adenylate cyclase inside the cell. The specification of the '337 patent describes alpha-2-adrenergic agonists as components that "are effective to act or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect." (col. 1, ll. 22-24)

11. The patents-in-suit concern solutions that may contain brimonidine. Brimonidine belongs to a chemical class of compounds known as the quinoxalines. Brimonidine, or 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxaline, has been known to function as an alpha-2-adrenergic agonist for decades. It was originally developed by Pfizer and patented by Pfizer in 1976.

12. Brimonidine is capable of reducing intraocular pressure in individuals suffering from glaucoma or elevated intraocular pressure, a fact that has long been known in the relevant scientific and medical communities.

13. Brimonidine tartrate is a salt that is frequently used to prepare solutions that contain brimonidine.

E. The Technology at Issue: Ophthalmic Formulations

14. An aqueous solution is a uniform mixture of substances in which one or more substances are dissolved in water. Such solutions are very common in biology and pharmacology.

15. The amount of a substance that is dissolved in a particular solution is known as its "concentration." Concentration is measured in a variety of ways, such as "milligrams per milliliter" (mg/mL), "parts per million" (ppm), and "percent weight/volume," (% w/v). For a solution with density about the same as water (most aqueous solutions have a density close to that of water, i.e., 1), the following is an example of the different concentration measures that apply when 12 mg of substance are dissolved in a 1-mL solution:

12 mg/mL = 12,000 ppm = 1.2%w/v

16. A given amount of a solid substance is said to be "soluble" in a given volume of solvent if all of that substance dissolves in the solvent, without any of it remaining undissolved, or precipitating out. The maximum amount of any substance that will dissolve depends on a number of factors, such as the actual solvent (e.g., water, alcohol, ether, etc.), the temperature, the presence of other substances in the solvent (solution), and the pH. It does not, however, depend on how much of the substance remains undissolved.

17. The "solubility" of a substance concerns the ability of that substance to dissolve in a solution. In some cases, "soluble" refers to whether a specified quantity of substance has been "solubilized" by, or dissolved in, the solution. If a known quantity of a substance has been dissolved in a solution, resulting in a clear solution, one can say that the amount dissolved is soluble in the solution. One can not determine from a clear solution what the maximum solubility of that substance is (i.e., equilibrium solubility), and in such cases would normally describe that quantity of the substance as being "fully soluble" or quantify its solubility as being greater than or equal to the

amount of the substance that is known to be dissolved in the composition. This later terminology was used in Table 2 of the '337 patent.

18. "Solubility" may sometimes refer to "equilibrium solubility," which is the maximum amount of a substance that can dissolve in solution when there is also excess, undissolved solid in contact with the solution. If there is undissolved solid in equilibrium with the solution, the equilibrium solubility of that substance in that solution may be determined by filtering off the undissolved solid, and use a technique such as HPLC (High Pressure Liquid Chromatography, a very common analytical technique) to measure the amount of substance in the solution.

19. One of the most important properties of any aqueous solution, for a pharmaceutical chemist, is known as its "pH," which is a measure of how acidic or basic (alkaline) the solution is. The property "pH" is measured on a scale from 0 to 14, with 7 indicating a "neutral" solution. An acidic solution has a pH below 7, and a basic solution has a pH above 7.

20. It is possible to set, or fix, the pH of a solution at a particular value by adding and substances known as "buffers."

21. Many pharmaceutical substances, including the drug brimonidine tartrate, change the pH of the water in which they are dissolved to make the solution either acidic (pH less than 7) or basic (pH more than 7). These substances are known as acids and bases, respectively. Brimonidine itself is a weak base that can exist in two forms, known as the "free-base" form "B," and the protonated form, "BH+."

Pharmacologists and those who work in related sciences use a number of terms interchangeably to refer to these two forms, which may have different properties:

Free-base form B	neutral form un-ionized form unprotonated form
Protonated form BH+	positively charged form ionized form protonated form

22. The strength of a base is measured by its equilibrium constant for ionization in water. This constant can be expressed as a pKa, and reflects the following reaction:

$$BH+ = B + H+ \qquad pKa$$

23. The pKa of an acid or base is often reported as the value measured or determined under certain standard, well-defined conditions, the thermodynamic pKa. The apparent pKa, however, that is actually determined for that acid or base in a particular solution will depend on the presence of the other substances in the solution that influence the relative stability of the ionized and un-ionized forms of the acid or base.

24. When a weakly basic drug that can exist in the two forms BH+ and B is put into a solution that is held at a particular pH, the pH of the solution and the pKa of the drug determine the relative proportion of the substance that will be present in each of the two forms according to the following equation:

$$pH - pKa = \log [B]/[HB+] \qquad \text{Equation 1}$$

25. Equation 1 is the Henderson-Hasselbach equation. When brimonidine tartrate is dissolved in water, all of the dissolved substance separates into a positively charged brimonidine ion (BH+) and a negatively charged tartrate ion. Depending on the pH and other properties of the solution, some of the brimonidine in the solution will be found in the B form, and some will be found in the BH+ form, in the proportion reflected by Equation 1 above.

26. In a solution at a particular pH, the relation between "S_t," the total amount of brimonidine in the solution, in any form, and the concentration "S_o" of the brimonidine in the free-base form (B), is given by the Equation 2:

$$\frac{S_t - S_o}{S_o} = 10^{(pKa - pH)} \qquad \text{Equation 2}$$

F. The Technology at Issue: Other Components of Ophthalmic Formulations

27. Aqueous drug formulations typically include the API ("active pharmaceutical ingredient"), which is the component believed to have the desired pharmaceutical effect. The other components comprise what is known as the "liquid carrier" or the "vehicle" of drug formulation. The components of the vehicle are preferably non-toxic, and should also not interfere with the efficacy of the API. These components are typically very well known by pharmaceutical scientists, and are routinely used in various formulations.

28. In addition to the API, aqueous solutions typically also contain "buffer" components so that the pH of the solution may be kept at a desired level. By

setting the pH, the formulator can control the total amount of API in solution (Equation 2), as well as the relative proportion of the API that might be present in the ionized or un-ionized form (Equation 1).

29. Ophthalmic solutions often also contain substances intended to increase the viscosity of the solution. Viscosity refers to the flow properties of a fluid. Honey, for example, is a very viscous liquid. Viscosity enhancement can be particularly important for ophthalmic solutions, to increase the amount of time the API stays on the eye and, consequently, provide its therapeutic effect or be absorbed, and reduce the amount that may enter other body systems.

30. Common viscosity agents include polyvinyl alcohol (PVA); derivatives of methylcellulose, such as carboxymethylcelluloses (CMC); and povidones (also known as a polyvinylpyrrolidone or PVP). These and other viscosity-enhancing substances, and their properties, have been well-known to pharmaceutical scientists for decades and have been frequently used to increase the viscosity of ophthalmic solutions. In fact, viscosity-enhancing substances such as PVA, CMC and povidone are commonly found today, and have been for many years, in ophthalmic products including those containing various glaucoma drugs and those, such as moisturizing drops (Tears Naturale®), that do not even contain a drug or API. Anyone formulating a liquid solution for application to the eye would consider using one of these common viscosity-enhancing agents simply because they make it possible for the solution to stay in the eye longer.

31. Tonicity agents are simple substances such as table salt (NaCl) that are added to pharmaceutical products to ensure that the "osmotic pressure" of the solution is approximately the same as the biological medium.

32. Solutions may also contain preservatives, which act to preserve the composition from contamination or breakdown. Some people do not consider the preservative to be part of the vehicle, but rather to be an additive. It is important that the other ingredients in the vehicle do not interfere with the efficacy of the preservative.

G. Allergan's Development of Its Alphagan® and Alphagan® P Products

33. Allergan has previously marketed a 0.20% brimonidine composition under the product name Alphagan®, and currently markets a 0.15% brimonidine composition under the product name Alphagan® P.

34. On September 6, 1996, the Food and Drug Administration ("FDA") approved Allergan's New Drug Application ("NDA") for a 0.2% brimonidine product for reducing intraocular pressure in patients with open-angle glaucoma or ocular hypertension, and granted Allergan five years of market exclusivity on that product. Allergan began to sell Alphagan shortly thereafter.

35. The active ingredient in Alphagan was 0.20% brimonidine tartrate. It also contained the preservative benzalkonium chloride (BAK), the viscosity enhancer polyvinyl alcohol (PVA), and buffers and tonicity agents.

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41. CMC is a water-soluble polymer commonly used in ophthalmic solutions to increase ocular comfort (i.e., a demulcent) and product viscosity.

REDACTED

42. Purite is a preservative.

REDACTED

REDACTED

46. There is no evidence that Allergan's purpose in using CMC in its Brimonidine-Purite reformulation was to increase the solubility of brimonidine tartrate in that composition. Indeed, there is no evidence that the solubility of the brimonidine was ever a concern to Allergan's scientists during their reformulation project.

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61. Allergan filed NDA No. 21-262 for its 0.15% brimonidine tartrate product (Alphagan P) on June 29, 2000. Approximately two weeks later, on July 14, 2000, Allergan filed the provisional application (serial no 60/218,200) from which the patents-in-suit each claim priority.

62. The results of the Phase III clinical trials were reported in the "Katz article," which was submitted to the Journal of Glaucoma on May 9, 2001. The Katz article reported that at some time points, there was statistically significant superiority in IOP reduction for the 0.2% brimonidine product in comparison to the 0.15% Brimoindine-Purite formulation. AGN0221655.

63. The incidence of allergic conjunctivitis was 9.2% for the 0.15% Brimonidine-Purite, as compared to 15.7% with the 0.2% Brimonidine formulation. The Katz article reported this difference as a "relative percent difference" of "at least 41%." AGN 0221657.

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66. Allergan's NDA 21-262 for its 0.15% Alphagan P product was approved on March 16, 2001, and Allergan was awarded a three-year period of marketing exclusivity. As a result of studies of Allergan's 0.2% Alphagan product, Allergan was also awarded a six-month period of pediatric exclusivity, which attached to the 3-year exclusivity grant, extending its effective marketing exclusivity to September 16, 2004. ALC61293.

67. Allergan began marketing Alphagan P in September 2001. AGN0063863

68. Less than one year later, Allergan began implementing a scheme that would ensure that there was no 0.2% product available whatsoever, and thereby forestall any competitor from introducing a generic brimonidine product.

69. Thus, on August 20, 2002, Allergan informed the FDA that it intended to withdraw its Alphagan 0.2% product from the market. ALC61294

70. Next, on October 25, 2002, Allergan filed a citizen petition requesting that the FDA refuse to approve or suspend approval of any ANDAs that referred to 0.2% Alphagan because Allergan's NDA for Alphagan had been withdrawn for safety and efficacy reasons. ALC61292.

