reserved the authority to make final claims determination regarding *pre-service* and *post service* claims[.]" *Id.* at 2, 86–87 (emphasis added). Thus, Ingenix's discretion as Claims Administrator is limited to "urgent care claims." See *id.* at 61. While the nature of Quintana's insurance claims are not expressly clear from the pleadings or motions, they appear to be "urgent care claims" over which Ingenix exercises discretion and responsibility to determine eligibility and amount. *Id.* at 2. Consequently, for purposes of this case, Ingenix may very well be an ERISA fiduciary. See, *e.g., Reich,* 55 F.3d at 1049. Because the court has determined that Quintana's claim is outside the scope of § 502, however, such a finding is immaterial. See, *e.g., Memorial Hospital,* 904 F.2d at 245.

III. *CONCLUSION*

For the above state reasons, the plaintiff's motion to remand the case to the state court from which it was previously removed is **GRANTED.** This case is **REMANDED** to the **193rd Judicial District Court of Dallas County, Texas.** The clerk shall mail a certified copy of this memorandum opinion and order to the district clerk of Dallas County, Texas. 28 U.S.C. § 1447(c).

SO ORDERED.

ALLERGAN, INC., Plaintiff,

v.

SANDOZ INC., Defendant.

Allergan, Inc., Plaintiff,

v.

Alcon Laboratories, Inc., Alcon Research, Ltd., Alcon, Inc. and Falcon Pharmaceuticals, Ltd., Defendants.

Allergan, Inc., Plaintiff,

v.

Apotex Inc. and Apotex Corp., Defendants.

Allergan, Inc., Plaintiff,

v.

Watson Laboratories, Inc., Defendant.

Civil Action Nos. 2:09–cv–97, 2:09–cv–348 TJW, 2:10–cv–200 TJW, 2:10–cv–344 TJW.

United States District Court,
E.D. Texas,
Marshall Division.

Aug. 22, 2011.

Background: Patentee brought action against competitors, alleging infringement of patents for a drug used to treat glaucoma and ocular hypertension.

Holdings: The District Court, T. John Ward, J., held that:

(1) patents were not invalid as anticipated by prior art reference, and

(2) patents were not invalid for obviousness.

Ordered accordingly.

1. Patents ⇐312(4), 314(5)

Patent infringement is a question of fact and must be proven by a preponder-

ance of the evidence. 35 U.S.C.A. § 271(e)(2).

2. Patents ⇐72(1)

A patent is invalid as anticipated if a single prior art reference discloses each element of the claimed invention. 35 U.S.C.A. § 102.

3. Patents ⇐65

A prior art reference may anticipate a patent claim, and, thus, render it invalid, when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. 35 U.S.C.A. § 102.

4. Patents ⇐58

If a claim limitation is not explicitly disclosed in an allegedly anticipating prior art reference, the party alleging patent invalidity bears the burden of showing that the limitation is inherently disclosed by the reference. 35 U.S.C.A. § 102.

5. Patents ⇐65

To establish that a claim limitation is inherent in an allegedly anticipating prior art reference, the anticipatory feature or result must be consistent, necessary, and inevitable, not simply possible or probable, and it should be clear that it would be so recognized by persons of ordinary skill. 35 U.S.C.A. § 102.

6. Patents ⇐65

In order to establish patent invalidity, an anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art and that such existence was recognized by persons of ordinary skill in the field of the invention. 35 U.S.C.A. § 102.

7. Patents ⇐65

Anticipation of a patent, rendering it invalid, requires enablement, whereby the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation. 35 U.S.C.A. § 102.

8. Patents ⇐62(2)

Generally, testimony concerning patent anticipation must be testimony from one skilled in the art and must identify each claim element, state the witness' interpretation of the claim element, and explain in detail how each claim element is disclosed in the prior art reference; testimony is insufficient if it is merely conclusory. 35 U.S.C.A. § 102.

9. Patents ⇐62(1)

Evidence of secondary considerations, such as unexpected results or commercial success, is irrelevant to the analysis of whether a patent in invalid as anticipated. 35 U.S.C.A. § 102.

10. Patents ⇐66(1.12)

Patents for a drug used to treat glaucoma and ocular hypertension were not invalid as anticipated by a prior art reference describing pharmaceutically acceptable compounds for controlling intraocular pressure in patients with glaucoma and ocular hypertension; prior art reference failed to describe a fixed combination of brimonidine and timolol or a method of treating glaucoma using such a combination. 35 U.S.C.A. § 102.

11. Patents ⇐16(2, 3), 16.13, 36.1(1)

A determination of obviousness is a legal determination based on four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the patent claims and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness. 35 U.S.C.A. § 103.

12. Patents ⇐16.5(1)

When the patented invention is a combination of known elements, in evaluating a claim of invalidity for obviousness, the court must determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue by considering the teach-

ings of multiple references, the effects of demands known to the design community or present in the marketplace, and the background knowledge possessed by a person having ordinary skill in the art. 35 U.S.C.A. § 103.

