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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

TAB 12

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

I. PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW RELEVANT TO INFRINGEMENT

A. The Parties and the Background Technology

1. This is a patent infringement suit in which plaintiffs Allergan, Inc. and Allergan Sales, LLC (collectively "Allergan") charged defendants Alcon, Inc., Alcon Laboratories, Inc., and Alcon Research, Ltd. (collectively "Alcon") with infringing two United States Patents. The patents-in-suit are United States Patent Nos. 6,641,834 ("the '834 patent"), and 6,673,337 ("the '337 patent"). 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. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 1.]

2. 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. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 2.]

3. Defendant Alcon Laboratories, Inc. is a corporation organized and existing under the laws of the State of Delaware and has a its principal place of business at 6201 South Freeway, Forth Worth, Texas. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 3.]

4. 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. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 4.]

5. 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, Ltd. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 5.]

6. Allergan brought suit against Alcon on August 24, 2004, for patent infringement under the laws of the United States, specifically, 35 U.S.C. § 271(e)(2). [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 26.]

7. Jurisdiction and venue in this Court are proper. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 27.]

8. Allergan, Inc. is the owner of the '834 and '337 patents. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 16.]

9. The claims of both patents-in-suit are directed to therapeutically effective ophthalmic compositions containing alpha-2-adrenergic agonists. ['834 patent, Col. 16, l. 45 to Col. 18, l. 22, and '337 patent, Col. 16, l. 41 to Col. 18, l. 6.]

10. Brimonidine tartrate (5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate) is an alpha-2-adrenergic agonist. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 25.] (The terms "brimonidine" and "brimonidine tartrate" are used interchangeably throughout this document unless specifically noted.)

11. Open-angle glaucoma is an incurable disease of the eye that causes gradual vision loss and can lead to blindness. Almost 70 million people worldwide suffer from glaucoma, which is the second leading cause of blindness worldwide. Allergan is a leader in the development of pharmaceutical treatments for glaucoma, investing millions of dollars annually in research and development.

12. Although there is no cure, there are various pharmaceutical and surgical treatments that may slow the progression of glaucoma. One of these treatments is to lower the pressure of the fluid in the eye, known as intra-ocular pressure ("IOP"). Scientists and medical personnel believe that the elevated IOP found in glaucoma patients contributes to the gradual retinal deterioration and loss of vision that are characteristics of the disease.

13. Topically-applied brimonidine assists in the lowering of IOP. The drug was originally used to treat high blood pressure, but in the early 1990's, Allergan scientists

discovered that it was also a powerful medication for lowering IOP. After investing millions of dollars to prove the safety and efficacy of the drug, Allergan received approval from the FDA and launched the drug in 1996 under the tradename Alphagan®. Alphagan® was a 0.2% formulation of brimonidine at a pH range of 6.3-6.5. After the expiration of Allergan's statutory exclusivity period, Alcon launched a generic version of Alphagan®, which Alcon sells to this very day.

14. Although brimonidine is very effective at treating glaucoma, it can cause significant side effects, including allergic conjunctivitis.

B. The Development of the Inventions Claimed in the Patents

15. Because of the significant side effects that can be caused by brimonidine, beginning in late 1996, Allergan set out to design an improved brimonidine product.

16. During the course of its research and development, Allergan tested numerous possible formulations of brimonidine.

17. Because of the observed side effects of Alphagan®, researchers recognized that it would be advantageous to formulate the drug with a lower concentration of brimonidine. However, simply lowering the concentration of brimonidine in the same formulation was not an option, as this would be expected to reduce the drug's efficacy.

18. Allergan scientists discovered that it was possible to use a lower concentration of brimonidine tartrate and maintain effectiveness ***if*** the pH of the formulation was elevated above 7.0. These higher pHs are closer to the pKa of brimonidine tartrate, a point at which the brimonidine is substantially un-ionized, allowing it to diffuse better across the lipid membranes of the eye, thus making the drug more bioavailable.

19. The fact that Allergan scientists were able to formulate a drug with a lower concentration of brimonidine at a pH of greater than about 7.0 was unexpected based on the solubility characteristics of brimonidine. The solubility of brimonidine significantly decreases at pH values above 7.

20. Allergan scientists also discovered that certain compounds could be used to assist in increasing the solubility of brimonidine. These compounds were referred to as solubility enhancing components ("SECs").

21. The use of an SEC assists in preparing formulations with higher pH values because it increases the solubility of brimonidine as compared to a formulation prepared without the SEC.

22. The patents at issue in this case are United States Patent No. 6,641,834, entitled "Compositions Containing Alpha-2-Adrenergic Agonist Components" issued on November 4, 2003, to Orest Olejnik and Edward Kerslake; and United States Patent No. 6,637,337 entitled "Compositions Containing Alpha-2-Adrenergic Agonist Components" issued on January 6, 2004, to Orest Olejnik and Edward Kerslake.

23. Both the '834 and the '337 patents claim priority to and are continuation applications of United States Patent Application No. 09/904,018, filed July 10, 2001, which claims priority to provisional application 60/218,200, filed on July 14, 2000. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 17.]

C. Alphagan® P

24. The result of Allergan's development efforts was Alphagan® P, which contains a target concentration of 0.15% brimonidine, a twenty-five percent reduction in target concentration over the original Alphagan® product, and a target pH of 7.2, which is 0.8 pH units higher than the target pH in the original Alphagan® product.

25. The "P" in Alphagan® P stands for Purite, the preservative used in Alphagan® P. The original Alphagan® product used benzalkonium chloride ("BAK") as its preservative.

26. Alphagan® P was shown in clinical studies to have comparable efficacy to Alphagan®, but with a better safety profile including forty percent reduction in allergy rate.

27. On June 29, 2000, Allergan filed NDA 21-262 on its Alphagan® P formulation.

28. On July 14, 2000, Allergan filed two provisional patent applications directed to the several inventions that had been discovered during the development of Alphagan® P.

29. Allergan was awarded a three-year market exclusivity period by the FDA for Alphagan® P, above and beyond that which Allergan had received for Alphagan®. The FDA granted this exclusivity when it approved Allergan's New Drug Application ("NDA") for Alphagan® P on March 16, 2001. The FDA later awarded Alphagan® P an additional six months of exclusivity for the pediatric studies conducted by Allergan.

30. Alphagan® P is manufactured according to the following target formulation:

REDACTED

[AGN0000311]

31. Pursuant to FDA requirements, the amounts of each ingredient, as well as the pH, may vary with certain parameters even further when on the shelf. Accordingly,

REDACTED

REDACTED

[AGN0000311]

D. Alphagan® P 0.1%

32. Even after Allergan filed its NDA application for Alphagan® P, it continued to research further improvements in the formulation.

33. Continuing to use a solubility enhancing component, in particular, carboxymethylcellulose ("CMC"), Allergan scientists were able to further raise the pH of the formulation and further lower the concentration while maintaining efficacy.

34. On May 27, 2004, Allergan filed NDA 21-770, directed to a drug formulation with a target brimonidine tartrate concentration of 0.1% and a target pH of 7.7.

35. The FDA approved NDA 21-770 on August 19, 2005.

E. Alcon's Proposed Brimonidine PQ Product

36. In April of 2001, shortly after Allergan obtained marketing approval for Alphagan® P, Alcon began work on a generic formulation of Alphagan® P based on information obtained by deformulating (reverse engineering) Alphagan® P, a Freedom Of Information Act request, and the FDA's Summary Basis of Approval.

37. From the beginning,

REDACTED [ALC50091]

38. The reason Alcon wanted to do this was simple—money.

REDACTED [ALC50092]

39.

REDACTED

[ALC59296-305]

40. On April 27, 2004, Alcon filed an application, NDA 21-764, pursuant to 21 U.S.C. § 505(b)(2), with the Food and Drug Administration for approval to market a generic version of Alphagan® P. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶ 10.]

41. Alcon filed an NDA under section 505(b)(2) rather than an ANDA under section 505(j).

42. Alcon's proposed product is named Brimonidine PQ, with the "PQ" standing for Polyquad, the preservative in the proposed product. The proposed product has the same active ingredient as Alphagan® P and shares eight of Alphagan® P's ten additional excipients. [ALC50139]

43. Moreover, Brimonidine PQ has the same dosage form, route of administration, dosing regimen, and indication as Alphagan® P.