71. Allergan's scheme was thwarted by the FDA, which denied Allergan's petition in a letter dated May 21, 2003. The FDA letter stated that (a) Alphagan® 0.2% was not withdrawn for reasons of safety or effectiveness; (b) any numerical decrease in allergy-related adverse events associated with the use of Alphagan

P 0.15% is offset by a numerical decrease in IOP lowering associated with that product; and (c) in neither case was the difference clinically significant.

72. The FDA reviewed the Phase III pivotal studies comparing the safety and effectiveness of Alphagan P 0.15% to that of Alphagan 0.2% and found that the risk-to-benefit ratio of Alphagan P 0.15% is essentially the same as that of Alphagan 0.2%. The patients taking Alphagan P had fewer incidents of allergic reactions than those taking Alphagan, but the IOP of the Alphagan subjects went down more than that of those taking Alphagan P. ALC61297.

73. The FDA concluded that the differences in IOP reduction and incidence of adverse events were not clinically significant and that Alphagan P 0.15% is neither safer nor more effective than Alphagan 0.2%. ALC61300.

74. In December 2003, despite the FDA's clear finding that Alphagan P 0.15% was not superior to Alphagan 0.2%,

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H. Alcon's Proposed Product

75. Alcon has been developing and manufacturing ophthalmic drugs since 1945 and has substantial research and development departments.

76. In 1994, Alcon created a new division, Falcon, which is dedicated entirely to the development and production of generic drugs. (Herrick Dep. 20:14-16, Aug. 24, 2005).

77. Falcon has six employees.

78. In 2001, Allergan's Alphagan P product was approved by the FDA and Alcon decided to create a generic 0.15% brimonidine tartrate product in order to provide a lower cost substitute to Allergan's Alphagan P product. (S. Robertson Dep. 27:14 – 28:15, Sept. 9, 2005). At that time, Alcon was still seeking FDA approval of its generic 0.2% brimonidine tartrate product, but that product, when approved, would not be substitutable for Alphagan P. In order to compete effectively in the market for brimonidine products, Alcon needed to have a generic 0.15% brimonidine tartrate product, which would be substitutable for Alphagan P. Alcon's decision to create a generic alternative to Alphagan P was thus motivated by market forces and considerations, not any determination or belief that a 0.15% brimonidine tartrate product was superior in any way to a 0.2% brimonidine tartrate product.

79. As a provider of generic medicines, it was natural for Falcon to follow the same path as the name brand manufacturer. (Id.).

80. The FDA based its finding that Allergan's Alphagan P product was not superior to its Alphagan product on Allergan's own clinical studies. (See FDA Letter). Those clinical trials are insufficient to support a claim of superiority or inferiority between the 0.2% and 0.15% products. (S. Robertson Dep., 84:6 – 15).

81. Alcon is not aware of any information that would contradict the FDA's finding regarding the alleged superiority of one product over another. (Id. at 83:22 – 84:5). Alcon did not believe that the 0.15% product was an advance over the 0.2% product. (Id. at 75:12 to 79:15).

82. In deciding to market a 0.15% product, Alcon did not intend to produce a better product than [either its existing 0.2% product, or Allergan's 0.15% Alphagan P product], but was simply trying to provide a low-cost alternative for patients whose doctors prescribed the name-brand 0.15% brimonidine product. (S. Robertson Dep., 14:22 to 15:21).

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84. Like Alphagan P, Alcon's proposed product is an aqueous topical solution containing 0.15% brimonidine as the active ingredient.

85. Although there is no patent covering brimonidine itself, or the use of brimonidine tartrate to treat IOP, Alcon developed its formula to respect any relevant valid patents.

REDACTED

88. None of Alcon's deformulation documents indicates that Alcon believed that the purpose of CMC in Alphagan P was to increase the solubility of the active ingredient. Alcon's documents show that Alcon understood the function of CMC in Alphagan P to be to increase viscosity.

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92. In April 2004, Alcon submitted an Abbreviated New Drug Application (ANDA) for its 0.15% brimonidine tartrate ophthalmic solution. Alcon's submission was a so called "paper NDA," because its proposed drug was a modified version of Allergan's brand name drug, rather than a generic copy, differing in a number of respects, as described above.

93. The NDA for Alcon's proposed generic 0.15% brimonidine product has been tentatively approved by the FDA since March 1, 2005. ALC 61397-15.

94. Allergan alleges that Alcon has infringed the '337 patent and the '834 patent under 35 U.S.C. § 271(e)(2) by seeking FDA approval of its proposed generic drug product.

95. Because of the filing of this suit, FDA approval of Alcon's new drug application ("NDA") has been stayed for up to 30 months or until the suit is resolved in Alcon's favor.

96. Between September 1996 and March 2001, Allergan enjoyed five and one-half years of exclusivity on the sale of its 0.2% Alphagan product in the United States.

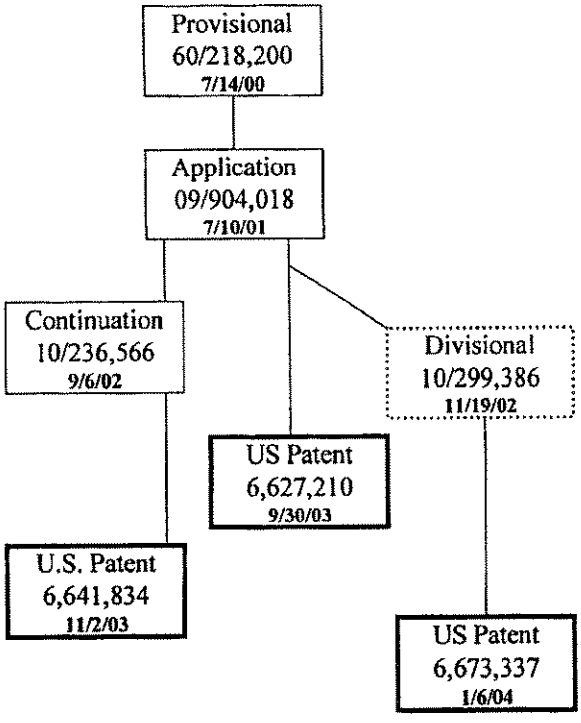
97. Allergan's market exclusivity for its 0.15% Alphagan P product would have ended on September 16, 2004, after the three and a one half years to which it was entitled under the Act. By filing this lawsuit, Allergan has extended that exclusivity until the earlier of Alcon's victory in this lawsuit, or until an additional 30 month period has passed.

1. The Patents-In-Suit

98. The '834 and '337 patents have a common specification and derive from the same parent application. Both patents claim the benefit of Provisional Application Serial No. 60/218,200, filed on July 14, 2000, and Application Serial No. 09/904,018 ("the Parent Application"), filed on July 10, 2001.

99. The Parent Application matured into United States Patent No. 6,627,210 ("the '210 patent") and its progeny applications matured into the two patents-in-suit.

100. As the diagram below illustrates, the '337 patent issued from Application Serial No. 10/299,386 (a divisional application of the Parent Application), and the '834 patent issued from Application Serial No. 10/236,566 (a continuation application of the Parent Application).



101. The '210, '337 and '834 patents share a common specification (hereafter, the "common specification").

102. The following errors are among those found in the common specification of the patents-in-suit:

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103. The common specification purports to describe the use of chemicals termed "solubility-enhancing components" in order to increase the solubility of brimonidine in an aqueous solution. The term "solubility-enhancing components" is not used in the pharmaceutical field to describe any chemical that purports to increase the solubility of a substance in solution. The principles that some components of a solution may affect the solubility of other components are well-known and well established. There is nothing new about the idea that some components may be used to modify the solubility of other solution components.

104. The common specification also purports to describe "solubility-enhancing components," or what the named inventors call "SECs," as though they were a class of chemical compounds. The SECs that are described in the patent do not belong to a single chemical class, or anything that is describable as such, and there is nothing in the patent that explains how one could determine whether or not a particular chemical would function as what they describe as an SEC short of making a composition and testing it. For example, the common specification lists a number of known viscosity enhancing agents and characterizes them as SECs, but provides no explanation as to why any would be expected to have such an effect. There is no common denominator among the broad ranges of substances described as SECs in the specification, except that a number of them, including CMC (the only putative SEC for which any data is provided) are polymers that are routinely used in ophthalmic formulations. In other words, the patent teaches that one should use something that improves solubility in order to improve solubility.

105. Moreover, the specification includes test results for just one substance – CMC – a polymer that is well known for its viscosity enhancing properties, and frequently used in ophthalmic and other formulations for that purpose. The common specification specifically teaches that CMC is "an SEC" without reference to any other characteristics of the composition that contains it. (col. 14, l.59) Nor does the common specification provide any data regarding solubility effects for any of the listed viscosity enhancers except for CMC. It provides no instructions as to how to do experiments to determine whether or not a particular substance is or is not an SEC, and provides no description as to what degree of putative change in solubility would make a substance qualify as an SEC.

106. The prior art literature is replete with descriptions of solutions that combine brimonidine with compounds that are used to improve the viscosity of the formulation, such as PVA, or CMC, or povidone. In fact, many of the compounds that are described in the patent to be "solubility-enhancing components" are typically used in ophthalmic and other formulations to increase viscosity.

107. The patent specification focuses on a group of compounds known as carboxymethylcelluloses, or "CMC." The named inventors purport to demonstrate that one particular type of CMC has the properties of enhancing solubility by preparing a series of solutions described in Table III (col. 15, lines 5-25), which vary in their pH and in their CMC content. They used 5 different concentrations of CMC, and for each, several different pHs. For each data point, only one measurement was taken. So few measurements are not appropriate in this type of scientific experiment.

108. The named inventors then claim to have measured the solubility of brimonidine in those solutions, as expressed in Table IV (col. 15, line 45 – col. 16, line 10). They then prepared graphs of the solubility of brimonidine tartrate, as a function of pH, for the solutions that contained different quantities of CMC, and obtained the results shown in Figure 1. To do so, they conducted a technique known as "regression analysis." Specifically, they used a modified Henderson-Hasselbach equation using a nonlinear least squares routine. (col. 15, ll 38-41) Although they claim the result of their analysis yields a fit between the experimental values and the equation plotted in Figure 1 to be 0.991, the data in Table IV do not disclose measured differences in solubility between compositions with and without CMC that are "statistically significant." Nor, as discussed above, do they state what difference would be sufficient to enable a substance to be characterized as a solubility enhancing component.