13. Patents ⇐36.1(1), 36.2(1)

Secondary considerations that provide evidence of the non-obviousness of a patent include copying, commercial success, failure of others, long-felt need, general skepticism of those in the art, and unexpected results. 35 U.S.C.A. § 103.

14. Patents ⇐36.2(7)

A presumption arises that the patented invention is commercially successful, as evidence that it is not invalid for obviousness, when a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent. 35 U.S.C.A. § 103.

15. Patents ⇐16.5(4)

If there is no proof that there were a finite number of identified and predictable solutions in the prior art at the time of the patented invention, this cuts against a finding of invalidity for obviousness. 35 U.S.C.A. § 103.

16. Patents ⇐16(3, 4)

Patent obviousness is analyzed from the perspective of one of skill in the art at the time of the invention, and the use of hindsight is not permitted. 35 U.S.C.A. § 103.

17. Patents ⇐16.25

Patents for a drug used to treat glaucoma and ocular hypertension were not rendered invalid for obviousness by a prior art reference describing pharmaceutically acceptable compounds for controlling intraocular pressure in patients with glaucoma and ocular hypertension; person of ordinary skill in art would not have had reason, after reading prior art reference, to develop claimed combination of brimonidine and timolol given unpredictable nature of field, patentee's clinical studies of drug demonstrated unexpected results, and there was a long felt need for a fixed combination product to treat glaucoma at time of patented invention. 35 U.S.C.A. § 103.

Patents ⇐328(2)

5,502,052. Cited as Prior Art.

Patents ⇐328(2)

7,030,149, 7,320,976, 7,323,463, 7,642,-258. Valid and Infringed.

W. Chad Shear, Fish & Richardson, Dallas, TX, A. Martina Tyreus Hufnal, Fish & Richardson, Wilmington, DE, Aine M. Skow, Deanna J. Reichel, Elizabeth M. Flanagan, Jonathan E. Singer, Susan M. Coletti, Fish & Richardson, Minneapolis, MN, Gregory Phillip Love, Todd Y. Brandt, Stevens Love Hill & Holt PLLC, Longview, TX, Juanita R. Brooks, Fish & Richardson, San Diego, CA, Otis W Carroll, Jr., Ireland Carroll & Kelley, Tyler, TX, for Plaintiffs.

Barry P. Golob, Kerry B. McTigue, William Blake Coblentz, Duane Morris LLP, Washington, DC, Ian Scott, Duane Morris LLP, New York, NY, Joseph M. Bennett-Paris, Duane Morris, Atlanta, GA, Richard T. Ruzich, Robert M. Gould, Duane Morris LLP, Chicago, IL, William Ellsworth Davis, III, The Davis Firm, PC, Longview, TX, for Defendants.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

T. JOHN WARD, District Judge.

I. INTRODUCTION

This is a consolidation of four patent infringement suits brought by Plaintiff Al-

lergan, Inc.'s ("Allergan") pursuant to the Hatch–Waxman Act.[1] *See* Drug Price Competition and Patent Term Restoration Act, which is commonly referred to as the Hatch–Waxman Act, in 1984. Pub. L. No. 98–417, 98 Stat. 1585. Defendants Sandoz, Inc. ("Sandoz"); Alcon Laboratories, Inc., Alcon Research, Ltd., Alcon, Inc., and Falcon Pharmaceuticals, Ltd. ("Alcon"); Apotex, Inc. and Apotex Corp. ("Apotex"); and Watson Laboratories, Inc. ("Watson") (collectively "Defendants") are each seeking approval from the Food and Drug Administration ("FDA") to market generic copies of Allergan's Combigan® product, used for the treatment of glaucoma and ocular hypertension.[2] In this consolidated action, Allergan alleges that Defendants' proposed generic pharmaceutical products infringe the asserted claims of United States Patent Nos. 7,030,149 ("the '149 patent"); 7,320,976 ("the '976 patent"); 7,323,463 ("the '463 patent"); and 7,642,258 ("the '258 patent") (collectively, the "patents-in-suit"). The Court held a four-day bench trial in the case on August 2, 2011 through August 5, 2011.

Pursuant to Fed.R.Civ.P. 52, and after having considered the entire record in this case and the applicable law, the Court concludes that: (1) each of the Defendants infringe claim 4 of the '149 Patent, claim 1 of the '976 patent, claims 1–6 of the '463 Patent, and claims 1–9 of the '258 Patent; and (2) the patents-in-suit are not invalid. These findings of fact and conclusion of law are set forth in further detail below. The Court's findings of fact are based on the admissible evidence. Any finding of fact that is actually a conclusion of law should be treated as such. Any conclusion of law that is actually a finding of fact should be treated as such.

II. FINDINGS OF FACT

A. The Parties

1. Allergan, Inc. is a Delaware corporation with its principal place of business at 2525 Dupont Drive, Irvine, California 92612.