REDACTED

44. Povidone is listed as a solubility enhancing component in the '337 patent.

45. Alcon has stated to the FDA that it intends to manufacture Brimonidine PQ with the following target formulation:

REDACTED

[ALC02638]

46. Pursuant to FDA requirements, the amounts of each ingredient in Alcon's proposed Brimonidine PQ, as well as the pH, may vary with certain parameters even further when on the shelf.

REDACTED

[ALC00189]

47. Because both the '834 patent and the '337 patent are listed in the Approved Drug Products with Therapeutic Equivalence Evaluations listing (more commonly referred to as the "Orange Book") as claiming aspects of Alphagan® P, on July 6, 2004, Alcon sent Allergan a letter as required by 21 U.S.C. § 355(b)(3)(B) and 21 C.F.R. 314.50(i)(1)(i)(A)(4) ("the Paragraph IV Certification") notifying Allergan of its § 505(b)(2) application. [Joint Pre-trial Order Ex. 1 (Statement of Uncontested Facts) ¶

23.] The letter also referenced the three additional patents that are listed in the Orange book as claiming an aspect of Alphagan® P: United States Patent Nos.: 5,424,078; 6,562,873; and 6,627,210. Allergan did not sue Alcon for infringement of these three patents.

48. Allergan filed suit on August 24, 2004, alleging that Alcon infringes both the '337 and '834 patents under 35 U.S.C. § 271(e)(2). Alcon has asserted a counterclaim for a declaratory judgment of patent invalidity. In its counterclaim, Alcon has raised the defenses of invalidity in view of the prior art on the basis of 35 U.S.C. § 102(b) and 103. Alcon has also alleged that the asserted claims of the '834 patent are invalid under 35 U.S.C. § 112 for violation of the written description and best mode requirements.

F. Alcon's Proposed Brimonidine PQ Formulation Infringes Both the '337 and '834 Patents.

1. Infringement of the '834 Patent

49. Allergan alleges that Alcon's proposed Brimonidine PQ product infringes claims 1-6, 10-14, 17-18, and 20 of the '834 patent.

50. Alcon's proposed Brimonidine PQ product contains up to about 0.15% (w/v) -bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, also known as brimonidine tartrate. REDACTED

[ALC00189]

51. REDACTED

[ALC00189]

52. The pH of Alcon's proposed Brimonidine PQ product is greater than about 7.0.

53. Alcon's application lists the drug's storage temperature range as 15-25°C.

54. Alcon indicated to the FDA that its proposed Brimonidine PQ product is an ophthalmic *solution*, and this is so indicated on the labeling.

55. The brimonidine tartrate in Alcon's proposed Brimonidine PQ product is soluble at 21° C.

56. Polyquad (Polyquaternium-1) is a preservative with a quaternary ammonium component.

2. Infringement of the '337 Patent

57. Allergan alleges that Alcon's proposed product infringes claims 1-4, 6, and 9-10 of the '337 patent.

58. Brimonidine tartrate is an alpha-2-adrenergic agonist.

59. Povidone ("PVP") is also known as polyvinylpyrrolidone.

60. Polyvinylpyrrolidone is identified in the specification of the '337 patent as an example of a compound that can be used as a solubility enhancing component ("SEC"). ['337 patent, col. 6, line 18 – col. 7, line 15.]

61.

REDACTED

[ALC00189]

62. The target brimonidine tartrate concentration for Alcon's proposed product is 0.15%.

REDACTED

[ALC00189]

63. The labeling for Alcon's proposed brimonidine product identifies the temperature range for storage of the product as 15-25° C.

64. In the pH range of 6.6 to 7.4, the solubility of brimonidine tartrate decreases as the pH of the formulation increases.

65. It is necessary for a pharmaceutical formulation to be robust enough to withstand the permissible variations in concentration, pH, and temperature and generally to withstand the conditions that the formulation will face in normal use. It must be

formulated to ensure that the brimondine tartrate will not fall out of solution (i.e., precipitate) during the product's life. As a result, a commercial product cannot be formulated too close to the solubility limits established under controlled laboratory conditions.

66. In the absence of an SEC, there are concentrations of brimonidine tartrate that fall within the specification for Alcon's proposed Brimonidine PQ product that are not fully soluble at pH values of 7.3 and 7.4. This is illustrated in Figure 1 of the '337 patent as well as in the solubility testing performed by Dr. Clive Wilson and Hardik Shah.

67. Alcon's proposed Brimonidine PQ product requires an SEC to maintain the solubility of brimonidine tartrate in the formulation over the range of expected conditions during the product's life. Alcon's proposed Brimonidine PQ product relies upon the increased solubility of brimonidine resulting from povidone's presence in the formulation.

68. The povidone in Alcon's proposed product is an SEC other than a cyclodextrin, present 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.

G. Conclusions of Law

69. This matter arises under the patent laws of the United States of America, United States Code, Title 35, Section 1 *et seq.*

70. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338.

71. Venue is proper in this Court under 28 U.S.C. §§ 1391 and 1400(b).

72. A determination of infringement requires a two-step analysis. The court must determine (1) "the scope and meaning of the patent claims asserted," and (2) how "the

properly construed claims ... compare[ ] to the allegedly infringing device." *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed.Cir.1998) (en banc). An infringement inquiry under 35 U.S.C. § 271(e)(2)(A) requires a comparison of the claims of the asserted patent against the product that is likely to be sold following FDA approval. *See Abbott Labs. V. Torpharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002)(noting that the application's specifications defining the proposed generic product ordinarily control the infringement inquiry).

1. '834 Patent

73. The Court held a Markman hearing on June 28, 2005. As to the '834 patent, the parties only requested that the Court construe the claim term "about." On July 26, 2005, the Court construed the term "about" as used in claims 1, 3, 10, and 12 in accordance with its ordinary meaning to mean "approximately."

74. As set forth in the claim chart below, after comparing the construed claim to Alcon's proposed product, the Court finds that Alcon's proposed product infringes each of the asserted claims of the '834 patent.

Asserted Claim	Claim Construction	Infringement Analysis
Claim 1		
1. A therapeutically effective aqueous ophthalmic composition comprising:	The claim requires a therapeutically effective ophthalmic composition, and the term "therapeutically effective" is used in its ordinary sense.	Alcon's proposed brimonidine product is a therapeutically effective ophthalmic composition. Alcon formulated it with the intention of making it therapeutically equivalent to Alphagan® P. [*See, e.g.*, NDA 21-764 – ALC00169]
up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate,	The claimed composition contains up to approximately 0.15% (w/v) brimondine tartrate.	Alcon's proposed brimondine product contains up to approximately 0.15% (w/v) brimonidine tartrate. [*See, e.g.*, ALC00169]
the composition having a pH of about 7.0 or greater,	The claimed composition has a pH of approximately 7.0 or greater.	REDACTED [*See, e.g.*, ALC00169]
and the 5-bromo-6-(2-	The brimonidine	The brimonidine tartrate in Alcon's

Asserted Claim	Claim Construction	Infringement Analysis
imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21° C.	tartrate must be soluble in the composition at approximately 21° C.	proposed brimonidine product is soluble in the composition at approximately 21° C. [*See, e.g.*, ALC00169; ALC00093; Ryan Deposition Tr. at 87:6-13]
Claim 2		
2. The composition of claim 1 which includes up to 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.	Claim 2 includes all the limitations of claim 1, with the additional requirement that the composition must include up to 0.15% (w/v) brimonidine tartrate.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, Alcon's proposed brimonidine product contains up to 0.15% (w/v) brimonidine tartrate. [*See, e.g.*, ALC00169]
Claim 3		
3. The composition of claim 1 which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.	Claim 3 includes all the limitations of claim 1, with the additional requirement that the composition must include approximately 0.15% brimonidine tartrate.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, Alcon's proposed brimonidine product contains approximately 0.15% (w/v) brimonidine tartrate. [*See, e.g.*, ALC00169]
Claim 4		
4. The composition of claim 1 which included 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.	Claim 4 includes all the limitations of claim 1, with the additional requirement that the composition must include 0.15% (w/v) brimonidine tartrate.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, Alcon's proposed brimonidine product contains 0.15% (w/v) brimonidine tartrate. [*See, e.g.*, ALC00169]
Claim 5		
5. The composition of claim 1 having a pH of 7.0 or greater.	Claim 5 includes all the limitations of claim 1, with the additional requirement that the pH of the composition must be 7.0 or greater.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, Alcon's proposed brimonidine product has a pH of 7.0 or greater. REDACTED [*See, e.g.*, ALC00169]
Claim 6		
6. The composition of claim 1 which further comprises a	Claim 6 includes all the limitations of claim 1 and further requires that	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally,