J. The '210 Patent

109. The '210 patent issued on September 30, 2003 directly from the Parent Application, which was filed on July 10, 2001.

110. In the first Office Action, the Examiner compelled the applicants to pursue prosecution of each of four groups of claims through separate applications. See '210 PH, Office Action dated September 16, 2002, at 1-3.

111. The applicants chose to pursue the group of claims (which matured into the '210 patent) requiring a "solubility enhancing component" in the Parent Application, and filed a divisional application (which matured into the '337 patent) to pursue claims requiring a preservative. See '210 PH, Response to Restriction

Requirement mailed October 16, 2002; '337 PH, Preliminary Amendment mailed November 19, 2002, at 1-3.

112. Accordingly, prosecution of the Parent Application proceeded on claims 1-30 of the original application. Then-pending claim 1, which is nearly identical to issued-claim 1 of the '337 patent, read:

> 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.

'210 PH, Application filed July 9, 2001, at 33 (emphasis added).

113. In the first substantive Office Action, the Examiner rejected all pending claims as obvious over Burke (U.S. Patent No. 5,215,991, "the '991 patent"), which is assigned to Allergan, in view of Remington's Pharmaceutical Sciences. '210 PH, Office Action dated January 9, 2003, Tab 7 at 3-5. The Examiner stated that it would have been obvious for an ordinarily skilled artisan to modify Burke's alpha-2-adrenergic agonist compositions by adding CMC (Allergan's purported SEC) as taught by Remington.

114. The examiner failed to recognize that no such combination was necessary. The Burke reference itself disclosed the use of CMC in brimonidine compositions (as well as other viscosity agents). See the '991 patent at col. 5, ll. 30-34.

115. At a subsequent interview, in an apparent effort to distinguish the anticipatory disclosure of Burke, Allergan's attorney argued that the pending claims were to "an invention of selection." '210 PH, Summary of Interview dated February 25, 2003. The attorney agreed to file a declaration showing unexpected results with regard to the "anionic solubility enhancing" agent in an attempt to distinguish it from the other identified viscosity agents (all non-ionic), as a basis upon which to argue that its selection would not have been obvious to those skilled in the art. Id.

116. Allergan submitted a written response to the Office Action shortly thereafter. See '210 PH, Reply to Office Action mailed March 11, 2003. In an effort to overcome the obviousness rejection, Allergan amended the claims to require that the "solubility enhancing component" be "polyanionic" or "anionic." They also acknowledged that the Burke reference disclosed brimonidine formulations with various "vehicles," including: polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, carboxymethylcellulose (CMC), and hydroxyethylcellulose. They forcefully distinguished the claimed invention from the disclosure of Burke by arguing that anionic components (such as CMC) had unexpected properties that non-anionic vehicles (polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, and hydroxyethylcellulose) did not:

> Of the "vehicles" specifically disclosed by the Burke patent, all will function to increase the viscosity of a liquid

> aqueous composition. However, of these vehicles only carboxymethylcellulose (CMC) is an anionic polymer. All of the other polymers are non-ionic. They may act to increase the solution's viscosity, but they do not have the same characteristics as an anionic polymer such as CMC.
>
> Id. at 6 (emphasis added).

117. On this basis, the applicants argued that they had made an invention of selection. Id. at 7 ("Burke contains no disclosure that would direct or motivate the person of ordinary skill in the art to select or want to select an anionic polymeric solubility enhancing component such as CMC from the list of optional viscous 'vehicles' contained in the [Burke reference]."). In other words, the applicants stressed that it was inventive to select the anionic component disclosed in Burke (CMC) – as opposed to the other five non-ionic "vehicles" listed in Burke – to formulate a brimonidine tartrate composition.

118. The applicants relied on a declaration from the lead inventor, Dr. Olejnik, in support of this argument. Like the applicants' attorney, Dr. Olejnik acknowledged that the Burke patent discloses brimonidine formulations with various "vehicles," including: polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, carboxymethylcellulose (CMC), and hydroxyethylcellulose. '210 PH, Declaration of Orest Olejnik, Ph.D. received March 17, 2003, at ¶ 4.

119. Yet Dr. Olejnik represented to the PTO that Burke would not have motivated a person skilled in the art specifically to select CMC to formulate a brimonidine tartrate composition. Dr. Olejnik opined that CMC was fundamentally

different from the other vehicles disclosed in Burke because it was anionic rather than non-ionic:

> Unlike the other listed polymers (polyvinyl alcohol, povidone, (polyvinylpyrollidone), hydroxypropylcellulose, poloxamers, and hydroxyethylcellulose), CMC is anionic at pH 7 or greater. The other listed polymers are non-ionic polymers. I have discovered . . . that CMC possesses the surprising advantages of both increasing the solubility of brimonidine in solution . . . and causing such solutions to have superior adherence to cell surfaces, including ocular surfaces such as the cornea.
>
> Id. at ¶ 7 (emphasis added).

120. Furthermore, Dr. Olejnik stated that the non-ionic vehicles disclosed in Burke would not work in his invention:

> It is also my belief that brimonidine solutions made using the other "vehicles" mentioned in the Burke patent would not possess this surprising combination of advantages. Therefore, the disclosures of Burke and Remington's in no way would render the presently claimed compositions obvious to the worker of ordinary (or even extraordinary) skill in the art.
>
> Id. at ¶ 8 (emphasis added).

121. The Examiner allowed the claims to issue without further prosecution.

122. Only three months after Dr. Olejnik submitted his declaration to the Examiner during prosecution of the '210 patent, he was named as co-inventor on an application (App. No. 10/621,053) which discloses five of the six polymer vehicles that had been disclosed in Burke as being mucoadhesives.

K. The '337 Patent

123. The '337 patent issued on January 6, 2004 from a divisional application filed on November 19, 2002 of the Parent Application. The divisional application was purportedly filed to pursue claims from the Parent Application involving compositions containing an oxy-chloro preservative.

124. In the first Office Action, the Examiner rejected the pending claims as obvious over the Burke patent in view of Beck et al. (U.S. Patent No. 6,358,935).[1] She observed that it would have been obvious to modify the compositions disclosed in Burke by substituting the chlorite preservative disclosed in Beck. '337 PH, Office Action dated March 3, 2003, at 3-5.

125. In response, Allergan broadened the claims by eliminating from all claims the requirement for an oxy-chloro preservative, despite the fact this was the very reason the divisional application was filed. '337 PH , Reply to Office Action mailed June 13, 2003, at 2-3. Allergan also amended the claims by adding the SEC limitation. Id. As amended, the pending claims of the divisional application were effectively the same as the claims the Examiner had rejected in the Parent Application over the Burke disclosure (which were allowed only after they were limited to compositions containing "anionic" SECs).

126. The applicants acknowledged that "Burke discloses that the combinations claimed may optionally be formulated using various vehicles, including carboxymethyl cellulose [CMC], various tonicity agents, and various preservatives,

[1] Edward Kerslake, a co-inventor on the patents-in-suit, is also listed as an inventor on the Beck patent.

including benzalkonium chloride." Id. at 5. The applicants, however, ignored their prior representations – made during the prosecution of the '210 patent – that the non-anionic "vehicles" disclosed in Burke would not function in their invention. To the contrary, they made an argument that was flatly inconsistent with those earlier representations:

> Applicants respectfully maintain that for all its discussion of possible formulations, nothing in Burke discloses or suggests the use of a solubility enhancing component in combination with an alpha adrenergic agonist. The present application, which also discloses the advantages of using such a component (such as greater flexibility with the concentration and pH at which such composition is formulated) is, to the Applicants' knowledge, the first reference to do so.
>
> Id. (emphasis added).

127. The Examiner did not identify this glaring inconsistency. The claims, which are essentially the same as those rejected during prosecution of the '210 patent over Burke, were allowed without further prosecution.

128. Claim 1 of the '337 patent is to:

> A therapeutically effective ophthalmic 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; and
> a solubility enhancing component other than a cyclodextrin 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.

129. Claim 2 of the '337 patent is to:

> The composition of claim 1 wherein the alpha-2-adrenergic component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof, and mixtures thereof.

130. Claim 3 of the '337 patent covers:

> The composition of claim 1 wherein the therapeutically active component includes a quinoxaline component.

131. Claim 4 of the '337 patent is to:

> The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

132. Claim 6 of the '337 patent is to:

> The composition of claim 1 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

133. The common specification describes the "biological environment" as referencing the environment of the cornea, which is a part of the eye. This biological environment contains a number of specialized molecules, including various proteins and other macromolecules, and has a specific tonicity, pH, and other features.

134. Claim 9 of the '337 patent is to:

> The composition of claim 1 which further comprises an effective amount of a preservative.

135. Claim 10 of the '337 patent is to:

The composition of claim 6 which further comprises an effective amount of a preservative.

136. The field of the claimed invention, or "art," is pharmacology or pharmaceutical chemistry. The level of ordinary skill in this art, to which this patent is directed, would be someone with a degree in pharamceutical chemistry or pharmacology or related fields, and several years of experience formulating drug compositions, especially liquid compositions.

L. The '834 Patent

137. The application for the '834 patent was filed on September 6, 2002, as a continuation from the Parent Application. That filing was accompanied by a preliminary amendment that cancelled all of the claims originally contained in the Parent Application and introduced a set of 19 new claims drawn to compositions of "up to about 0.15%(w/v) [brimonidine] tartrate" soluble at about pH 7.0 and 21°C. Preliminary Amendment submitted 9/6/02.

138. In the first Office Action, the claims were also rejected as obvious over the same Burke reference. The only component that the Examiner found that Burke did not disclose was the oxychloro component. The Examiner did find that it would be obvious for one of skill in the art to modify the composition of Burke by substituting the preservative disclosed in the Beck reference. Office Action dated 12/18/2002 at 5.

139. At a subsequent interview with the Examiner, Allergan argued that the advantages of a composition comprising 0.15%(w/v) active ingredient were unexpected and agreed to file a declaration to that effect. Summary of Interview dated 2/25/2003. In response to the rejections based on Burke, Allergan, argued that:

> the present invention is the result of the surprising finding that increasing the pH of a brimonidine solution to a pH of greater than about 7.0 leads to similar efficacy at a 25% lower concentration (from 0.2%(w/v) to about 0.15%(w/v) or less) than is seen in a brimonidine solution at a pH of about 6.6-6.8.

Reply to Office Action dated 3/17/2003 at 4 (emphasis added).