2. Sandoz Inc. is a Colorado corporation with its principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.

3. Alcon Laboratories, Inc. is a Delaware corporation, with a place of business in Texas.

4. Alcon Research, Ltd. is a Delaware corporation, with a place of business in Texas.

5. Alcon, Inc. no longer exists, based on a merger with Novartis AG.

6. Falcon Pharmaceuticals, Ltd. is a Texas corporation, with a place of business in Texas.

7. Apotex, Inc. is a Canadian corporation with a place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9.

8. Apotex Corp. is a Delaware corporation with its principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida, 33326.

9. Watson Laboratories, Inc. is a Nevada corporation with a place of business at 400 Interpace Parkway, Parsippany, NJ 07054.

1. A fifth action, *Allergan, Inc. v. Hi–Tech Pharmacal Co., Inc.*, C.A. No. 2:09–cv–182 (TJW) was also consolidated with these four actions. However, Allergan and Hi–Tech resolved the dispute and filed a stipulation of dismissal (D.I. 168), which was ordered by this court on May 31, 2011. (D.I. 175.)

2. Specifically, these consolidated suits relate to the filing of Abbreviated New Drug Application ("ANDA") No. 91–087 by Sandoz, ANDA No. 91–574 by Alcon, ANDA No. 91–442 by Apotex, and ANDA No. 201949 by Watson with the FDA, pursuant to the Federal Food, Drug, and Cosmetic Act.

B. Glaucoma and Ocular Hypertension

10. Glaucoma is an incurable disease of the eye that causes gradual damage to the optic nerve resulting in vision loss that, ultimately, can lead to blindness. (D.I. 238, Trial Tr. Day 1(AM) at 51:24–52:2; 52:21–53:7 (Whitcup).)[3] About 2 million people in the United States are diagnosed with glaucoma every year. (*Id.* at 52:7–10 (Whitcup).)

11. While incurable, glaucoma can be managed by pharmaceutical and surgical treatment options that slow the progression of the disease. (D.I. 242, Trial Tr. Day 3(AM) at 71:4–9 (Noecker).) One such treatment option is to use medication to lower the intraocular pressure ("IOP") in the eye. (*Id.* at 72:20–73:7 (Noecker).) Scientists and medical professionals 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. (D.I. 238, Trial Tr. Day 1(AM) at 53:15–21; 54:10–21 (Whitcup); D.I. 242, Trial Tr. Day 3(AM) at 66:3–15 (Noecker).) Intraocular pressure is measured in millimeters of mercury ("mm Hg"). (D.I. 242, Trial Tr. Day 3(AM) at 66:3–8 (Noecker).) For each millimeter of mercury IOP is lowered, patients are 10% less likely to suffer visual field loss. (*Id.* at 67:14–18 (Noecker).)

12. Patients suffering from ocular hypertension ("OHT") also have elevated IOP and, although not diagnosed with glaucoma, must be observed closely for its onset. (D.I. 242, Trial Tr. Day 3(AM) at 66:21–67:25 (Noecker).) These patients can utilize the same pharmaceutical and surgical options used by glaucoma patients to attempt to reduce IOP. (*Id.* at 71:4–9 (Noecker).)

C. Treatment of Glaucoma and Ocular Hypertension with Brimonidine and Timolol

13. One treatment method for patients with glaucoma or ocular hypertension is the use of eye drops. This form of treatment is the most convenient and acceptable to patients. (D.I. 242, Trial Tr. Day 3(AM) at 71:4–9; 81:20–84:25 (Noecker).)

14. There are at least 20 different glaucoma drugs on the market today that can be used in such treatments. (D.I. 238, Trial Tr. Day 1(AM) at 54:22–55:5 (Whitcup).) Those that are commonly used in clinical practice fall into several different classes of medication, and have different mechanisms of action. (D.I. 240, Trial Tr. Day 2(AM) at 50:10–18; (Tanna); D.I. 242, Trial Tr. Day 3(AM) at 72:6–78:8 (Noecker).) Most relevant here are two classes of medication, alpha$_2$ adrenergic agonists and so-called "beta blockers."

15. Brimonidine tartrate 0.2% was marketed by Allergan as Alphagan®, and was first developed by Allergan as a new glaucoma medication in the late 1980s and early 1990s. (D.I. 239, Trial Tr. Day 1(PM) at 75:8–10 (Batoosingh).) Brimonidine is an alpha$_2$ adrenergic agonist that lowers IOP in glaucoma patients by reducing fluid production in the eye while also increasing outflow of that fluid from the eye. (D.I. 238, Trial Tr. Day 1(AM) at 59:22–60:7 (Whitcup); D.I. 239, Trial Tr. Day 1(PM) at 74:14–75:7 (Batoosingh).) The FDA approved Alphagan® in 1996. (D.I. 239, Trial Tr. Day 1(PM) at 75:8–10 (Batoosingh).)

3. As used herein, "DTX," "PTX," and "JTX" refer to Defendants' exhibit, Plaintiffs exhibit, and Joint Exhibit respectively, and will be followed by the exhibit number. "Trial Tr. Day" refers to the trial transcript and will be followed by the day, page number, and line numbers. For example, "Trial Tr. Day 1(AM) at 53:15–21" refers to the morning trial transcript, day 1, page 53, lines 15–21.