Asserted Claim	Claim Construction	Infringement Analysis
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.	the composition must contain either an oxy-chloro or quaternary ammonium preservative in an amount effective to assist in preserving the composition.	Alcon's proposed brimonidine product contains Polyquad, which is a quaternary ammonium preservative. The Polyquad is present in an amount effective to assist in preserving the composition. [*See, e.g.*, ALC00169; ALC02071-73]
Claim 8		
8. The composition of claim 1 which is substantially free of anionic cellulosic derivatives.	Claim 8 includes all the limitations of claim 1 and further requires that the composition is substantially free of anionic cellulosic derivatives.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, the formulation of Alcon's proposed brimonidine product is substantially free of anionic cellulosic derivatives. Povidone is not an anionic cellulosic derivative. [*See, e.g.*, ALC00169]
Claim 9		
The composition of claim 1 which is substantially free of carboxymethyl cellulose.	Claim 9 includes all the limitations of claim 1 and further requires that the composition is substantially free of carboxymethyl cellulose.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, the formulation of Alcon's proposed brimonidine product is substantially free of carboxymethyl cellulose. [*See, e.g.*, ALC00169]
Claim 10		
10. A therapeutically effective aqueous ophthalmic composition comprising:	The claim requires a therapeutically effective ophthalmic composition, and the term "therapeutically effective" is used in its ordinary sense.	Alcon's proposed brimonidine product is a therapeutically effective ophthalmic composition. Alcon formulated it with the intention of making it therapeutically equivalent to Alphagan® P. [*See, e.g.*, ALC00169]
up to about 0.15% (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	The claimed composition contains up to approximately 0.15% (w/v) brimondine, salts of brimonidine, esters of brimonidine, or mixtures of the foregoing.	Alcon's proposed brimondine product contains up to approximately 0.15% (w/v) brimonidine tartrate, which falls within the category of brimondine, salts of brimonidine, esters of brimonidine, or mixtures of the foregoing.

Asserted Claim	Claim Construction	Infringement Analysis
5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof,		[*See, e.g.*, ALC00169]
the composition having a pH of about 7.0 or greater,	The claimed composition has a pH of approximately 7.0 or greater.	REDACTED [*See, e.g.*, ALC00169]
and the component being soluble in the composition at about 21° C.	The brimonidine tartrate must be soluble in the composition at approximately 21° C.	The brimonidine tartrate in Alcon's proposed brimonidine product is soluble in the composition at approximately 21° C. [*See, e.g.*, ALC00169; ALC00093; Ryan Deposition Tr. at 87:6-13]
Claim 11		
11. The composition of claim 10 which includes up to 0.15% (w/v) of the component.	Claim 11 includes all the limitations of claim 10, with the additional requirement that the composition must include up to 0.15% (w/v) of the component selected from the group described in claim 10.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 10. Additionally, Alcon's proposed brimonidine product contains up to 0.15% (w/v) of brimonidine tartrate, which is a component listed in the group described in claim 10. [*See, e.g.*, ALC00169]
Claim 12		
12. The composition of claim 10 which includes about 0.15% (w/v) of the component	Claim 12 includes all the limitations of claim 10, with the additional requirement that the composition must include approximately 0.15% (w/v) of the component selected from the group described in claim 10.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 10. Additionally, Alcon's proposed brimonidine product contains approximately 0.15% (w/v) of brimonidine tartrate, which is a component listed in the group described in claim 10. [*See, e.g.*, ALC00169]
Claim 13		
13. The composition of claim 10 which includes 0.15% (w/v) of the component	Claim 13 includes all the limitations of claim 10, with the additional requirement that the composition must	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 10. Additionally, Alcon's proposed brimonidine product contains 0.15%

Asserted Claim	Claim Construction	Infringement Analysis
	include 0.15% (w/v) of the component selected from the group described in claim 10.	(w/v) of brimonidine tartrate, which is a component listed in the group described in claim 10. [*See, e.g.*, ALC00169]
Claim 14		
14. The composition of claim 10 having a pH of 7.0 or greater.	Claim 14 includes all the limitations of claim 10, with the additional requirement that the pH of the composition must be 7.0 or greater.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 10. Additionally, Alcon's proposed brimonidine product has a pH of 7.0 or greater. [*See, e.g.*, ALC00169]
Claim 17		
17. The composition of claim 10 which is substantially free of anionic cellulosic derivatives.	Claim17 includes all the limitations of claim 10 and further requires that the composition is substantially free of anionic cellulosic derivatives.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 10. Additionally, the formulation of Alcon's proposed brimonidine product is substantially free of anionic cellulosic derivatives. Povidone is not an anionic cellulosic derivative. [*See, e.g.*, ALC00169]
Claim 18		
18. The composition of claim 10 which is substantially free of carboxymethyl cellulose.	Claim 18 includes all the limitations of claim 10 and further requires that the composition is substantially free of carboxymethyl cellulose.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 10. Additionally, the formulation of Alcon's proposed brimonidine product is substantially free of carboxymethyl cellulose. [*See, e.g.*, ALC00169]
Claim 20		
20. The composition of claim 10 which further comprises a preservative selected from the group consisting of an oxy-chloro component and	Claim 20 includes all the limitations of claim 10 and further requires that the composition must contain either an oxy-chloro or quaternary ammonium	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 10. Additionally, Alcon's proposed brimonidine product contains Polyquad, which is a quaternary ammonium preservative. The

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Asserted Claim	Claim Construction	Infringement Analysis
a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.	preservative in an amount effective to assist in preserving the composition.	Polyquad is present in an amount effective to assist in preserving the composition. [*See, e.g.*, ALC00169; ALC02071-73]

75. As is set forth in the claim chart above, because Alcon's proposed product meets each and every limitation of the asserted claims of the '834 patent, Alcon infringes the asserted claims of the '834 patent.

2. '337 Patent

76. The Court held a Markman hearing on June 28, 2005. The parties requested construction of the terms "solubility enhancing component" and "similar." The Court construed the term "solubility enhancing component" to mean "a component that enhances the solubility of the alpha-2-adrenergic agonist component other than a cyclodextrin." The Court construed the term "similar" to carry its ordinary and accustomed meaning.

77. As set forth in the claim chart below, after comparing the construed claims to Alcon's proposed product, the Court finds that Alcon's proposed product infringes each of the asserted claims of the '337 patent.

Asserted Claim	**Claim Construction Based on Parties' Joint Claim Chart and Court's Markman Order**	**Infringement Analysis**
Claim 1		
1. A therapeutically effective ophthalmic composition comprising:	The claim requires a therapeutically effective ophthalmic composition, and the term "therapeutically effective" is used in its ordinary sense.	Alcon's proposed brimonidine product is a therapeutically effective ophthalmic composition. Alcon formulated it with the intention of making it therapeutically equivalent to Alphagan® P. [*See, e.g.*, ALC00169]
an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic	The claimed composition must contain an alpha-2-adrenergic agonist	Alcon's proposed brimondine product contains brimonidine tartrate, which is an alpha-2-adrenergic agonist. The proposed product contains

benefit to a patient in whom the composition is administered; and	component in an amount that is effective to provide a therapeutic benefit to a patient.	approximately 0.15% brimonidine tartrate, and this amount has been shown to be effective to provide a therapeutic benefit to a patient. [*See, e.g.*, ALC00169; ALC420-21]
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.	The claimed composition contains a solubility enhancing component, which is a component that enhances the solubility of the alpha-2-adrenergic agonist component, and any solubility enhancing component other than a cylclodextrin is covered by the claim. The solubility enhancing component must be present in such an amount that the solubility of the alpha-2-adrenergic agonist component in the composition is increased relative to its solubility in a similar composition without the solubility enhancing component.	REDACTED, which is also known as polyvinylpyrrolidone. Povidone acts as a solubility enhancing component ("SEC") in Alcon's proposed brimonidine product. [*See, e.g.*, Stella Expert Report; ALC58425]
Claim 2		
2. The composition of claim 1 wherein the alpha-2-adrenegic component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof, and mixtures thereof.	Claim 2 contains all the limitations of claim 1, with the additional requirement that the alpha-2-adrenergic agonist component must be: an imino-imidazoline, imidazoline, imidazole, azepine, thiazine, oxazoline, guanidine, catecholamine, derivative of one of the foregoing, or a mixture of one of the foregoing.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, the alpha-2-adrenergic agonist in Alcon's proposed brimonidine product is brimonidine tartrate. Brimonidine tartrate is an imidazoline. [*See, e.g.*, Stella Expert Report; ALC00169]