140. In connection with this argument, Allergan submitted the Declaration of Amy Batoosingh and an article by L. Jay Katz M.D. Ms. Batoosingh stated that the results reported in the Katz article led to the conclusion that "brimonidine 0.2% and brimonidine-Purite 0.15% showed comparable efficacy when each was used for the treatment of ocular hypertension in glaucoma and/or ocular hypertensive human patients over a 12 month period." Declaration of Amy Batoosingh at ¶4.

141. The brimonidine-Purite composition used in the Katz study was formulated at pH7.1-7.3, according to Ms. Batoosingh's declaration at ¶3. Indeed, Allergan concluded its arguments by stating that:

> the present invention is drawn to surprising new therapeutic compositions comprising at least a 25% lower concentration of brimonidine than previous ophthalmic formulations, at pH closer to both to the solubility limits of brimonidine, and to the pKa of the compound.
>
> Id. at 5.

142. After requiring a further limitation of "about 21°C" to be added, the Examiner allowed the claims subject to the relevant terminal disclaimers. Claim 1 of the '834 patent is to:

> A therapeutically effective aqueous ophthalmic composition comprising up to about 0.15%(w/v) of 5-

bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21°C.

143. Claims 2-6 of the '834 patent depend from claim 1 and are to:

2. The composition of claim 1 which includes up to 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

3. The composition of claim 1 which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

4. The composition of claim 1 which includes 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

5. The composition of claim 1 having a pH of 7.0 or greater.

6. The composition of claim 1 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

144. Claims 8-14 of the '834 patent are to:

8. The composition of claim 1 which is substantially free of anionic cellulosic derivatives.

9. The composition of claim 1 which is substantially free of carboxymethyl cellulose.

10. A therapeutically effective aqueous ophthalmic composition comprising up to about .15% (w/v) of a component selected from the group consisting of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, the composition having a pH of about 7.0 or greater, and the component being soluble in the composition at about 21° C.

11. The composition of claim 10 which includes up to 0.15% (w/v) of the component.

12. The composition of claim 10 which includes about 0.15% (w/v) of the component.

13. The composition of claim 10 which includes 0.15% (w/v) of the component.

14. The composition of claim 10 having a pH of 7.0 or greater.

145. Claims 17-18 and 20 of the '834 patent are to:

17. The composition of claim 10 which is substantially free of anionic cellulosic derivatives.

18. The composition of claim 10 which is substantially free of carboxymethyl cellulose.

20. The composition of claim 10 which further comprises a preservative selected from the group consisting of an oxy-chloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

146. The field of the claimed invention is pharmacology and its related basic and applied sciences. The level of ordinary skill in this art, to which this patent is directed, would be someone with a degree in medicine or pharmaceutical chemistry or pharmacology, with experience in evaluating and selecting pharmaceutical therapies for the treatment of glaucoma or elevated intraocular pressure.

147. Every one of the asserted claims of the '834 patent requires, inter alia, a particular concentration of the active ingredient. For example, claims 1 and 10 require "up to about 0.15% w/v"; claims 2 and 11 include "up to 0.15% w/v"; claims 3 and 10 include "about 0.15% w/v" and claims 4 and 13 include "0.15% w/v."

148. The narrative portions of the '834 patent do not make reference to any of the particular concentrations listed in the claims. Nor did the originally-filed claims of the application that matured into the '834 patent.

149. To the contrary, only one concentration of adrenergic agonist is identified in the common specification as being "therapeutically active." That reference appears in col. 13, ll. 19-22 ('834 patent) where it is stated: "It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity."

150. Example 1 of the common specification contains a single formulation of an ophthalmic solution, and that formulation, which is set forth in Table 1 (col. 14) includes 0.5% brimonidine tartrate.

151. Example 2 provides in Table 3 (col. 15) five different compositions of ophthalmic solutions, all of which contain 0.2% brimonidine tartrate.

152. No information is contained in the common specification or originally filed claims describing clinical data or otherwise demonstrating therapeutic activity of any concentration of brimonidine tartrate or of any other adrenergic agonist.

153. Table 4 reflects solubility measurements for the five different compositions identified in Table 3, and shows that under various pH conditions with varying amounts or no CMC in the composition, as few as 218 ppm (0.0218 %) and as many as 14,464 ppm (1.4464 %) of brimonidine tartrate can be dissolved in a standard

ophthalmic solution. No information is provided regarding the therapeutic activity, or lack thereof, of any particular concentration at any particular pH.

154. Nothing in the common specification or the originally filed claims of the '834 patent would suggest to one of ordinary skill in the art that the inventors considered their invention as being limited in any way to a particular concentration, approximate concentration, or maximum concentration of any adrenergic agonist. Although the common specification contains ranges for various ingredients and properties of ophthalmic compositions, including the amount of the putative solubility enhancing component (col. 3, ll. 13-17), the pH of the compositions (col. 3, ll. 19-22), the quantity of preservative components (col. 9, ll. 43-49), tonicity levels (col. 11, ll. 66-10), and viscosities (col. 11, ll. 16-20), there is no reference whatsoever for the concentration (dose level) of the active ingredient apart from the statement that it should be present in some undefined and unspecified "therapeutically effective" amount.

155. At col. 12, lines 30-35, the common specification states:

> The specific dose level [of the adrenergic agonist] for any particular human or animal depends upon a variety of factors, including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular condition undergoing therapy.

156. Neither the common specification nor the originally filed claims provides any data or teaching of how the interplay of those multiple factors should result in the use of a particular concentration of alpha-2-adrenergic agonist and nothing in the common specification or originally filed claims states or suggests that neither the 0.5%

nor the 0.2% brimonidine tartrate concentrations used in Examples 1 and 2 would be outside the scope of the claimed invention.

157. Dr. Stella's testimony that one of ordinary skill in the art would immediately recognize that the inventors considered their invention to include a composition having no more than about 0.15% brimonidine tartrate is unsupported by the common specification and initially filed claims.

158. In light of the language of the later-filed claims, an appropriate written description would include, for example, one or more of the following elements: a narrative statement providing a range of concentrations of the active pharmaceutical ingredient (e.g., CIP, [0045-46]); an example setting forth the components of a composition within the scope of the claims (e.g., CIP, [0147-148]); an example setting forth clinical trial data comparing a composition within the scope of the claims to a composition outside the scope of the claims and a statement reflecting the inventor's preference for the claimed composition (e.g., CIP,[0148-150]). No such elements are present in the common specification or the originally filed claims.

M. The Burke '991 Patent

159. United States Patent Number 5,215,991 (the "'991 patent" or the "Burke '991 patent") was issued on June 1, 1993 and names Dr. Burke, an Allergan scientist, as inventor.

160. The '991 patent discloses "therapeutically effective ophthalmic compositions." Indeed, the following quotations from the '991 patent make clear that such compositions are the subject of the patent:

- the title of Table I ("exemplary topical ophthalmic formulation[s]")
- the title of the patent (referring to "lowering intraocular pressure")
- the abstract (referring to a therapeutic amount of alpha-2-agonist" for "lowering IOP and treatment of intraocular hypertension")
- the specification ("The alpha 2 agonists of the present invention exhibit hypotensive activity in lowering IOP" (col. 2, ll. 63-65))
- Claim 1: "A method for lowering intraocular pressure (IOP) comprising co-administering to the eye of the a mammal an effective IOP lowering amount of an alpha2agonist . . ." (col. 8, ll. 15-19)
- Claim 7: "An ophthalmically acceptable composition for lowering intraocular pressure (IOP) comprising an effective, IOP lowering amount of alpha2 agonist . . ." (col. 8, ll. 36-39)

161. The '991 patent discloses the use of brimonidine in such therapeutically the disclosed compositions. Brimonidine is an "alpha-2-adrenergic agonist" and is also a quinoxaline, and an imidazoline, and thus the use of those classes of compounds is also disclosed. The disclosure of alpha-2-adrenergic agonists, and brimonidine in particular, occurs in many places in the '991 patent:

- Table I expressly discloses "alpha2 agonist" in the amount (% w/v) of "about 0.00001 to about 1.0" (col. 5, l. 15)
- Brimonidine is one of the patents' three "most preferred" alpha-2 adrenergic agonists
- "The preferred alpha2 agonist of the present invention are derived from imidazolidines and their tautomers." (col. 2, ll. 63-65)

- "The most preferred imidazoline-derived alpha2 agonist compounds are clonidine, p-aminoclonidine and 5-bromo-6-(2-imidazoline-2-ylamino)quinoxaline." (col. 3, ll. 49-51)
- Claims 5, 10, and 11 of the '991 patent specifically identify brimonidine (5-bromo-6-(2-imidazolidine-2-ylamino)quinoxaline).

162. The '991 patent discloses that the alpha-2-adrenergic agonist must be present "in an amount effective to provide a therapeutic benefit":

- ". . . the preferred effective dose range of alpha2 agonist having a therapeutic effect in mammals is from about 0.001% to about 1.0% weight/volume" (col. 4, ll. 38-40)
- See also, col. 6, l. 9-col. 7, l. 4; Figs 2A, B, C: specification teaches that, after pretreatment with an Na+/H+ exchange inhibitor, there was a reduction in IOP in rabbits after treatment with 0.1, 0.01, and 0.001 (% w/v) brimonidine dissolved in water

163. The '991 patent discloses the inclusion in the compositions of the following compounds, in the following specified amounts:

- Table I includes "vehicle" in the amount of 0-40 (%w/v) (col. 5, l. 18)
- The '991 patent identifies seven "preferred" substances that are to be used in the amount of 0-40 (%w/v) (col. 5, l. 18), six of which meet the requirements placed on SECs: "polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose, and purified water." (col. 5, ll. 28-34)

164. The '991 patent discloses the use of 0-40% w/v of the following known viscosity enhancing agents as "preferred" components for ophthalmic solutions of

brimonidine: "polyvinyl alcohol [PVA], povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose [CMC], hydroxethyl cellulose." (col. 5 ll 29-33). The foregoing six polymers has the inherent property that it would function as an "SEC" in solutions of alpha-2-adrenergic agonists such as brimonidine, when used in the amounts indicated.

165. The evidence includes statements made by Allergan to the Patent Office in connection with the prosecution of Application Serial No. 10/928,906 ("the '906 application"), on which Dr. Olejnik is a named inventor (CMC, PVA, povidone, hydroxypropylmethylcellulose, hydroxyethyl cellulose).