16. Unlike many glaucoma medications, which are dosed twice a day (once in the morning and once in the evening, i.e., "BI") or once a day (once in the morning or evening, i.e., "QD"), the FDA only approved Alphagan® for dosing three times a day (i.e., "TID") due to a lowered efficacy of the drug with less frequent dosing. (PTX–75 at AGN_COMBI0478532; D.I. 238, Trial Tr. Day 1(AM) at 60:11–24 (Whitcup); D.I. 239, Trial Tr. Day 1(PM) at 75:11–89–19 (Batoosingh).) As explained further below, BID dosing with Alphagan® 0.2% results in an approximately 3.25 to 3.5 mm Hg higher IOP in the afternoon than TID. (D.I. 239, Trial Tr. Day 1(PM) at 79:24–80:4 (Batoosingh); DTX–137 at DEFS(B/T) 000346; PTX–134 at AGN_COMBI0676465; D.I. 241, Trial Tr. Day 2(PM) at 4:24–5:19.) This difference is both numerically significant and clinically relevant. (D.I. 239, Trial Tr. Day 1(PM) at 80:5–8 (Batoosingh); D.I. 241, Trial Tr. Day 2(PM) at 5:10–19 (Tanna).) This was referred to at trial as the "afternoon trough." (D.I. 239, Trial Tr. Day 1(PM) at 77:13–17; 78:3–7 (Batoosingh).)

17. Although this third recommended dose, along with a substantial incidence of allergy, was a significant drawback of brimonidine, it still achieved commercial success as a therapy for glaucoma patients. (D.I. 239, Trial Tr. Day 1(PM) at 90:16–91:10 (Batoosingh).) Allergan attempted to secure FDA approval for Alphagan® as a BID drug but was unable to do so. (*Id.* at 75:14–20 (Batoosingh).)

18. Upon Alphagan®'s introduction to the market, it was apparent that brimonidine 0.2% had significant and problematic side-effects that limited its utility. (D.I. 239, Trial Tr. Day 1(PM) at 90:6–91:10 (Batoosingh).) Brimonidine 0.2% was found to cause a high rate of ocular allergy, which led patients to discontinue using the drug. (*Id.*) Once a patient develops an allergy to brimonidine, brimonidine is no longer available as a treatment option for that patient. (D.I. 242, Trial Tr. Day 3(AM) at 74:11–16 (Noecker).) Additionally, brimonidine was also known to cause systemic side effects, including somnolence and dry mouth. (D.I. 239, Trial Tr. Day 1(PM) at 90:6–91:10 (Batoosingh).) The high incidence of these various side effects in patients treated with brimonidine monotherapy is reported throughout the literature. (*See, e.g.*, PTX–180 at AGN_COMBI0677278; PTX–77 at AGN_COMBI0481545.)

19. These side effects of Alphagan® were so significant that, as soon as Alphagan® was approved, Allergan began looking for a way to ameliorate them. After Alphagan®'s approval, Allergan began working on developing a better product, ultimately developing two products with lower concentrations of brimonidine that reduced many of problems that had been seen with Alphagan®. (D.I. 239, Trial Tr. Day 1(PM) at 91:11–23 (Batoosingh).) These products were known as Alphagan® P 0.15% and 0.1%.

20. As with Alphagan®, Allergan attempted to secure FDA approval for BID dosing for Alphagan® P. (D.I. 239, Trial Tr. Day 1(PM) at 92:15–20 (Batoosingh).) This effort was unsuccessful, and both Alphagan® P 0.15%, and Alphagan® P 0.1%, were approved only for TID dosing. (PTX–75; D.I. 239, Trial Tr. Day 1(PM) at 91:24–92:14 (Batoosingh).) Allergan received approval for Alphagan® P 0.15% and Alphagan® P 0.1% in 2001 and 2006, respectively. (PTX–75; D.I. 239, Trial Tr. Day 1(PM) at 92:21–22 (Batoosingh); D.I. 242, Trial Tr. Day 3(AM) at 12:14–18 (LeCause).) Alphagan® P 0.15% was approved on March 16, 2001, over a year before the filing date of the patents-in-suit. (D.I. 243, Trial Tr. Day 3(PM) at 79:17–25 (Noecker).) Clinical studies on Alphagan® P 0.15% showed that it was signifi-

cantly less likely to cause allergic reactions and certain systemic side-effects than was original Alphagan®. (D.I. 242, Trial Tr. Day 3(AM) at 138:1–13 (Noecker).)

21. Timolol, a beta-blocker, was developed by Merck in the 1970s. The FDA first approved it as a treatment for glaucoma in 1978. (D.I. 241, Trial Tr. Day 2(PM) at 58:22–25 (Tanna).) Timolol is typically prescribed either once or twice daily. (D.I. 240, Trial Tr. Day 2(AM) at 95:14–15 (Tanna).) Timolol lowers IOP by suppressing aqueous humor production. (D.I. 242, Trial Tr. Day 3(AM) at 81:11–19 (Noecker).)