Claim 3		
3. The composition of claim 1 wherein the therapeutically active component includes a quinoxaline component.	Claim 3 includes all the limitations of claim 1, with the further requirement that the composition must contain a quinoxaline component.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, the alpha-2-adrenergic agonist in Alcon's proposed brimonidine product is brimonidine tartrate. Brimonidine tartrate is a quinoxaline. [*See, e.g.*, Stella Expert Report; ALC00169]
Claim 4		
4. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.	Claim 4 includes all the limitations of claims 1 and 3, with the further requirement that the quinoxaline component must be a quinoxaline, a derivative of quinoxaline, or mixture of two or more of the foregoing.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally, the alpha-2-adrenergic agonist in Alcon's proposed brimonidine product is brimonidine tartrate. Brimonidine tartrate is a quinoxaline. [*See, e.g.*, Stella Expert Report; ALC00169]
Claim 6		
6. 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.	Claim 6 includes all the limitations of claim 1, with the further requirement that the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to its solubility in a similar composition without the solubility enhancing component.	REDACTED which is also known as polyvinylpyrrolidone. Povidone acts as a solubility enhancing component ("SEC") in Alcon's proposed brimonidine product. Additionally, the testing referred to in the Stella and Wilson reports was performed at pH values are representative of pH values within the biological environment of the cornea. The povidone in Alcon's proposed brimonidine product is effective to increase the solubility in a biological environment of brimonidine relative to its solubility in a similar composition without the povidone. [*See, e.g.*, Wilson Expert Report; Stella Expert Report; ALC58425]
Claim 9		
The composition of claim 1 which further comprises an effective	Claim 9 includes all the limitations of claim 1 with the further	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 1. Additionally,

amount of a preservative.	requirement that the composition must contain a component that assists in the preservation of the composition.	Alcon's proposed brimonidine product contains a Polyquad, which is a quaternary ammonium preservative. The Polyquad is present in an amount effective to assist in preserving the composition. [*See, e.g.*, Stella Expert Report; ALC00169; ALC02071-73]
Claim 10		
The composition of claim 6 which further comprises an effective amount of a preservative.	Claim 10 includes all the limitations of claim 6 with the further requirement that the composition must contain an effective amount of a component that assists in the preservation of the composition.	As set forth above, Alcon's proposed brimonidine product meets all the limitations of claim 6. Additionally, Alcon's proposed brimonidine product contains a Polyquad, which is a quaternary ammonium preservative. The Polyquad is present in an amount effective to assist in preserving the composition. [*See, e.g.*, Stella Expert Report; ALC00169; ALC02071-73]

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELEVANT TO VALIDITY

A. '834 Patent

78. Alcon has alleged that the asserted claims of the '834 patent are invalid for three reasons: (1) the asserted claims are obvious over various prior art references, either alone or in combination; (2) the asserted claims fail to comply with the written description requirement of 35 U.S.C. § 112; and (3) the '834 patent fails to comply with the best mode requirement of 35 U.S.C. § 112.

1. Obviousness

a. Background and applicable law

79. Alcon contends that the claims of the '834 patent fail to satisfy the requirements of 35 U.S.C. § 103(a).

80. One of Alcon's experts, Dr. Robin, opined that the '834 patent was obvious over an article by Derick, an article by Small and/or U.S. Patent Number 5,021,410.

81. Allergan maintains that the properly construed claims of the '834 patent were not obvious to one of ordinary skill in the art at the time the invention was made.

82. The claims of the '834 patent are generally directed to therapeutically effective aqueous ophthalmic compositions of up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, having a pH of about 7.0 or greater, where the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate is soluble in the composition at about 21°C. (See, e.g., claim 1 of the '834 patent.)

83. There is a strong presumption of validity and the burden of proof is on the accused infringer to prove invalidity by clear and convincing evidence. *Robotic Vision Sys., Inc. v. View Engineering, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999); *see also American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir. 1984)("[35 U.S.C.] § 282 creates a presumption that a patent is valid and imposes the burden of proving invalidity on the attacker. That burden is constant and never changes and is to convince the court of invalidity by clear evidence.")

84. A determination of obviousness is a legal determination based on four factual inquiries. The underlying factual inquiries must address: (1) the scope and content of the prior art references; (2) the differences between the claims and the prior art reference; (3) the level of ordinary skill in the art, and (4) secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Secondary considerations include commercial success, failure of others, long-felt need and unexpected results. *See Minnesota Mining and Manufacturing Co. v. Johnson & Johnson Orthopaedics*, 976 F.2d 1559, 1573 (Fed. Cir. 1992)(stating that these factors must be considered and are often "the most probative and cogent evidence in the record.")

85. An obviousness analysis requires a determination of whether there was some suggestion in the prior art to make the claimed composition, and whether the prior art would have revealed to one of ordinary skill in the art that there was a reasonable expectation of success in making the claimed invention. *See Boehringer Ingelheim*

Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1353 (Fed. Cir. 2003). Finding only that the prior art makes it "obvious to try" to create the claimed invention is not sufficient. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986)("The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumption of validity, as a whole." *Id.* at 1383 (internal citation omitted).).

86. Obviousness is analyzed from the perspective of one of skill in the art at the time the invention was made; the use of hindsight is not permitted. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051 (Fed. Cir. 1988) (noting that the district court misapplied the obviousness standard by impermissibly using hindsight to reconstruct the claimed invention from prior art with the invention before it and aided by the defendant's expert, rather than viewing the invention from the position of a person of ordinary skill at the time the invention was made).

87. When two or more references are cited as allegedly rendering a claim obvious, there must be a motivation to one of skill in the art to combine the references. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1578-79 (Fed.Cir.1997) ("[T]he record must provide a teaching, suggestion, or reason to substitute.... The absence of such a suggestion to combine is dispositive in an obviousness determination."); *see also SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988)(the defendant "cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention.").

b. Findings of Fact

Level of ordinary skill:

88. One of ordinary skill in the art of the '834 patent would be a person possessing a Bachelor's or PharmD Degree in Pharmacy, Pharmaceutical Sciences or related science disciplines, having three to five years of formulation experience, and

being supervised by a Ph.D. or someone with substantially longer formulation experience.

89. The person would likely be a member of a formulation development team that may include analytical chemists and related development scientists.

Scope and content of the prior art and differences from the claimed invention:

Derick reference:

90. The Derick article discusses an IOP-lowering study that was performed in the course of formulating the Alphagan® product. The investigators looked at the IOP lowering effect of three different brimonidine concentrations – 0.08%, 0.2% and 0.5%. The investigators concluded that "brimonidine 0.2% appears to be the appropriate concentration for further long-term studies."

91. The Derick article does not indicate the pH of the tested formulation; however, one of skill in the art would likely have been aware that the Derick article relates to trials on the Alphagan® product. Alphagan® has a pH of 6.3-6.5, and, if a person of skill were to make any assumptions about the pH of the formulation in Derick, it would likely be that they were within the pH range of Alphagan®.

92. One of skill in the art would have recognized that as the pH of a brimonidine solution increases, the solubility of the drug decreases resulting in the drug precipitating out of solution.

93. Because of solubility concerns, one of skill in the art would not have expected, based on the disclosure in the Derick article, that it would have been possible to formulate brimonidine tartrate above a pH of 7.0.

94. Furthermore, one of skill in the art would not have expected to be able to achieve a therapeutically effective formulation at a concentration below 0.2%.

95. The Derick article does not provide one of skill in the art any teaching that overcomes the concerns regarding the solubility of brimonidine tartrate, and would not have provided a reasonable expectation of success in preparing a therapeutically effective

brimonidine tartrate solutions at pH values of 7.0 or greater with concentrations of up to about 0.15% brimonidine tartrate where the brinonidine was fully soluble at 21° C..