> "Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethyl cellulose and its derivatives." (p. 3, ¶0030)
>
> "preferred SECs include carboxymethyl cellulose, polyvinyl alcohol, or polyvinyl pyrrolidone." (p. 4, ¶0051)
>
> "In one embodiment, the SECs include uncharged SECs, such as, without limitation, pyrrolidone components, polyvinyl alcohol (PVA), uncharged cellulosic derivatives, Pemulin, carbomers, Carbopols, and the like." (p.6, ¶0071)
>
> "A particularly useful and preferred class of polyanionic component includes anionic cellulosic derivatives. Anionic cellulose derivatives include metal carboxymethylcelluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof. (p. 7, ¶0104)

166. In addition, the common specification itself identified CMC as "an SEC" and also listed povidone as an expected SEC (col. 6, ll. 19-21)), as well as hydroxypropyl methyl cellulose and carboxymethyl cellulose (col. 8, ll. 26-31).

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167. Dr. Olejnik so testified at his deposition even though he was a named inventor on a continuation-in-part application derived from the application that issued as the '834 patent (App. No. 10/928,906, "the '924 CIP") that discloses a brimonidine composition that utilizes PVA as a "preferred SEC." '924 CIP at [0051-52].

168. Two experiments further verify that PVA acts as an SEC with respect to brimonidine tartrate in the same manner that CMC is characterized as so doing, and thus has inherent solubility-enhancing properties. Both experiments were conducted by Dr. Chandresakhar, a Ph.D.-level laboratory worker with decades of experience conducting solubility experiments. Both experiments were conducted under the direction of Alcon's expert witness, Dr. Gordon Amidon, a noted authority on solubility science, with years of experience conducting and analyzing solubility studies. The results of both of these experiments are reliable.

169. In one experiment, the equilibrium solubility of brimonidine tartrate was measured in two compositions. One composition was identical to that of Alphagan, which contained 1.4% PVA, except that an excess amount of brimonidine tartrate was used in order to determine the equilibrium solubility. In the other composition, no PVA was included. Enough excess brimonidine tartrate was used so that not all of it dissolved. Multiple measurements demonstrated that the presence of the 1.4% polyvinyl alcohol increased the overall total solubility of brimonidine tartrate by more than 17%, thus demonstrating that PVA acted as an "SEC" in Alphagan in the same

manner that CMC is said to act as such in Alphagan P. The data obtained from this experiment also demonstrates that at pH 7.4, the 1.4% polyvinyl alcohol would increase the total solubility of brimonidine tartrate by approximately 20%.

170. In the second experiment additional solutions were prepared of the above formulation, but various concentrations of PVA were used (0%, 1.0%, 1.4%, and 1.8%) and the solutions were prepared at pH 6.5, 7.0, 7.5, 8, 8.5, and 10. The solubility of brimonidine in the two solutions was determined by adding an excess amount of brimonidine tartrate, and stirring the solutions for two days. Enough excess brimonidine tartrate was used so that not all of it dissolved. The results, which in all of the experiments were based on multiple samples and multiple measurements, were used to prepare graphs of solubility versus pH for each of the different concentrations of PVA, just as the named inventors of the '337 patent claimed to have done in preparing Figure 1. The experiment demonstrated that the presence of increasing concentrations of PVA moved the solubility curves to the right (i.e., increasing) in the same manner that the '337 patent describes the addition of CMC as moving the brimonidine solubility curves to the right. In addition, this effect was statistically significant, whereas the results reported in the '337 patent were not. Thus, this experiment also demonstrates that PVA acts as an SEC in the same way that CMC is said to act as an SEC in the '337 patent.

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172. The Burke '991 patent discloses the use of effective amounts of preservatives in the disclosed compositions. For example, Table I includes "preservative" in the amount (%w/v) of "0-0.10" (col. 5, l.17). In addition, col 5, at ll.24-28, teaches that "Various preservatives may be used in the ophthalmic preparation described in Table I above. Preferred preservatives include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, and phenylmercuric nitrate." (col. 5, ll. 24-28).

N. Alcon's Proposed Product

173. The accused product that Alcon intends to sell for the treatment of elevated intraocular pressure and glaucoma is

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O. Findings of Fact Relating to Alleged Infringement By Alcon's Proposed Product

175. The parties have proffered the results of a number of experiments and analyses that purport to bear on the factual question of whether

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Alcon's proposed product acts as a "solubility enhancing component" in that composition.

176. I conclude from two relevant sets of experiments that all of the 0.15% brimonidine tartrate in Alcon's proposed product is fully soluble in the similar composition, at the same pH,

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177. Dr. Amidon prepared a composition corresponding to Alcon's proposed product,

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178. The 0.15% brimonidine tartrate that was in solution remained in solution. There was no visible precipitate or cloudiness, even after a considerable amount of time. This provides compelling evidence that

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does not act to keep the brimonidine tartrate soluble.

179. Alcon scientists prepared a number of compositions that contained brimonidine tartrate as well as the components of Alcon's proposed product,

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. The concentration of the brimonidine tartrate varied from solution to solution, as did the pH.

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Alcon's proposed product, the solubility of brimonidine tartrate was determined to be greater than 0.15% w/v. This further supports the finding that all of the brimonidine

tartrate in Alcon's proposed product will go fully into solution without the need for

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181. Allergan's expert witness, Dr. Valentino Stella, relied on the results of two sets of experiments as a basis for his opinion REDACTED proposed product acts as an SEC within the meaning of the asserted claims of the '337 patent. These experiments do not support such a finding.

182. The first set of experiments – which Dr. Stella played no part in either designing or analyzing – were conducted for another Allergan expert witness, Clive Wilson, by Dr. Wilson's graduate student, Hardik Shah. Mr. Shah is a PhD candidate in Scotland with no prior experience in solubility determinations or measurements. Dr. Wilson has ongoing links to Allergan, and is a colleague of Dr. Olejnik, a named inventor on both patents-in-suit. Dr. Wilson and Mr. Shah have limited or no experience in solubility determinations or measurements. Neither of them has expertise in the statistical analysis of solubility experiments.

183. Mr. Shah intended to design his experiments in order to determine whether the presence REDACTED : increased the equilibrium solubility of brimonidine tartrate in that product at certain pHs. Mr. Shah attempted to prepare compositions with the same formulation as Alcon's proposed product, and similar compositions without REDACTED

184. The solutions that Mr. Shah used, however, varied from Alcon's proposed product in several significant ways. First, Mr. Shah's solutions did not contain

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186. Finally, in each of Mr. Shah's studies, the solutions that Dr. Wilson studied were quite different than Alcon's proposed product in three ways with respect to the concentration of the brimonidine tartrate: (i) they used more than thirteen times the amount (0.15% w/v) that is in Alcon's proposed product; (ii) they used a saturated solution of brimonidine tartrate, although I am aware of no evidence that Alcon's proposed product is so formulated; and (iii) the saturated solutions that were used would have had undissolved solid brimonidine tartrate in contact with them – unlike Alcon's proposed composition – and such undissolved substance confers on the solution different "thermodynamic" and other properties than solutions that contain no excess, undissolved solid.

187. Mr. Shah conducted three studies, the first at 21°C, the second at 15°C, and the third at 21°C but at a narrower pH range than the first group. Mr. Shah analyzed his experimental results using a statistical method called "ANOVA," or analysis of variance.

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189. First, in order to evaluate the solubility properties of brimonidine tartrate in Alcon's proposed product, it would be necessary to study a solution with the same composition as that proposed product. The solutions that Mr. Shah used contained

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190. Second, even if it was appropriate to measure how much solid brimonidine tartrate was able to dissolve after a certain number of hours, Mr. Shah's methodology makes his results unreliable. Mr. Shah only measured the pH of his compositions before filtering them. He never measured the pH of the actual composition whose solubility he measured using HPLC.

191. Third, the results obtained from Mr. Shah's experiments do not REDACTED . Indeed, Mr. Shah's own calculations and analysis demonstrated that in his first experiment, which covered the broadest pH range, the REDACTED brimonidine tartrate. Mr. Shah and Dr. Wilson then analyzed their data using incorrect

and inappropriate selections of certain data measurements, and using an inappropriate statistical method.

192. By contrast, when all of the experimental results are analyzed together using appropriate methodology, as Dr. Amidon did, they do not provide statistically reliable evidence REDACTED solubility of the brimonidine tartrate. The proper, accepted methodology for analyzing solubility data employs regression analysis, rather than ANOVA analysis, and uses equations based on the Henderson-Hasselbach equation. I credit Alcon's expert witness, Dr. Amidon, that this is the correct methodology for analyzing solubility data. Dr. Amidon has taught statistics at the college level for ten years and has conducted dozens of solubility studies. He has also written textbook chapters on solubility analysis. This was also the methodology used by Allergan in its own internal analyses of the effect of CMC on brimonidine tartrate solubility, and in the '337 patent.

193. Thus, I find that the experiments conducted by Mr. Shah do not provide reliable evidence REDACTED

194. Dr. Stella also relied on certain internal Alcon experiments for his . The studies do not support his opinion, and his analysis of them is incorrect.

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195. With respect to the functioning of

"biological environment" – namely, in the eye – Allergan has only proffered evidence

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acts as an SEC in an environment having any of the other properties of the eye besides pH.

196. No evidence has been proffered concerning the alleged infringement of the '834 patent.

P. Other Prior Art References

197. Before bringing 0.2% Alphagan® to market in 1996, Allergan undertook a study of the IOP-lowering effect of three brimonidine tartrate compositions: 0.08%, 0.2%, and 0.5%. This study, published in Derick et al., [title] (the "Derick

article"), was available to one of ordinary skill in the art at the time of the alleged invention.

198. The Derick article discloses that all three compositions significantly reduced IOP compared to baseline and placebo.

199. Because the pH of the compositions used in the Derick study are not disclosed, a person of skill in the art would assume that such compositions were formulated within the normal range of products intended for use in the eye, namely pH 6-8. Further, it would have been obvious to one of ordinary skill that a composition containing 0.15% brimonidine tartrate would likely be more effective than the 0.08% composition.

200. A person of ordinary skill in the art would find the asserted claims of the '834 patent to be obvious in view of the Small reference which exemplifies the utility of the pH partition theory for brimonidine by demonstrating that the efficacy of an alpha adrenergic agonist (AGN191103) – with a chemical structure nearly identical to that of brimonidine – can be retained at a lower concentration by increasing the formulation's pH to near the component's pKa.

201. The theory and results of the Small reference provided proof-of-principle for the claimed subject matter of the '834 patent. By demonstrating that adjusting pH could compensate for losses in efficacy attributable to lower concentrations of a compound nearly identical to brimonidine, the Small article made it obvious that the same would be true for brimonidine.