22. Although timolol is an established and commonly used drug, it is known to have serious and potentially life-threatening side effects, including pulmonary and cardiovascular side-effects. (D.I. 243, Trial Tr. Day 3(PM) at 125:25–127:11; 129:5–18 (Laskar).) Timolol is known to slow both heart and respiratory rates, and to lower blood pressure. (DTX–135 at 1960 (stating that the systemic absorption of beta-blockers like timolol "can produce significant side effects such as bradycardia, arrhythmias, bronchoconstriction, or bronchospasm as a result of interaction with the $beta_1$ and $beta_2$ receptors in the heart, lungs, and blood vessels. The use of nonselective beta-blocker therapy is contraindicated in patients with actual or suspected cardiovascular or pulmonary dysfunction as beta-blockers can produce further arrhythmias or bronchospasm."); DTX 123 at 1:64–67; DTX 157 at 45–46; D.I. 243, Trial Tr. Day 3(PM) at 125:25–127:11 (Laskar).)

23. Because of these side effects, treatment with timolol is contraindicated in a number of patients. (D.I. 242, Trial Tr. Day 3(AM) at 74:17–75:20 (Noecker).) For example, the label of the Alphagan® products contains the following warning about using brimonidine with a beta-blocker like timolol:

> However, since alpha-agonists, as a class, may reduce pulse and blood pressure, caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

(DTX–129 at DEFS(B/T) 000233.)

D. Glaucoma Treatment with Multiple Medications: Fixed and Unfixed Combinations

24. Although there are many individual medications available, for many patients, one glaucoma medication is not enough to treat their disease effectively. (D.I. 238, Trial Tr. Day 1(AM) at 54:22–55:17 (Whitcup).) For patients whose glaucoma cannot be effectively controlled with a single drug, the most common form of treatment is the serial or concomitant administration of two or more different medications, provided in two or more separate bottles, at least several minutes apart to prevent one of the drops from washing the other out. (D.I. 238, Trial Tr. Day 1(AM) at 55:1–56:2; 56:14–57:16 (Whitcup).)

25. This type of treatment is referred to by various terms, including adjunctive, concomitant, or serial therapy, and the combination of the products is considered "unfixed" because the amount the patient gets of each drug at any particular time is dependent on the treatment regimen prescribed by the doctor and on whether the patient properly administers the drugs. (D.I. 239, Trial Tr. Day 1(PM) at 64:10–66:3 (Batoosingh).) By contrast, a "fixed combination"[4] combines two glaucoma drugs in the same bottle. (D.I. 240, Trial Tr. Day 2(AM) at 17:21–18:3 (Tanna).) It

4. As used herein, "fixed combination" and "single composition" are used interchangeably.

is "fixed" because the patient gets the same amount of each drug each time a drop of the combination is delivered to the eye. (D.I. 239, Trial Tr. Day 1(PM) at 64:10–24 (Batoosingh).)

26. There are advantages to using unfixed combinations over fixed combinations. For example, if a patient needs a smaller dose of one medication, a physician can prescribe a smaller dose of that medication without modifying the dose of the other. Unfixed combinations thus give physicians wide flexibility in treatment options. (D.I. 239, Trial Tr. Day 1(PM) at 64:10–20 (Batoosingh); D.I. 240, Trial Tr. Day 2(AM) at 132:14–133:3 (Tanna); D.I. 242, Trial Tr. Day 3(AM) at 79:7–18 (Noecker).)

27. Serial or concomitant administration of two drugs is different than administering them in a fixed combination. (D.I. 238, Trial Tr. Day 1(AM) at 56:14–57:19 (Whitcup).) When two ophthalmic products are used together in a concomitant regimen, they do not interact in a patient's eye. The human eye maintains only a small volume of liquid, approximately 10 microliters, on its outer surface. Eyedrops (about 35–40 microliters) are absorbed or drain away quickly through the eye's drainage ducts. (*Id.;* D.I. 242, Trial Tr. Day 3(AM) at 64:24–65:3 (Noecker) ("And then the biggest problem is the window of delivery. It's there, you blink a bunch, and the eye is gone. So you have about a minute to get this right and get it into the eye. So if you're a little slow out of the gate, it's gone.").) Thus, under recommended dosing, which requires administration of drugs in an adjunctive regimen at least five minutes apart, the second administered drug given as part of an adjunctive regimen would not interact with the first administered drug. (D.I. 238, Trial Tr. Day 1(AM) at 57:13–16 (Whitcup).)

28. Because serial therapy with an unfixed combination can necessitate application of five or more separate doses throughout the day, compliance can be difficult. (D.I. 239, Trial Tr. Day 1(PM) at 64:25–66:6 (Batoosingh).) Most patients, particularly the elderly (who are most susceptible to developing glaucoma), fail to comply with such demanding dosing regimens. (D.I. 240, Trial Tr. Day 2(AM) at 15:2–16:3 (Tanna).) As a consequence, their disease is not adequately treated and may progress more rapidly than it would with proper treatment.