Small reference:

96. The Small reference discusses the effects of pH on the ocular bioavailability of AGN191103, a different alpha-2-adrenergic agonist than brimonidine tartrate.

97. The alpha-2-adrenergic agonist studied showed an increase in the ocular bioavailability as the pH was raised from 7.4 to 8.5. The author explained that, "AGN 119103 concentrations in aqueous humor and cornea increase with increasing pH." AGN 119103, however, is not brimonidine tartrate; the pKa of AGN 119103 is 9.5, whereas the pKa of brimonidine tartrate has been measured to be about 7.8. This pKa difference significantly impacts drug formulation considerations because of the effect that it has on the percentage of the drug that is ionized at various pH values, and thus, on the solubility of the alpha-2-adrenergic agonist.

98. While Alcon makes passing reference to a Chien article and another Small article, but it is unclear whether Alcon is using these references for background information or attempting to combine them with the main Small article. To the extent that Alcon's analysis depends on a combination of multiple references, there is no motivation to combine either the Chien article or the second Small article with the first Small article, and Alcon provides none.

99. The Chien article, which discusses the bioavailability effect that a pH increase may have on certain brimonidine-containing formulations, does not provide any teaching on how to make a brimonidine formulation with an elevated pH. The second Small article, which discusses the concept of a higher pH formulation containing an alpha-2-adrenergic agonist other than brimonidine tartrate providing comparable efficacy at a lower concentration, similarly does not provide any such teaching. Nothing in the first Small article alone, nor in combination with these other references, makes obvious a

therapeutically effective formulation containing up to about 0.15% brimonidine tartrate at a pH of greater than about 7.0, which is soluble at room temperature.

100. Nothing in the general teaching that an increase in pH tends to increase the bioavailability of a drug gives any guidance to one skilled in the art that a therapeutically effective formulation with a pH greater than about 7.0 could be made with brimonidine tartrate.

101. The Small article does not provide one of skill in the art any teaching that overcomes the concerns regarding the solubility of brimonidine tartrate, and would not have provided a reasonable expectation of success in preparing a the formulation claimed in the '834 patent. Therefore, it does not render the asserted claims of the '834 patent obvious, either alone or in combination with other references.

United States Patent No. 5,021,410:

102. The '410 patent discusses the utility of combination products that would allow one to use a low concentration of an alpha-2-adrenergic agonist such as brimonidine tartrate by combining it with an alpha-3-antagonist in order to lower IOP. The '410 patent discusses the use of this combination along with preservatives and pH adjusters. It sets out a very broad preferred concentration range of about 0.001% to about 1.0% for the alpha-2-adrenergic agonist and states that the pH is adjusted to 4.5 to 7.5.

103. These teachings do not render obvious the particular claimed formulations of the '834 patent.

104. Even though one of the examples uses a 0.1% brimonidine formulation, there is no direction to one skilled in the art to select a pH of greater than 7.0. The '410 patent itself indicates that the pH of the final solutions in one of its examples ranged from about 4 to about 7.5 "as indicated by the characteristics of the individual drugs." '410 patent, col. 8, lines 10-12. Brimonidine exhibits drastically reduced solubility at pH values greater than 7.0. This would direct one skilled in the art to pursue formulations of brimonidine at lower pH values.

105. The broad concentration ranges and pH ranges set forth in the table in Burke are simply general acceptable ranges. [Burke Tr. 47:16-48:8; 48:25-49:22] They are not teachings of how to make particular formulations.

106. The '410 patent does not provide one of skill in the art any teaching that overcomes the concerns regarding the solubility of brimonidine tartrate, and would not have provided a reasonable expectation of success in preparing a therapeutically effective brimonidine tartrate solution at a pH of 7.0 or greater with less than about 0.15% brimonidine, even if such a formulation were surmised to be desirable.

Secondary Considerations:

107. In assessing whether an invention claimed in a patent would have been obvious to one of skill in the art at the time the invention was made, a Court must consider any secondary factors that may tend to suggest non-obviousness. For example, evidence of commercial success of the embodying product or copying by the alleged infringer evidences non-obviousness of the invention.

108. Alcon purposely copied some portions of the Alphagan® P formulation,

REDACTED

[ALC00174.]

109. The ability to prepare a therapeutically effective formulation of brimonidine tartrate at a concentration of up to about 0.15% at a pH of about 7.0 or greater, with the brimonidine tartrate remaining soluble at about 21° C, was unexpected by people of skill in the art because of concerns that raising the pH would cause the drug to fall out of solution (i.e., precipitate).

110. Allergan has also shown that the Alphagan® P product was initially met with skepticism regarding whether it would provide any benefit to the efficacy/safety profile of Alphagan®. However, the commercial adoption of the product over less expensive 0.2% brimonidine tartrate solutions (generic Alphagan®), as well as the significance of the 40% reduction in the incidence of allergy, are compelling evidence of

nonobviousness of the claimed invention. In fact, Alphagan® P has a market share of greater than 90% and generic 0.2% brimonidine tartrate has a market share of less than 10%, despite the generic products' lower price. [AGN0225271-278]

111. The largest segment of the eye care pharmaceutical market is that for prescription drugs for the treatment of glaucoma. Allergan's largest selling eye care pharmaceutical products are Alphagan® and Alphagan® P, which combined were the third best selling glaucoma products in the world in 2004.

c. Conclusions of Law

112. Alcon has not met its burden to provide clear and convincing evidence that the asserted claims of the '834 patent are invalid under 35 U.S.C. § 103.

113. Where Alcon has suggested that any claim of the '834 patent is invalid over a single reference, it has not provided clear and convincing evidence that one of ordinary skill in the art would have had a reasonable expectation of success in making the claimed invention.

114. Where Alcon has suggested that any claim of the '834 patent is invalid over a combination of references, it has not provided clear and convincing evidence of any motivation to combine those references.

115. The evidence regarding the secondary factors supports the conclusion that the claims of the '834 patent are non-obvious.

116. The '834 patent is entitled to a priority date of July 14, 2000, and therefore the Alphagan® P product insert cannot be used as a prior art reference in determining the validity of the '834 patent claims under 35 U.S.C. § 103.

2. Written Description

a. Background and Applicable Law

117. Alcon must show that the '834 patent is invalid for failure to comply with the written description requirement by clear and convincing evidence. *Intertool, Ltd. v. Texar Corp.*, 369 F.3d 1289, 1294 (Fed. Cir. 2004). Moreover, because the Examiner did

not reject the claims as "new matter" under 35 U.S.C. § 132, that the '834 patent complies with the written description requirement is entitled to "an especially weighty presumption of correctness." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1575-76 (Fed. Cir. 1993); *In re Smythe*, 480 F.2d 1376, 1385 (CCPA 1973).

118. Whether a specification complies with the written description requirement is a question of fact. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003).

119. "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to 'recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.'" *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003) (quoting *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d. 1313, 1330 (Fed. Cir. 2003)); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991).

120. "Adequate description of the invention safeguards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991).

121. "The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003) (quoting *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976)).

122. The applicant is not required to describe what is novel or important in the specification. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1565 (Fed. Cir. 1991). To require the specification to describe what is novel or important is legal error. *Id.*

123. "The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1564 (Fed. Cir. 1991) (emphasis in original).

124. "The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claims – not comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the same product is made." *Amgen, Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1331-32 (Fed. Cir. 2003) (citing with approval, *Amgen, Inc. v. Hoechst Marion Roussel*, 126 F.Supp.2d 69, 150 (D. Mass. 2001)).

125. The description includes all the drawings, figures and examples of the patent, as well as the written text. *See Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 405 F.3d 985, 987 (Fed. Cir. 2005); *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (holding that the written description requirement can be satisfied by "words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention."). Drawings alone may be sufficient to prove the "written description of the invention" required by § 112, first paragraph. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1564 (Fed. Cir. 1991).

126. "One shows that one is 'in possession' of the invention by describing the invention, with all of its claimed limitations, not that which makes it obvious. One does that by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention. Although the exact terms need not be used *in haec verba*." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (citations omitted) (emphasis in original).

127. The Court must separately analyze for each claim whether the written description requirement has been met. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1567 (Fed. Cir. 1991).

128. In judging the "sufficiency under § 112, first paragraph, [the '834 patent] must be judged as of the filing date." *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251 (Fed. Cir. 1989) (emphasis added). Therefore, the Court must judge sufficiency of the written description of the '834 patent based on the provisional application and the original claims.