202. A second reference, also by Small, and published in the same journal volume tested the hypothesis that a lower concentration/higher PH formulation would have the same efficacy as a higher concentration/lower pH formulation. The study concluded that the lower concentration/higher pH formulation provided comparable aqueous humor concentrations with lower plasma concentrations. The study attributes the observed effects to the pH partition theory.

203. The Small reference also relies on Chien et al. which reports that increasing the pH of a brimonidine formulation would enhance brimonidine's bioavailability by increasing the increasing the amount of unionized drug – precisely what Allergan claims to have discovered a decade later in the '834 patent.

204. United States Patent No. 5,021,410 (the "'410 Patent") discloses general formulations that include an "alpha 2 adrenergic agonist," a "preservative," and a "pH adjuster." (Table I) Brimonidine is disclosed as one of the "most preferred" (col. 4 ll. 45-48) of the alpha-2-adrenergic agonists, and the "preferred effective conc. range" is disclosed to be "about 0.001% to about 1.0% weight/volume." The pH adjuster is used to set the pH of the solution at 4.5-7.5. Table II also teaches the use of "benzalkonium chloride" in the formulations, as well as polyvinyl alcohol.

205. Examples 1 and 2 of the '410 patent teach the use of 0.1% brimonidine dissolved in distilled water, among formulations with pHs of 4.5-7.5, which are shown to be efficacious in rabbits and monkeys. 0.1% brimonidine is virtually the same concentration of brimonidine that results from the dissolution of 0.15% brimonidine

tartrate (the difference is accounted for by the weight of the tartrate portion of the molecule).

II. CONCLUSIONS OF LAW

206. This matter arises under the Hatch-Waxman Act, which is codified at 35 U.S.C. §271(e)(2) of the United States Patent Laws.

207. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

208. Venue is proper pursuant to 28 U.S.C. §§ 1391 and 1400(b).

A. Claim Construction

209. The Court has already construed the disputed terms of the asserted claims of the '337 and '834 patents and incorporates herein its claim construction decision. All other terms are given their plain and ordinary meaning.

B. Non-infringement

210. In making a determination on allegations of literal infringement, the fact finder compares the properly construed claim with the allegedly infringing product. Kemco Sales, Inc. v. Control Papers Co., 208 F.3d 1352, 1359 (Fed. Cir. 2000).

211. The burden of proof is on the patentee to show that the accused product contains or performs each limitation of the asserted claim. Mas-Hamilton Group v. LaGard, Inc., 156 F.3d 1206, 1211 (Fed. Cir. 1998).

1. **The '337 Patent**

212. If the patent-holder fails to prove by a preponderance of the evidence that any element of an asserted claim is present in the accused product, the Court must find that there is no infringement.

213. Each of the asserted claims of '337 patent depends from independent claim 1. Claim 1 includes the limitation that the accused composition must contain a "solubility enhancing component other than a cyclodextrin." Claim 1 further requires that such SEC must be present "in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relataive [sic] to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without" the SEC. Alphagan contends that the brimonidine tartrate in Alcon's proposed product serves as the alpha-2-adrenergic agonist required by the claim, and that the

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214. Allergan has failed to prove, by a preponderance of the evidence, that REDACTED acts or functions as an SEC within that product. As explained above, Allergan has not shown by a preponderance of the evidence that the brimonidine tartrate in Alcon's product would not be dissolved in the REDACTED indeed, the preponderance of the evidence leads to the conclusion that all of the brimonidine tartrate in Alcon's product would be soluble even

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215. Allergan has also attempted to show that REDACTED product is an SEC through experiments that purport to show that the equilibrium solubility of brimonidine tartrate is higher compared to the same composition Allergan has failed to show, however, that REDACTED such an effect. The studies that Allergan proffers suffer from various deficiencies; they

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Additionally, the analysis of the results relied upon by Allergan is not reliable or persuasive.

216. Indeed, Mr. Shah's tests did not compare Alcon's proposed product to a "similar composition." The tests were designed to measure the tonicity of the compositions, as reflected by their "osmolality." Yet the tonicity was only measured for

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217. Having failed to prove by a preponderance of evidence that Alcon's proposed product contains a "solubility enhancing component" with the properties required by claim 1, Allergan has not met its burden of proving infringement of claim 1, or any of the other asserted claims, all of which depend from claim 1.

218. Allergan has failed to prove infringement of claim 6 for an additional, independent reason. Claim 6 requires that the SEC increases the solubility "in a biological environment of the alpha-2-adrenergic agonist relative to the solubility in a

biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component." Allergan has only presented evidence concerning the pH range in which it contends

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environment" is determined by many more features than its pH, and Allergan has failed to proffer any evidence whatsoever in a "biological environment." Accordingly, it has not met its burden of proving infringement of claim 6, or claim 10, which depends from claim 6, for this additional reason.[2]

2. **The '834 Patent**

219. Allergan has failed to meet its burden of showing that Alcon's proposed product infringes the asserted claims of the '834 patent and, accordingly, I find that there is no infringement.

C. **Invalidity**

220. Alcon contends that both patents-in-suit are invalid as obvious over prior art and that the '337 patent is also invalid as anticipated by the Burke '991 patent and by the public use and sale of Allergan's 0.2% Alphagan product and

[2] Claim 6 is a composition claim, but it also requires that the composition be administered to the eye (or to another biological environment) and that the SEC function as such in that environment. Because Claim 6 impermissibly combines method limitations and composition limitations in the same claim, it is invalid as indefinite under 35 U.S.C. §112 para. 2. See IPXL Holdings, L.L.C. v. Amazon.com, Inc., 430 F.3d 1377 (Fed. Cir. 2005) (claims that combine apparatus limitations and method limitations invalid as indefinite).

publication of that product's formulation in the Product Insert, and as obvious over the prior art. Alcon also contends that the '834 patent is invalid as obvious over prior art, and that it is also invalid for lack of written description.

221. Issued patents are presumed valid, and each claim is presumed valid regardless of the validity of the other claims. 35 U.S.C. §282; Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 446 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987). A party alleging that a claim is invalid must overcome this statutory presumption "by proving invalidity by facts supported by clear and convincing evidence." Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360, 1367 (Fed. Cir. 2000).

1. Anticipation/Inherency

222. Anticipation is a question of fact. Rapoport v. Dement, 254 F.3d 1053, 1057 (Fed. Cir. 2001). A patent claim is invalid for anticipation where each and every element of the claimed invention is disclosed in a single prior art reference 35 U.S. § 102; e.g., In re Paulsen, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). "[T]he four corners of a single, prior art document [must] describe each and every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed. Cir. 2000). "If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not § 102, but § 103 obviousness." Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1577 (Fed. Cir. 1991).

223. "A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." Celeritas Techs., Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1361 (Fed. Cir. 1998), cert. Denied 525 U.S. 1106 (1999).

224. Moreover, "'[t]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.'" EMI Group North America, Inc. v. Cypress Semiconductor Corp., 268 F.3d 1342, 1349 (Fed. Cir. 2001) (quoting Atlas Power Co. v. Ireco Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999))

225. "[I]nherent anticipation does not require a person of ordinary skill in the art to recognize the inherent disclosure in the prior art at the time the prior art is created." SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343 (Fed. Cir. 2005) (holding that because "anticipation requires only an enabling disclosure . . . whether it was actually possible to make [the inherently disclosed product] before the critical date of the [patent in suit] is irrelevant;" the prior art reference is anticipatory "if it discloses in an enabling manner the production of [the inherently disclosed product]"); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1321 (Fed. Cir. 2004) ("Simply put, the fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.").

(a) The '337 Patent

Anticipation Under Section 102(b) By The Burke '991 Patent

226. The asserted claims of the '337 patent, claims 1-6, 9, and 10, are anticipated under 35 U.S.C. §102(b) by United States Patent Number 5,215,991. The '991 patent was issued and publicly available on June 1, 1993, which is more than one year before July 14, 2000, which is the earliest possible priority date for the '337 patent.

227. As discussed in the findings of fact, there is clear and convincing evidence that the '991 patent discloses each and every element of the asserted claims of the '337 patent, either explicitly or inherently. Notably, all of the preferred substances identified in the '991 patent qualify as an SEC within the meaning of the '337 patent claims by virtue of the named inventor's own testimony and admissions, as well as Allergan's representations to the PTO during the prosecution of the CIP. At least three including CMC, povidone and PVA, and possibly as many as all six of these compounds, are inherently SECs. The '337 patent itself unambiguously describes CMC, which is disclosed in the '991 patent, as "an SEC." Moreover,

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in a particular composition, such that Alcon's proposed product would infringe the claims of the '337 patent, then the Burke '991 patent would anticipate those same claims under the doctrine that "that which infringes if later, anticipates if earlier."

Anticipation Under Section 102(b) by the Public Use and Sale of Alphagan

228. Asserted claims 1-6, 9, and 10 of the '337 patent are anticipated under 35 U.S.C. §102(b) by the public use and sale of Allergan's Alphagan product. That

product was publicly used and sold well more than one year prior to July 14, 2000. The Product Insert dated October 1998, and a formulation sheet of that product, establish the composition of that product.

229. There is clear and convincing evidence that the Alphagan product meets all of the limitations of the asserted claims. First, it is "[a] therapeutically effective ophthalmic composition," as referenced in the 2000 version of the Physician's Desk Reference (ALC60142-44) and in an October 1998 product insert that states, "Alphagan has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters."

230. Next, Alphagan contains 0.2% brimonidine tartrate, which is an "alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered." Again, this is reflected in the 1998 Product Insert, which states, "Alphagan® (brimonidine tartrate ophthalmic solution) 0.2% is a relatively selective alpha-2-adrenergic agonist for ophthalmic use," and the formulation sheet for Alphagan indicating that it contains "Brimonidine Tartrate (0.20)" at 0.20 %w/v (AGN0061393). Claim 2 requires that the agonist belong to the group "imidazolines," and brimonidine tartrate belongs to the group. Claim 3 requires that the composition "include a quinoxaline component," and brimonidine tartrate does include such a chemical group, and indeed is a quinoxaline or quinoxaline derivative, as required by Claim 4.

231. Alphagan also contains 1.4% polyvinyl alcohol ("PVA"), as disclosed in the product insert, which states ("Each mL of ALPHAGAN Solution

contains: . . . INACTIVES: polyvinyl alcohol") and in the formulation document AGN0061393 (listing formulation for "Original Alphagan®" and indicating that it contains "Polyvinyl Alcohol 20-90 Grade (1.4)" at %w/v). PVA is not a cyclodextrin.