29. Although, in theory, the problem of patient compliance could be addressed by the use of fixed combinations, historically, they have been difficult to develop. As of 2001, there was only one marketed, FDA-approved fixed combination, Cosopt®. (D.I. 238, Trial Tr. Day 1(AM) at 68:6–12 (Whitcup).) Alcon's Betoptic® Pilo fixed combination product was approved in 1997 but was never marketed. (PTX–129 at AGN_COMBI06762992; D.I. 238, Trial Tr. Day 1(AM) at 68:13–25 (Whitcup).) As Dr. Whitcup described, development of a fixed combination is the "most difficult" task in ophthalmological drug development. (D.I. 238, Trial Tr. Day 1(AM) at 65:19–23 (Whitcup).)

30. The FDA has repeatedly expressed skepticism about fixed combination products and has set a high bar for approval. In the early 2000s, the FDA referred to the clinical results it had seen with fixed combination products as "very disappointing," and the applications for several different combination ophthalmic products at that time remained pending and unapproved. (PTX–129 at AGNCOMBI0672993 (quoting the FDA's Dr. Wiley Chambers as saying that the results for combination products "ha[ve] been very disappointing to a number of people including myself"); PTX–53 at AGN_COM-

BI0437800 ("Dr. Chambers did say he thinks the results with the combination drops have been 'terribly disappointing.' "); D.I. 238, Trial Tr. Day 1(AM) at 89:18–91:11 (Whitcup).) Despite the fact that there are at least 20 different glaucoma drugs on the market, almost all of which are used in one unfixed combination or another, there are only two fixed combination glaucoma products currently approved and sold for glaucoma treatment in the United States—Cosopt® and the product at issue in this litigation, Combigan®. (D.I. 238, Trial Tr. Day 1(AM) at 54:22–55:5; 68:6–12 (Whitcup).)

E. The Patents–in–Suit

31. The patents-in-suit are U.S. Patent Nos. 7,030,149 ("the '149 patent"); 7,320,976 ("the '976 patent"); 7,323,463 ("the '463 patent"); and 7,642,258 ("the '258 patent"). The effective filing date for each of the patents-in-suit is April 19, 2002. (*See* JTX 1, JTX 2, JTX 3, and JTX 4 at p. 1.)

32. The named inventors of the patents-in-suit are Chin–Ming Chang, Gary J. Beck, Cynthia C. Pratt, and Amy L. Batoosingh. (JTX 1, JTX 2, JTX 3, and JTX 4 at p. 1.)

33. The four patents-in-suit generally relate to a fixed combination composition of 0.2% brimonidine and 0.5% timolol, a method of treating glaucoma or ocular hypertension by administering the aforementioned composition twice daily, or an article of manufacture comprising packaging material indicating that twice daily administration of the composition is useful for treating glaucoma or ocular hypertension. (*See* JTX 1–4.) Like the brimonidine tartrate and timolol maleate single agent products (Alphagan® and Timoptic®), the combination product of the patents-in-suit is applied topically to the eye. (*See e.g.*, JTX 1 at Abstract.)

34. The patents-in-suit also describe suitable preservatives for the combination product. (*See id.* at col. 2, ll. 29 *et seq.*) The patents-in-suit list BAK as the first such preservative. The patents-in-suit acknowledge that "typically such preservatives are employed at a level of from 0.004% to 0.02%". (*Id.*) The patents-in-suit further state that the preservative, preferably BAK, "may be employed at a level of from 0.001% to less than 0.01%, *e.g.* from 0.001% to 0.008%, preferably about 0.005% by weight." (*Id.*)

35. The '149 patent issued on April 18, 2006, and is titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use." The application for the '149 patent was filed on April 19, 2002. (JTX 1 at p. 1.) The '149 patent has four claims to methods of treating glaucoma or ocular hypertension with a 0.2% brimonidine tartrate/0.5% timolol formulation administered twice a day. Claims 1–3, as construed by the Court, require that combination treatment to be as effective as serial administration with 0.2% brimonidine 3 times a day and 0.5% timolol twice a day. The Court granted summary judgment of non-infringement to Defendants of claims 1 through 3 before trial. Claim 4 of the '149 patent covers the improvement in the prior three times a day brimonidine therapy "without loss of efficacy" whereby the brimonidine is combined with timolol in twice daily dosing. (JTX–1.) As construed by the Court in its *Markman* order, "without loss of efficacy" means "without decrease in lowering intraocular pressure (IOP)." (D.I. 151 at 20–21.)

36. The '976 patent issued on January 22, 2008, and is titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use." The application for the '976 patent was filed on October 14, 2003, and is a continuation of the application for the '149 patent. (JTX 2 at p. 1.) The '976 patent has one claim to a method of treat-

ing glaucoma or ocular hypertension with a therapeutically effective amount of a formulation containing 0.2% brimonidine tartrate and 0.5% timolol administered twice a day. (JTX–2.)