129. The later filed CIP is irrelevant the written description analysis. *See United States Steel Corp. v. Phillips Pertoleum Co.*, 865 F.2d 1247, 1252 (Fed. Cir. 1989) (concluding that defendant's post-filing evidence was immaterial to a § 112, ¶ 1 inquiry); *see also Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1566 (Fed. Cir. 1991) (district court erred in taking Mahurkar's other patents into account).

130. The primary consideration of the written description analysis is factual and depends on the nature of the invention and the amount of knowledge imparted to those of skill in the art by the disclosure. *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976). Each case must be decided on its own facts. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991) (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (CCPA 1977)). "Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (CCPA 1977)).

b. Findings of Fact

131. U.S. Patent 6,641,834, entitled "Compositions containing alpha-2-adrenergic agonist components," issued on November 4, 2003. Dr. Orest Olejnik and Dr. Edward Kerslake are the named inventors on the '834 patent.

132. The invention of the '834 patent resulted from the inventors' work on the Brimo-X project, a project at Allergan to develop a new and improved brimonidine tartrate formulation. The Brimo-X project resulted in a formulation that was subsequently approved by FDA and is currently sold by Allergan as Alphagan® P. The '834 patent covers the Alphagan® P formulation.

133. Alpha-2-adrenergic agonist components include chemical entities which are effective to act on or bind to alpha-2-adrenergic receptors and provide a therapeutic effect. (col. 1, ll. 20-23) One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration. (col. 1., ll. 26-33)

134. Some alpha-2-adrenergic agonist components with higher pKa's, for example, greater than about 7, tend to diffuse very well through lipid membranes at pH values near their pKa, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments. However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological environments. (col. 1, ll. 38-44)

135. In one embodiment of the invention, the alpha-2-adrenergic agonists, for example brimonidine tartrate, are substantially unionized. (col. 2, ll. 47-48; col. 6, ll. 8-10)

136. The unionized form of the drug passes most readily across membrane lipid bilayers of the cornea of the eye. (col. 6, ll. 8-17) Drugs in the ionized state cannot readily pass through lipid membranes; however, unionized drugs can pass through more readily.

137. In one embodiment of the invention, the compositions have pH values of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable. (col. 3, ll. 18-22)

138. In a preferred embodiment of the invention, the present compositions are ophthalmically acceptable, e.g., the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered. (col. 3, ll. 36-40)

139. Brimonidine tartrate is an alpha-2-adrenergic agonist component with a pKa of approximately 7.8.

140. The data in the specification shows that the solubility of brimonidine tartrate drops precipitously (i.e., becomes insoluble) at pH values above 7. (Examples 1 and 2)

141. At pHs greater than about 7, brimonidine tartrate becomes substantially unionized.

142. Prior to the invention disclosed and claimed in the '834 patent, Allergan was selling the only FDA approved brimonidine solution for ophthalmic use under the trade name Alphagan. Alphagan was formulated with a target concentration of 0.2% brimonidine at a pH of about 6.3-6.5.

143. Persons of skill in the art would have known at the time of filing that Alphagan was therapeutically effective and formulated with a 0.2% target concentration of brimonidine tartrate at a pH of 6.3-6.5.

144. Prior to the invention of the '834 patent, persons of ordinary skill in the art did not think it would be possible to formulate a therapeutically effective brimonidine tartrate composition at pHs greater than about 7 because of the precipitous drop in solubility in that pH range.

145. It was particularly surprising that a therapeutically effective dosage of brimonidine tartrate could be formulated in an ophthalmically acceptable, aqueous solution at a pH greater than about 7.0.

146. The originally filed claims indicate that inventors considered the ability to formulate therapeutically effective concentration brimonidine tartrate at a pH of about 7 or greater where the brimonidine tartrate was fully soluble to be one aspect of their invention. For example, the originally filed claim 1 included the following limitation:

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

The phrase "amount effective to provide a therapeutic benefit to a patient" refers to the amount (i.e., concentration) of the alpha-2-adrenergic agonist component.[1] The originally filed claims also included dependent claims that focused on the ability to formulate at an elevated pH:

> 7 . The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized.
>
> 8. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized in a biological environment to which the composition is administered.
>
> 21. The composition of claim 1 which has a pH of about 7 or greater.

Finally, other dependent claims focused on the fact that the brimonidine tartrate was fully soluble in the composition:

> 20. The composition of claim 1 which is a solution.
>
> 23. The composition of claim 1 which is ophthalmically acceptable.

147. The applicants made clear that the invention that was being claimed was the ability to formulate at higher pHs when arguing for the ultimately issued claims:

> However, it is particularly surprising that such a therapeutically effective dosage of brimonidine could be formulated in aqueous solution at a pH greater than about 7.0 Figure 1 of the present specification shows the brimonidine's solubility decreases precipitously at pH values above 7.0.

148. In addition, the most preferred embodiment disclosed in the specification is at a pH of 7.5: "[t]he aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5." '834 patent, col. 11, lines 3-6. (A "carrier" is the pH-controlled aqueous solution isotonic with tear fluids into which the brimonidine is dissolved.)

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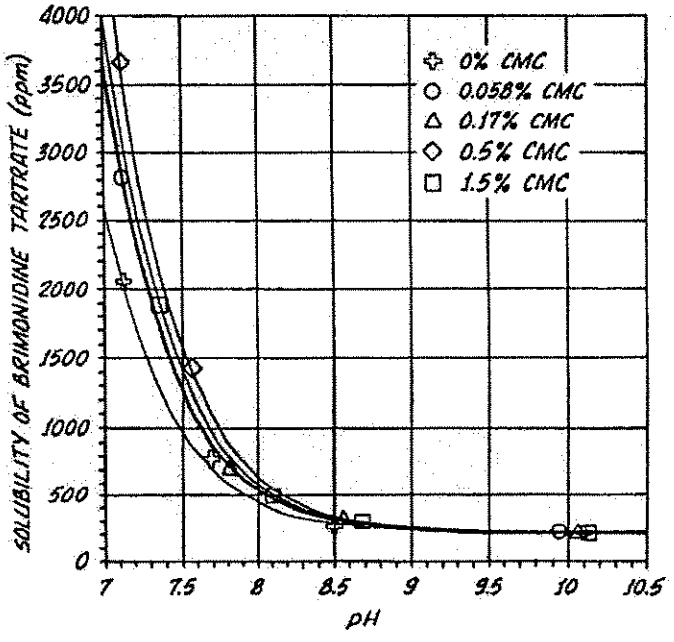
[1] One of skill in the art can determine the appropriate concentration by developing a dose response curve. The methods for developing a dose response curve are well know in this art

149. The preferred embodiment's pH of 7.5 is much higher than the then existing brimonidine forumulation's pH of 6.3-6.5. Because a pH of 7.5 is much higher than 6.3-6.5 and because a pH of 7.5 is much closer to brimonidine's pKa of 7.8, formulating a brimonidine tartrate solution at a pH of 7.5 will result in a substantial amount of unionized drug and much more unionized drug as compared to the existing commercial formulations with a pH of around 6.3-6.5.

150. At the pH range of 6.3-6.5, the amount of unionized brimonidine is approximately 3% to 5% of the total brimonidine in solution. In comparison, at a pH of 7.5, the amount of unionized brimonidine is approximately 34% of the total brimonidine in solution.

151. In Example 2 of the '834 patent, the pH-solubility profiles of brimonidine tartrate solutions were determined. As shown in Table III, starting solutions were prepared that included 0.2% brimonidine tartrate (the concentration used in the commercially available Alphagan product) with varying amounts of CMC. The solutions also included isotonic components, buffer components, and stabilized cholorine dioxide (Purite). The samples were subjected to a range of pH's from about 7 to 10. Brimonidine tartrate was added to the samples as necessary.

152. Figure 1 of the '834 patent plots the resulting solubility data:



153. At the patent's most preferred pH, 7.5, the concentration limit of brimonidine formulations represented by the graph is about 1500 ppm, or 0.15% (w/v).

154. Table IV of the '834 patent contains the data that was used to generate the curves in Figure 1.

TABLE IV

Solubility of Brimonidine tartrate (%)

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

155. The plot in Figure 1 that showed the best solubility profile was a formulation containing 0.5% CMC.

156. At around the most preferred pH of 7.5, Table IV discloses a concentration of brimonidine tartrate of 0.1451, which is "about 0.15%."