232. As discussed above, there is clear and convincing evidence that PVA is an SEC. This includes clear and convincing evidence that the 1.4% PVA in Alphagan increased the equilibrium solubility of brimonidine tartrate in that very composition. To the extent that the claims include as "SECs" substances that increase the equilibrium solubility of an alpha-2-adrenergic agonist generally in a solution compared to the same solution without the putative SEC, regardless of whether all of the agonist used is soluble without the putative SEC, then there is clear and convincing evidence that 1.4% PVA is such an SEC, and so functions in Alphagan, and indeed is "a solubility enhancing component other than a cyclodextrin in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relataive [sic: relative] to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component." (claims 1-4, 9).

233. Furthermore, in the '924 CIP PVA is disclosed as a "preferred SEC". Although, Allergan did not call PVA an SEC until it was disclosed in the '924 CIP, the compound possessed all the same inherent properties both before and after Allergan labeled it an SEC in the '924 CIP.

234. Thus, for all of these reasons, individually and together, PVA has the same effect in the prior art Alphagan formulations that CMC is purported to have had on the brimonidine solutions disclosed in the '337 patent.

235. Claims 6 and 10 of the '337 patent further require that

> "the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component." (claims 6, 10)

236. The Court finds that a biological environment is composed of more than simply pH and Allergan has failed in its burden of proving infringement of claims 6 and 10. However, if the Court were to consider pH a surrogate for a biological environment, Alcon also takes the alternative position claims 6 and 10 are anticipated by Alphagan in which PVA acts as an SEC at the relevant pH.

237. a just a pH Failure of proof be/c biological environment is more than pH and pH alone not surragote – in the alternative Claims 9 and 10 of the '337 patent require a preservative. The Alphagan formulation includes the preservative benzalkonium chloride.

Anticipation Under Section 102(b) by the Publication of the Alphagan Product Insert

238. Asserted claims 1-6, 9, and 10 of the '337 patent are anticipated under 35 U.S.C. §102(b) by the publication of the Alphagan product insert. The Product Insert dated October 1998 was published well more than one year prior to July 14, 2000. The formulation sheet of that product establishes the composition of that product and also was published early enough to establish that formulation as prior art.

239. For the same reasons that the public use and sale of Allergan's Alphagan product anticipated the asserted claims of the '337 patent, the Product Insert

dated October 1998 was a publication that anticipated the asserted claims. As set forth above, that document sufficiently disclosed the composition of Alphagan, including the presence of PVA in the composition. That composition meets the limitations of the asserted claims in the manner explained above.

2. Obviousness

240. Under 35 U.S.C. § 103,

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art of which said subject matter pertains. .

241. Whether or not a patent claim is obvious over the prior art is a question of law. See Richardson-Vicks, Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir.1997); see also Karsten Mfg. Corp. v. Cleveland Golf Co., 242 F.3d 1376, 1384-85 (Fed Cir.2001). An invention is invalid if "the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 14 (1966). Obviousness cannot be based on "the hindsight combination of components selectively culled from the prior art to fit the parameters of the invention." ADT Corp. v. Lydall, Inc., 159 F.3d 534, 546 (Fed Cir.1998). The Supreme Court has set forth four factors relevant to determining obviousness: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) other secondary consideration. Graham, 383 U.S. at 17-18.

242. The test of obviousness is an objective one, referenced to the person of ordinary skill in the art rather than the specific inventor. The level of ordinary skill in the art is determined by evaluating a variety of factors, including: the sophistication of the technology, the types of problems encountered in the field, and the levels of education and experience of persons working in the field. See, e.g., Ruiz v. A.B. Chance Co., 234 F.3d 654 (Fed. Cir. 2000) at 666-67. Differences between the prior art and the claims at issue are then evaluated to determine whether the claimed invention would have been obvious to a person of ordinary skill in the art at the time of the invention. See, e.g., Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1342-45 (Fed. Cir. 2000).

243. In addition to such inquiries as the scope and content of the prior art, the level of ordinary skill in the art, and the differences between the claimed invention and the prior art, a court should consider certain "secondary considerations," or objective indicia, of non-obviousness. Id. These secondary considerations may include evidence of commercial success and evidence of copying. Id. The mere presence of a particular secondary consideration does not mean that it is relevant to non-obviousness, however, because the secondary consideration must serve as an objective indicia of the non-obviousness of the claimed invention in order to be relevant. For example, relevancy requires that a nexus exist between the claimed invention and the secondary consideration. In re Huang, 100 F.3d 135, 140 (Fed. Cir. 1996).

244. Commercial success may be relevant to non-obviousness "only if there is proof that the sales were a direct result of unique characteristics of the claimed invention -- as opposed to other economic and commercial factors unrelated to the quality

of the patented subject matter." Id. Thus, when a party has the right to exclude others from selling a drug, either because of patent protection or marketing exclusivity granted by the FDA, commercial success of the product is not evidence of non-obviousness. See Merck & Co., Inc. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1376 (Fed. Cir. 2005) (In a case brought under the Hatch-Waxman Act, the Federal Circuit found that because market entry was precluded by others due to patent protection and FDA marketing exclusivity, the rationale of commercial success as a secondary consideration of non-obviousness "has no force.").

(a) The '337 Patent

245. The level of ordinary skill in this art, to which the '337 patent is directed, would be someone with a degree in pharmaceutical chemistry or pharmacology or related fields, and several years of experience formulating drug compositions, especially liquid compositions.

246. The asserted claims of the '337 patent are "composition" claims, which means that the claims are to compositions or mixtures having certain properties and ingredients. In particular, the compositions claimed in the '337 patent must be therapeutically effective, must contain at least an alpha-2-adrenergic agonist component, and must contain a component that has the effect of increasing the solubility of the alpha-2-adrenergic agonist in the composition. That last component, denominated by Allergan as a "solubility enhancing component," may have other properties such as increasing the viscosity of the composition. There is no requirement that the putative SEC be included in the composition for the express purpose of enhancing solubility, only that it have that

effect. For instance, the solubility enhancing component purportedly exemplified in the specification of the '337 patent, CMC, is a well-known viscosity agent.

247. The preparation of a therapeutically effective ophthalmic composition that contains an alpha-2-adrenergic agonist (in the required amount) and a substance that the inventors of the '337 patent would call a "solubility enhancing component" would have been obvious to one of ordinary skill in the art at the time of the claimed invention. The reason for this is that brimonidine tartrate and other alpha-2-adrenergic agonist compounds were well known to have desirable ophthalmic properties, and as a result many ophthalmic compositions containing those APIs were prepared and disclosed. In addition, it was well known that because watery (i.e., very low viscosity) ophthalmic solutions would likely wash out of the eye before the optimal delivery of the API to the target tissue, it was important for ophthalmic solutions to include components that would make them easier to dispense and apply, and more effective in delivering the API to the site of action in the eye. One of the most common approaches to address this need was to include "viscosity-enhancing agents" in ophthalmic solutions. As a result, it was routine to include such agents in the formulation of ophthalmic solutions.

248. For these reasons, it would have been obvious to one of ordinary skill in the art who was formulating an ophthalmic solution that contained an alpha-2-adrenergic agonist component, to also include a viscosity-enhancing agent. Viscosity agents known in the relevant prior art included: PVA, which was contained in Allergan's prior art product marketed under the trade name Alphagan (discussed above), and in Alcon's generic version thereof; CMC, which Allergan uses in its 0.15% product; and

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these or other viscosity-enhancing agents disclosed in the prior art meet the requirements for "solubility-enhancing components," it would have been obvious to make a composition that met all of the limitations of the asserted claims of the '337 patent.

Obviousness in View of the Burke '991 Patent

249. The asserted claims of the '337 patent are obvious, for example, over the Burke '991 patent, which is discussed above. That patent discloses ophthalmic compositions containing brimonidine tartrate and administered to animals to reduce their intraocular pressure (IOP). The Burke '991 patent teaches that the ophthalmic preparations such as "ocular drops" were "preferred because of ease of application, ease of dose delivery," among other reasons. Moreover, the patent teaches the inclusion of "polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, polaoxamers, carboxymethyl cellulose, hydroxyethyl cellulose." ('991 patent, col. 5, ll30-33). Although the Burke '991 patent does not refer to these compounds as "solubility enhancing components," that is irrelevant to the obviousness inquiry. The patent unambiguously teaches the inclusion of those well-known components in the ophthalmic preparations, and in amounts (0-40% w/v) at which they would have their putative solubility-enhancing effect. The Burke '991 patent also teaches the use of preservatives in such compositions, as discussed above. One of ordinary skill in the art would find the claimed invention of the '337 patent obvious in view of the Burke '991 patent.

250. Allergan asserts that during prosecution of the '337 patent, it overcame an obviousness rejection over the Burke '991 patent, particularly in view of the Remington reference, which disclosed the use of CMC "as a suspending agent or viscosity-increasing agent." (Prosecution History, at AGN0221882). In response to the

rejection, Allergan submitted an affidavit by the first named inventor of the '337 patent, Dr. Olejnik, and a response in support of allowance. Allergan stated that the components expressly disclosed in the Burke '337 patent "all will function to increase viscosity of a liquid aqueous composition." (AGN 0221898). This, of course, supports my conclusion that these substances would have been used as viscosity-enhancing agents. Moreover, Allergan overcame the objection by underscoring that CMC is both an SEC and mucoadhesive; that is irrelevant to the obviousness inquiry before the Court, because the claims only require one property – solubility enhancement.

251. The Patent Examiner also stated that the Burke '991 patent did not disclose the use of carboxymethylcellulose (CMC) in the composition (AGN221882), and therefore required the combination of Burke with the Remington reference in order to render the proposed claims obvious. The Burke '991 patent did, however, expressly include carboxymethyl cellulose in the list of vehicles, so that it is not necessary to combine Burke with Remington in order to disclose the use of CMC in combination with brimonidine tartrate. The Examiner was correct, however, that Remington does disclose the use of CMC as a viscosity-increasing agent, or for other purposes in the preparation of ophthalmic compositions, and therefore the combination of Burke together with Remington also renders the asserted claims of the '991 patent obvious.

Obviousness In Light of the '991 Patent Combined With Other References

252. A person of ordinary skill would have found the claims of the '337 patent to have been obvious in view of the Burke '991 patent standing alone. The claims would also have been obvious in view of the Burke '991 patent in combination with other

references that disclosed the properties and uses of various agents that the '337 patent characterizes as SECs. The reason these additives would have been included in the formulations is irrelevant, so long as the resulting compositions met the limitations of the '337 patent claims. A person of ordinary skill, working to formulate therapeutically effective ophthalmic solutions, and armed with the Burke '991 patent, would have read about the properties of the various "vehicles" that Burke advised should be included in his disclosed formulations. Many of these references would have made clear additional reasons for using the recommended vehicles, as well as recommended ranges. Thus, the motivation to combine arises from the formulator's need to read about properties about the recommended components, to ensure, for example, that they do not present a known interaction with the therapeutive effectiveness of the API, or some other formulation problem.