37. The '463 patent issued on January 29, 2008, and is titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use." The application for the '463 patent was filed on February 3, 2003, and is a division of the application for the '149 patent. (JTX 3 at p. 1.) The '463 patent has six claims to compositions containing 0.2% brimonidine tartrate and 0.5% timolol and articles of manufacture containing these compositions along with packaging material indicating use twice a day for glaucoma treatment. (JTX–3.)

38. The '258 patent issued on January 5, 2010, and is titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use." The application for the '258 Patent was filed on August 24, 2007, and is a continuation-in-part of the application for the '976 patent. (JTX 4 at p. 1.) The '258 patent also has nine claims to certain compositions containing 0.2% brimonidine tartrate and 0.5% timolol and articles of manufacture that include those compositions. (JTX–4.)

39. The claims of the patents-in-suit all have an effective filing date of April 19, 2002.

40. The '149, '976, and '463 patents provide two examples, one relating to the formulation of the combination product and the second to a clinical study using the combination product.

41. Example I of the patents-in-suit describes what is stated to be a representative pharmaceutical composition of the invention. As set out in the corresponding Table, the composition includes mono and dibasic sodium phosphate as buffers, sodium hydroxide and hydrochloric acid to adjust pH, if necessary, and BAK as the preservative.

42. The '149, '976, and '463 patents share a common specification, and the '258 patent is a continuation-in-part of the '149 patent. The specification of the '258 patent is the same as the specifications of the '149, '976, and '463 patents, but adds two additional Examples. (*See* Trial Tr. Day 2(PM) at 45:24–46:3; 46:12–14 (Laskar).) The new Example II [5] in the '258 patent is the same as the composition described in Example I, but specifies that "0.5% timolol free base is used instead of timolol maleate" and states that "[t]he composition is effective as described in Example I, but is more stable." Example III is also the same as the composition described in Example I, but specifies that "0.5% timolol free base is used instead of timolol maleate and 0.18% brimonidine free base is used instead of brimonidine tartrate" and states that "[t]he composition is effective as described in Example I, but is more stable." [6] Allergan has asserted all claims of all four patents-in-suit against the Defendants. (*See infra* at fn 3.)

43. The patents-in-suit discuss the prior art concomitant (serial) administration of brimonidine and timolol. (*See, e.g.,* JTX 1 at col. 1:7–12; *see also* Trial Tr. Day 2(AM) at 14:7–25 (Tanna).) Specifically, the patents-in-suit discuss the prior art serial administration of Alphagan® (brimonidine 0.2%) TID and Timoptic® (0.5% timolol maleate) BID. (*See, e.g.,* JTX 1 at

5. The Examples in the '258 patent are misnumbered. The specification adds an "Example II" which is in addition to the two examples which appear in the '149 patent. The Example II appears twice in the specification of the '258 patent at columns 9 and 10.

6. Due to the similarities in the specifications of the patents-in-suit, the Court's Findings may reference only the '149 specification. However, the same disclosure is provided by each of the specifications of the patents-in-suit.

col. 2, ll. 58–64; *see also* Trial Tr. Day 1(AM) at 142:9–13 (Beck).) Ms. Amy Batoosingh, one of the inventors, stated that an advantage of a fixed combination is that patient compliance is increased because only one drop is needed in place of multiple drops of the individual active agents; in fact, she stated this is a "huge advantage." (Trial Tr. Day 1(AM) at 64:25–66:6 (Batoosingh).)

F. Nature of the Action

44. This civil case is brought before the United States District Court for the Eastern District of Texas. This action arises under the Patent Laws of the United States, 35 U.S.C. §§ 1 *et seq.*,

45. Congress passed the Drug Price Competition and Patent Term Restoration Act, which is commonly referred to as the Hatch–Waxman Act, in 1984. Pub. L. No. 98–417, 98 Stat. 1585. The Hatch–Waxman Act (the "Act") amended the Federal Food, Drug, and Cosmetic Act, Pub. L. No. 52–675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.* (1994)) (the "FDCA"), as well as the patent laws. *See Bristol–Myers Squibb Co. v. Royce Lab., Inc.*, 69 F.3d 1130, 1131–32 (Fed.Cir.1995).

46. As the statute's name suggests, "Congress sought to strike a balance between incentives, on the one hand, for innovation, and on the other, for quickly getting lower-cost generic drugs to market." *Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 54 (D.C.Cir.2005). "The Hatch–Waxman Amendments help to expedite the marketing of generic drugs." *Teva Pharm., USA, Inc. v. Leavitt*, 548 F.3d 103, 104 (D.C.Cir.2008).

47. The Act allows generics to obtain FDA approval by submitting bioequivalence studies as opposed to clinical evidence of safety or efficacy, which would be costlier and more time consuming. *Crawford*, 410 F.3d at 54 (citing 21 U.S.C. § 355(j)). Under the FDCA, as amended by the Act, a pharmaceutical manufacturer submits an ANDA when seeking expedited FDA approval of a generic version of a drug previously approved by the FDA (a "listed drug"). *See* 21 U.S.C. § 355(j). An ANDA can be filed if the generic drug manufacturer's active ingredient is the "bioequivalent" of the listed drug. *See* 21 U.S.C. § 355(j)(2)(A)(iv). When submitting an ANDA, a manufacturer must certify one of four statements concerning the applicable listed drug.[7] If an ANDA is certified under Paragraph IV, the applicant must notify the patent's owner of the certification. *See* 21 U.S.C. § 355(j)(2)(B).