157. The Court has construed the term "about" to mean "approximately."

158. The greater the solubility the less likely the drug is to precipitate out of solution. Therefore, greater solubility is preferred.

159. One of skill in the art, knowing that the most soluble drug would be the preferred drug would be instantly drawn to the 0.5% CMC column. As mentioned above, the most desirable pH as stated in the patent is 7.5, therefore, tracking down the 0.5 % CMC column, the data point in the area of pH 7.5 is 0.1451% brimonidine tartrate - 0.1451% is about 0.15%.

160. Also, the only pH selected for discussion by the inventors was pH 7.5. (col. 16, ll. 1-3) This discussion, which is based on Figure 1, also demonstrates that the inventors believed that no more than about 1600 ppm brimonidine could be dissolved in solution at their preferred pH value, no matter how much solubility enhancing agent they used. Therefore, the Court finds that that at the most preferred pH of 7.5, the specification discloses compositions containing "up to about 0.15%" brimonidine tartrate.

161. Moreover, the 0.1451% brimonidine tartrate composition is identical to the Alphagan P formulation for purposes of the written description analysis. In particular, both compositions include up to about 0.15% brimonidine tartrate. Both are at pH values greater than about 7.0. Both include an oxy-chloro preservative and the preservative is a chlorite.[2] Finally, in both solutions the brimonidine tartrate is fully soluble at about 21° C. The 0.1451% formulation is essentially the Alphagan® P formulation at a slightly higher pH.

162. The claims of the '834 patent that cover Alphagan® P also cover the exact formulation disclosed by the 0.1451% brimonidine tartrate composition in Table III and Table IV of Example 2.

163. The asserted claims of the '834 patent were added by preliminary amendment on the same date the continuation application leading to the grant of the '834

[2] In addition, the formulations in Table III and Table IV contain virtually the same isotonic and buffer components as those used in Alphagan P.

patent was filed, September 6, 2002. When the asserted claims of the '834 patent were added, the examiner did not reject them as new matter.

c. Conclusions of Law

164. After having reviewed the entire specification of the '834 patent, including the patent figures, and the originally filed claims, considering the testimony of the witnesses, and given the above findings of fact, the Court concludes that Alcon has failed to show by clear and convincing evidence that claims 1-6, 10-14, 17-18, and 20 of the '834 patent are invalid for failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

165. Dr. Stella, an expert in the field of ophthalmic formulations and one of skill in the art offered the opinion that one of skill in the art would immediately recognize that the inventors of the '834 patent had possession of the claimed inventions.

166. From the '834 patent's disclosure, a person of ordinary skill would understand that the inventors were claiming therapeutically effective formulations. Also, the originally filed claim 1 was directed to "therapeutic[ally] benefi[cial]," solubilized alpha-2-adrenergic agonists. Brimonidine tartrate is an alpha-2-adrenergic agonist.

167. From the '834 patent's disclosure, a person of ordinary skill would understand that the inventors were claiming therapeutically effective compositions at elevated pHs. For example, the specification describes embodiments where the brimonidine tartrate is substantially unionized. (col. 2, ll. 47-48; col. 6, ll. 8-10) In addition, original dependent claims 7 and 8 required that the alpha-2-adrenergic agonist be "substantially unionized." The concentration of the unionized form increases as the pH of the solution approaches the pKa of the drug. The pKa of brimonidine tartrate is 7.78. '834 patent, col. 13, line 16. Moreover, the specification describes embodiments that have pHs greater than about 7 and are ophthalmically acceptable. (col. 3, ll. 36-40) The most preferred pH is disclosed as 7.5. Likewise, dependent claim 21 claimed

compositions with a pH greater than about 7.0. As noted in the findings of fact, at pHs greater than about 7, brimonidine tartrate becomes substantially unionized.

168. From the '834 patent's disclosure, including Figure 1, a person of ordinary skill would understand that at the most preferred pH of 7.5, the inventors disclosed compositions containing up to about 0.15% brimonidine tartrate where the brimonidine tartrate was fully soluble at about 21° C.

169. The 0.1451% brimonidine tartrate formulation—the formulation closest to the most preferred pH described in the patent—described in Example 2, particularly Table III and Table IV, is a composition that embodies *the invention.*

170. Based on the foregoing, the Court concludes that Alcon has not shown by clear and convincing evidence that claims 1-6, 10-14, 17-18, and 20 of the '834 patent are invalid for failure to satisfy the written description requirement of § 112, first paragraph.

B. '337 Patent

171. Alcon has alleged that the asserted claims of the '337 patent are invalid for two reasons: (1) anticipation over various prior art references, and (2) obviousness over various prior art references, either alone or in combination.

1. Anticipation

a. Background and Applicable Law

172. 35 U.S.C. § 102 provides that a person shall be entitled to a patent unless:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the application for patent, or
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or …
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by

> the application for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

173. For a patent to be anticipated, it must be shown by clear and convincing evidence that the claimed invention is, in fact, not "new" – requiring that a single prior art reference discloses each and every element of the claims. *See Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002).

174. An anticipation inquiry first requires proper construction of the claim, and secondly identification of each and every corresponding element disclosed in the allegedly anticipating reference. *See Lindemann Machinenfabrick Gmbh. v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984).

175. For a claim to be anticipated by prior public use, the party asserting invalidity must show that the allegedly anticipating activity met each of the limitations of the claims, and thus was an embodiment of the claimed invention. *See Juicy Whip, Inc. v Orange Bang, Inc.*, 292 F.3d 728, 737 (Fed. Cir. 2002).

176. When an allegedly anticipating reference is silent about a claim element, and the party asserting invalidity suggests that the missing element is inherent in the disclosure, it must be clear that the missing descriptive matter is necessarily present in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (emphasis added) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269 (citing *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939) (emphasis in original))).

177. "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec*

Indus., Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1295 (Fed.Cir.2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed.Cir.1999)).

178. A reference simply disclosing that a compound could be used in a pharmaceutical preparation does not anticipate a method of using that compound where the reference does not suggest the claimed use. *See, e.g., Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 347 F.3d 1367, 1372 (Fed. Cir. 2003).

179. The Federal Circuit has *rejected* the proposition that "if a prior art reference discloses the same structure as claimed by a patent, the resulting property ... should be assumed." *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377-78 (Fed. Cir. 2002) (finding that a party that only offers an assumption and its own contentions has failed to show by clear and convincing evidence that the limitation was necessarily present.).

180. The burden on a party challenging patent validity "is especially difficult when the prior art was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed.Cir.1990).

b. Findings of Fact

Level of Ordinary Skill in the Art

181. The person of ordinary skill of art would be a person possessing a Bachelor's or PharmD Degree in Pharmacy, Pharmaceutical Sciences, or related science disciplines; having three to five years of formulation experience; and being supervised by a Ph.D. or someone with substantially longer formulation experience. The person would likely be a member of a formulation development team that may include analytical chemists and related development scientists.

Scope and Content of the Prior Art and Differences from the Claimed Invention

U.S. Patent No. 5,215,991

182. U.S. Patent No. 5,215,991 ("the Burke patent") was before the Examiner during prosecution of the '337 patent and considered by the Examiner when allowing the claims of the '337 patent.

183. The Burke patent discloses combination products that would allow one to use a low concentration of an alpha-2-adrenergic agonist such as brimonidine by combining it with a Na+/H+ exchange inhibitor. It mentions the combination of an alpha-2-adrenergic agonist with a Na+/H+ exchange inhibitor as the preferred embodiment, col. 4, line 67 – col. 6, line 5.

184. The Burke patent makes clear that any number of formulations are possible. Table I provides a list of ingredients but does not specify any formulations.

185. Table I uses the term "vehicle," which generally refers to the component into which the rest of the components of the formulation are dissolved. The "vehicle" of Table I is optional.

186. There is no mention in the Burke patent of any solubility concerns. Burke teaches nothing about enhancing the solubility of any component.

187. The Burke patent lists povidone, CMC, and PVA as potential "vehicles," but it mentions nothing about the potential use of these components to affect solubility of another component.

188. None of the components listed in the Burke patent as potential "vehicles" is inherently an SEC. Whether or not any of those components will act as an SEC in a given formulation depends on the characteristics of that formulation.