253. The references that may be combined with the Burke '991 patent include J.L. Greaves, O. Olejnik, and C.G. Wilson, 1992, Polymers and the precorneal tear film, S.T.P. Pharma Sciences, 2:13-33, which teaches about the desirability of including polymers in ophthalmic formulations generally, and PVA, hydroxypropylmethylcellulose, and hydroxyethyl cellulose more specifically:

> "Polymers are incorporated into ophthalmic drug delivery preparations in order to increase the residence time on the ocular surface and thereby increase drug bioavailability." (p.13)
>
> "Traditional dosage forms for delivery of drugs and tear deficiency preparations to the eye have been and remain, solutions and ointments. Several approaches have been used which aim to improve the precorneal residence time and enhance corneal penetration. Increasing the viscosity of solutions by using polymers such as polyvinyl alcohol (PVA), or hydroxypropylmethylcellulose (HPMC) is known to increase residence time and drug bioavailability." (p. 13)

254. In the section entitled "Polymer solutions," with the subheadings dedicated to Hydroxypropylmethylcellulose (HPMC), Hydroxyethylcellulose (HEC), Polyvinyl alcohol (PVA), and Sodium hyaluronate (at 17-18), the reference states:

> "Polyvinyl alcohol was introduced into ophthalmic preparations in the early 1960s and was reported to have a superior corneal contact time based on animal studies. PVA can lower the surface tension of water, reduce interfacial tension at an oil/water interface and enhance tear film stability. This film-forming property together with ease of sterilization, compatibility with a range of ophthalmic drugs and an apparent lack of epithelial toxicity has lead to the widespread use of PVA as a drug delivery vehicle and artificial tear preparation." (p.18)

255. The claims do not require that the "solubility enhancing component" be included in the composition for a particular reason, such as enhancing the solubility of the alpha-2-adrenergic component. The only requirement is that the claimed composition contain a component that has that claimed effect – regardless of the purpose for which it was included. Even if, however, there were such a requirement, there were still numerous disclosures in the prior art that the "vehicles" identified in the Burke '991 article could act to increase the solubility of an API, and one of ordinary skill in the art would have expected that the components had those properties. For example, a BASF August 1993 brochure indicated that Kollidon (povidone), "can be used in . . topical solutions to improve the solubility of active substances," (p. 113) and more particularly, that the ability povidone "to increase[s] the solubility of active substances is just as useful in eye drops," noting as well the "film-forming and viscosity-increasing effects" of those products that make them particularly useful in "ophthalmic solutions." (p. 116) (Kollidon: Polyvinylpyrrolidone for the pharmaceutical industry brochure). Similarly, the Handbook of Pharmaceutical Excipients, 1994, 2d ed. (A. Wade & P. Weller, eds),

The Pharmaceutical Press, London notes that "The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone" (at 392) and that "[p]oloxamers are . . .used primarily in pharmaceutical formulations as emulsifying or solubilizing agents." (at 386).

256. The Burke '991 patent could be combined with any of these references to render the '337 patent claims obvious. The motivation to combine the references is found in the Burke patent itself, which teaches the use of those components within the formulation; it would be routine for one who is preparing a formulation to read the standard and readily available references that describe the uses and property of those components before including them in an actual formulation.

257. A number of other references may also be combined with each other or the Burke '991 patent to render the '337 claims obvious. These include United States Patent No. 5,091,528, which teaches a brimonidine formulation that includes either CMC or carbopol (col. 6, lines 24-26); United States Patent No. 5,776,445, which teaches apraclonidine and related imidazolines together with metal alginates, which the '337 patent states to be SECs, and United States Patent No. 5,834,470, which discloses the combination of alpha-2-adrenergic agonists with celluloses and povidone. Additional references that could be combined with the '991 patent include United States Patent No. 5,663,205, which relates to glaucoma drugs, and which teaches the use of povidone in order to stabilize the solution, and United States Patent No. 5,212,196, which discloses clonidine derivatives that contain either CMC or carbopol. This body of patents, in whole or in part, would be used by someone researching appropriate components for ophthalmic formulations.

(b) The '834 Patent

258. A person of ordinary skill in this art, to which the '834 patent is directed, would be a clinician with an advanced degree in medicine, pharmaceutical chemistry, pharmacology or optometry, with several years or more experience in evaluating and selecting pharmaceutical therapies for the treatment of glaucoma or elevated intraocular pressure.

259. Alcon asserts that the asserted claims of the '834 patent are obvious over prior art including an article by Derrick, an article by Small and/or U.S. Patent number 5,021,410.

260. The claims of the '834 patent are to therapeutically effective aqueous ophthalmic compositions of up to about 0.15% w/v brimonidine tartrate, having a pH of about 7.0 or greater, where the brimonidine tartrate is soluble at about 21°C .

261. Because nearly all ophthalmic drugs used treat glaucoma are soluble at room temperature, it would have been obvious to an ordinarily skilled artisan that the ingredients should be soluble at or about 21°C, which is room temperature.

Derick Article

262. The Derick article was available to one of ordinary skill in the art at the time of the alleged invention claimed in the '834 patent. From the results of the Derick article, it would have been obvious to one of skill in the art that a composition containing 0.15% brimonidine tartrate would likely be more effective than the 0.08%

composition. Since the pH of the eye is about 7.0-7.4, it would have been obvious to make a 0.15% composition at a pH of about 7 or greater.

263. The 0.08% and the 0.2% products are the closest prior art to the asserted claims – the 0.08% product being closest to claim 1 and 10 ("up to about 0.15%") and claims 2 and 11 ("up to 0.15%"), and the 0.2% product being closest to claims 3 and 12 ("about 0.15%") and 4 and 13 ("includes 0.15%").

264. These prior art products, together with the other cited references and the background knowledge of one of ordinary skill in the art render all of the claimed compositions obvious.

The Small Articles and Chien

265. A person of ordinary skill in the art would also find the asserted claims of the '834 patent to be obvious in view of the Small reference, which teaches that increasing pH could compensate for losses in efficacy attributable to lower concentrations of a compound such as brimonidine. The same teachings from the second Small article, or Chien, would have similarly rendered the asserted claims of the '834 patent obvious.

The '410 Patent

266. United States Patent No. 5,021,410 (the "'410 Patent") discloses general formulations that include an "alpha 2 adrenergic agonist," a "preservative," and a "pH adjuster." (Table I) As explained in the Findings of Fact, the '410 patent teaches the

use of compositions with concentrations of brimonidine virtually identical to 0.15% brimonidine tartrate; the use of pH adjusters to reach a pH of 4.5-7.5; and the use of preservatives.

267. It would therefore have been obvious to one of ordinary skill in the art to prepare the compositions claimed in the '834 patent based on the disclosure of the '410 patent alone, or in combination with such common knowledge as the desirability of using a pH of 7.0 or 7.5 in an ophthalmic composition.

(c) Secondary Considerations

268. There are no surprising or unexpected results, and there has been no evidence of commercial success or any other secondary considerations of obviousness attributable to the inventions claimed in the '834 patent. Accordingly, the overall calculus required under section 103 leads to the conclusion that the asserted claims of the '834 patent are invalid as obvious over the prior art discussed in the foregoing paragraphs.

3. Written Description

269. The written description requirement of 35 U.S.C. § 112 states that "The specification shall contain a written description of the invention, and of the manner and process of making and using it . . ." "The United States Supreme Court [has] acknowledged written description as a statutory requirement distinct not only from the best mode requirement but also from enablement." Univ. of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 921 (Fed. Cir. 2004) (citing Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 736 (2002)).

270. "The policy behind the written description requirement is to prevent overreaching and *post hoc* claims that were not part of the original invention." Purdue Pharma, L.P. v. F.H. Faulding & Co., 48 F. Supp. 2d 420, 427 (D. Del. 1999), aff'd, 230 F.3d 1320 (Fed. Cir. 2000); see also, Univ. of Rochester, 358 F.3d at 920, quoting Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345 (Fed. Cir. 2000) (noting that the written description requirement is designed to "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification"); Lizardtech, Inc. v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005) (finding inadequate written description where a person of skill in the art would not have been convinced that the inventors where in possession of the claimed invention).

271. To satisfy the written description requirement, the disclosure does not have to provide *in haec verba* support for the claimed subject matter, but it must "convey with reasonable clarity to those skilled in the art that the inventor was in possession of the claimed invention" as of the priority date. Purdue Pharma L.P., 230 F.3d at 1323 (emphasis added).

272. In other words, "one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." Id. (emphasis added); see also Regents of the Univ. of California v. Eli Lilly & Co., 119 F.3d 1559, 1566 (Fed. Cir. 1997) (quoting Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997)) (an invention must be described "in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention'."). The Federal Circuit illustrated the issue by noting that:

> [O]ne cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.

Purdue Pharma L.P., 230 F.3d at 1326-27 (emphasis added).

(a) The '834 Patent

273. Because compliance with the written description requirement must be analyzed with reference to the priority date of the claimed invention, the materials that may be examined include the common specification, and the originally filed claims of the application that matured into the '834 patent. The Court cannot look to the claims that were ultimately issued in order to determine whether that claimed invention was disclosed.

274. The invention claimed in the '834 patent requires the presence of a specified concentration of active ingredient, namely, 0.15%, or up to, about, or up to about that concentration. There is simply nothing in the common specification or the originally filed claims of the '834 patent to suggest to one of ordinary skill in the art that the inventors considered their invention to be limited in any way to a particular concentration, approximate concentration, or maximum concentration of any adrenergic agonist, and in particular there is no suggestion that such concentration would be 0.15%. The issued claim appears unrelated to the specification and originally filed claims, which called for compositions containing a solubility enhancing component and/or an oxy-chloro preservative. See Univ. of Rochester, 358 F.3d at 927; Purdue Pharma L.P., 230 F.3d at 1326-27.

275. The Court finds that there is no evidence in the original disclosure that the named inventors had possession of any invention involving the 0.15%

concentration limitation at the time the provisional application was filed in July 2000. Since each of the asserted claims of the '834 patent contain such a limitation, they are each invalid and the patent fails to satisfy the written description requirement of 35 U.S.C. § 112

276. The Court also finds that the '834 patent is invalid pursuant to 35 U.S.C. § 102(f) because neither of the named inventors, Olejnik and Kerslake, invented the claimed subject matter.

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Dated: January 17, 2006