189. There is nothing in the Burke reference that discloses to a person of ordinary skill in the art the use of an alpha-2-adrenergic agonist in combination with an SEC 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.

The Alphagan® Product and Label

190. The Alphagan® product contained 0.2% brimonidine tartrate and 1.4% polyvinyl alcohol ("PVA"), used as a viscosity agent. It is formulated in a pH range of 6.3-6.5.

191. At a pH range of 6.3-6.5, 0.2% brimonidine tartrate is nowhere near the solubility limit. According to the data presented by Dr. Amidon, between 2 and 3 percent brimonidine tartrate is soluble at that pH range. In contrast, the 0.15% brimonidine tartrate in Alcon's proposed product is near the solubility limit at the target pH of 7.2.

192. The solubility tests performed by Dr. Amidon are not reflective of the Alphagan® product. At the pH range of the Alphagan® product, the samples tested had a brimonidine tartrate concentration of near 3%, over ten times greater than the concentration in Alphagan®.

193. The '337 patent refers to the need for "comparable concentrations" in evaluating whether a component is acting as an SEC. ['337 patent, col. 4, lines 26-31.]

194. The behavior of a drug at high concentrations is not necessarily reflective of its behavior at much lower concentrations because of different association properties and other chemical behaviors. For example, self-association or "stacking" at high concentrations may increase the solubility of a drug over what would otherwise be expected.

195. Because of the magnitude of the concentration differences between Alphagan® and the samples tested by Dr. Amidon in the pH range of Alphagan®, Dr. Amidon's experiments do not demonstrate that PVA acts as an SEC in Alphagan®.

196. As described in the '337 patent, an SEC acts in two ways. It increases the equilibrium solubility of alpha-2-adrenergic agonist by direct interaction with the alpha-2-adrenergic agonist component. It also acts as a nucleation inhibitor, enhancing the stability of a formulation by preventing the alpha-2-adrenergic agonist component from precipitating out of solution.

197. Both the equilibrium solubility and nucleation inhibitor effect are present at conditions near the solubility limit of the alpha-2-adrenergic agonist component.

198. In Alphagan®, the nucleation inhibition effect cannot be present because 0.2% is not close to the limit of solubility for brimonidine at a pH range of 6.3-6.5. The PVA in Alphagan® does not act to prevent the brimonidine tartrate from falling out of solution.

c. Conclusions of Law

199. Alcon has not met its burden to provide clear and convincing evidence that the asserted claims of the '337 patent are invalid as anticipated under section 102.

200. Anticipation requires that each and every limitation of a claim be taught in a single prior art reference, either expressly or inherently. None of the references relied upon by Alcon teach the use of an SEC.

201. To find a claim limitation inherently present in a prior art reference, it must be necessarily present. An SEC is not necessarily present in the prior art relied on by Alcon.

202. Although the Burke patent mentions the possible use of CMC and povidone, compounds which may act as SECs under certain circumstances, these compounds are not inherently SECs, and the Burke patent does not teach their use as SECs.

203. Dr. Amidon's experiments fail to demonstrate that the PVA in Alphagan® acts as an SEC. To the contrary, the experiments suggest that no SEC was needed in Alphagan®.

2. Obviousness

a. Background and Applicable Law

204. There is a strong presumption of validity and the burden of proof is on the accused infringer to prove invalidity by clear and convincing evidence. *Robotic Vision Sys., Inc. v. View Engineering, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999); *see also American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir.

1984)("[35 U.S.C.] § 282 creates a presumption that a patent is valid and imposes the burden of proving invalidity on the attacker. That burden is constant and never changes and is to convince the court of invalidity by clear evidence.").

205. A determination of obviousness is a legal determination based on four factual inquiries. The underlying factual inquiries must address: (1) the scope and content of the prior art references; (2) the differences between the claims and the prior art reference; (3) the level of ordinary skill in the art, and (4) secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Secondary considerations include commercial success, failure of others, long-felt need and unexpected results. *See Minnesota Mining and Manufacturing Co. v. Johnson & Johnson Orthopaedics*, 976 F.2d 1559, 1573 (Fed. Cir. 1992)(stating that these factors must be considered and are often "the most probative and cogent evidence in the record").

206. An obviousness analysis requires a determination of whether there was some suggestion in the prior art to make the claimed composition, and whether the prior art would have revealed to one of ordinary skill in the art that there was a reasonable expectation of success in making the claimed invention. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1353 (Fed. Cir. 2003). Finding only that the prior art makes it "obvious to try" to create the claimed invention is not sufficient. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986)("The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumption of validity, as a whole." *Id.* at 1383 (internal citation omitted).).

207. Obviousness is analyzed from the perspective of the time the invention was made; the use of hindsight is not permitted. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051 (Fed. Cir. 1988) (noting that the district court misapplied the obviousness standard by impermissibly using hindsight to reconstruct the claimed

invention from prior art with the invention before it and aided by the defendant's expert, rather than viewing the invention from the position of a person of ordinary skill at the time it was made).

208. When two or more references are cited as allegedly rendering a claim obvious, there must be a motivation to one of skill in the art to combine the references. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1578-79 (Fed.Cir.1997)("[T]he record must provide a teaching, suggestion, or reason to substitute.... The absence of such a suggestion to combine is dispositive in an obviousness determination."); *see also SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988) (the defendant "cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention").

b. Findings of Fact

Level of Ordinary Skill in the Art

209. The person of ordinary skill of art would be a person possessing a Bachelor's or PharmD Degree in Pharmacy, Pharmaceutical Sciences, or related science disciplines; having three to five years of formulation experience; and being supervised by a Ph.D. or someone with substantially longer formulation experience. The person would likely be a member of a formulation development team that may include analytical chemists and related development scientists.

Scope and Content of the Prior Art and Differences from the Claimed Invention

Burke Patent

210. The Burke patent is discussed above at paragraphs 18-25, and those findings are incorporated here as well.

211. The Burke patent teaches that a pH range of 4-7.5 may be used for formulations, "as indicated by the characteristics of the individual drugs." [Burke patent, col. 6, lines 25-27.] The characteristics of brimonidine would have led a person of skill

in the art to select a pH range similar to the Alphagan® product. In that range, there is no solubility concern at therapeutically effective concentrations. A person skilled in the art would not have been motivated to select a higher pH.

212. The disclosure of an SEC or the suggestion of any need for an SEC is entirely absent in the Burke patent.

213. The Burke patent provides no motivation to design a formulation that uses any of the disclosed "vehicles" as SECs.

Burke Patent in Combination with Other References

214. The Greaves reference explains that certain polymers may be used to affect the viscosity of pharmaceutical formulations. It does not teach to use any of these polymers as SECs.

215. Just as with the Burke patent, the polymers mentioned in Greaves are not inherently SECs, and there is no teaching to use them as such.

216. Neither the Burke patent nor the Greaves references teaches the use of SECs, and neither reference provides any motivation for a person skilled in the art to use any of the disclosed polymers as SECs.

217. The BASF brochure discusses many of the properties and functions of Kollidon, also known as povidone, explaining that povidone may in some situations be used to "improve the solubility of active substances." The BASF brochure does not, however, provide any examples of specific formulations.

218. There would be no motivation for one of skill in art to combine the teachings of the Burke patent, which makes no reference to any concern about solubility, with the BASF brochure.

219. The Handbook of Pharmaceutical Excipients notes that povidone may be used to increase the solubility of certain drugs. However, because the Burke reference makes no reference to solubility concerns, there is nothing to motivate one of skill in the

art to combine it with a reference merely teaching that certain substances may increase the solubility of certain drugs.

220. The '337 patent is also not rendered obvious by the combination of the Burke patent with any of the other references referred to, but not discussed, by Dr. Amidon. These references include U.S. Patents No. 5,091,528, 5,776,445, 5,834,470, 5,663,205, and 5,212,196.

c. Conclusions of Law

221. Alcon has not met its burden to provide clear and convincing evidence that the asserted claims of the '337 patent are invalid as obvious under section 103.

222. Alcon has not provided clear and convincing evidence of any motivation to use any of the components disclosed in the Burke patent as an SEC.

223. Alcon has not provided clear and convincing evidence of any motivation to combine the Burke patent with any of the other cited references.

Dated: January 17, 2006