48. The Act created an incentive for generic drug companies to challenge patents believed to be unnecessary or invalid by granting the generic drug company, if its challenge is successful, 180 days of exclusive marketing rights of the generic version of the drug. *Leavitt*, 548 F.3d at 104 (citing 21 U.S.C. §§ 355(j)(2)(A)(vii), 355(j)(5)(B)(iv)).

49. Allergan is the holder of approved New Drug Application ("NDA") No. 21–398 for Combigan® 0.2% brimonidine/0.5% timolol ophthalmic solution. It is undisputed that Allergan owns all rights, title, and interest in and to the patents-in-suit. (D.I. 207 at 18.) It is also undisputed that each of the four patents-in-suit is listed in the FDA Orange Book for Combigan®. (D.I. 207 at 18.)

7. These four statements include certifying that either: (i) the listed drug is not patented (a "Paragraph I certification"); (ii) the listed drug's patent has expired (a "Paragraph II certification"); (iii) the expiration date of the listed drug's patent (a "Paragraph III certification"); or (iv) the listed drug's patent "is invalid or ... it will not be infringed by the manufacture, use, or sale of the new drug" covered by the ANDA (a "Paragraph IV certification"). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

50. The Patent Act provides that "(i)t shall be an act of infringement to submit ... an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). "Under § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed.Cir.1997).

51. "If the court determines that the patent is not invalid and that infringement would occur, and that therefore the ANDA applicant's Paragraph IV certification is incorrect, the patent owner is entitled to an order that FDA approval of the ANDA containing the Paragraph IV certification not be effective until the patent expires." *Royce Lab.*, 69 F.3d at 1135 (emphasis omitted).

G. The Accused Products

1. Sandoz's ANDA 91–087

52. On or about February 23, 2009, Allergan received a Paragraph IV letter from Sandoz regarding the '149 and '976 patents. The letter indicated that Sandoz had submitted ANDA No. 91–087 for the purpose of obtaining approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan® prior to the expiration of the '149 and '976.

53. On April 7, 2009, Allergan filed a Complaint for infringement of the '149 and '976 patents against Sandoz, alleging that the filing of ANDA No. 91–087 constituted an act of infringement of the '149 and '976 patents. (Civil Action No. 2:09–cv–97).

54. On October 20, 2009, Allergan received a second Paragraph IV letter from Sandoz regarding the '463 Patent.

55. On November 9, 2009, Allergan filed an Amended Complaint against Sandoz to additionally assert the '463 patent.

56. On or about February 16, 2010, Allergan received a third Paragraph IV letter from Sandoz regarding the '258 patent.

57. On March 19, 2010, Allergan filed a Second Amended Complaint against Sandoz to additionally assert the '258 patent.

2. Alcon's ANDA No. 91–574

58. On or about September 29, 2009, Allergan received a Paragraph IV letter from Alcon regarding the '149, '976, and '463 patents. The letter indicated that Alcon had submitted ANDA No. 91–574 for the purpose of obtaining approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan® prior to the expiration of the '149, '976, and '463 patents.

59. On November 6, 2009, Allergan filed a Complaint for infringement of the '149, '976, and '463 patents against Alcon, alleging that the filing of ANDA No. 91–574 constituted an act of infringement of the '149, '976, and '463 patents. (Civil Action No. 2:09–cv–348).

60. On or about April 2, 2010, Allergan received a second Paragraph IV letter from Alcon regarding the '258 patent.

61. On April 28, 2010, Allergan filed an Amended Complaint against Alcon to additionally assert the '258 patent.

3. Apotex's ANDA No. 91–442

62. On or about May 4, 2010, Allergan received a Paragraph IV letter from Apotex regarding the '149, '976, '463, and '258 patents. The letter indicated that Apotex had submitted ANDA No. 91–442 for the purpose of obtaining approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan® prior

to the expiration of the '149, '976, '463, and '258 patents.

63. On June 15, 2010, Allergan filed a Complaint for infringement of the '149, '976, '463, and '258 patents against Apotex, alleging that the filing of ANDA No. 91–442 constituted an act of infringement of the '149, '976, '463, and '258 patents. (Civil Action No. 2:09–cv–348).

4. Watson's ANDA No. 201949

64. On or about July 30, 2010, Allergan received a Paragraph IV letter from Watson dated July 26, 2010. The letter indicated that Watson had submitted ANDA No. 201949 for the purpose of obtaining approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan® prior to the expiration of the '149, '976, '463, and '258 patents.

65. On September 2, 2010, Allergan filed a Complaint for infringement of the '149, '976, '463, and '258 patents against Watson, alleging that the filing of ANDA No. 201949 constituted an act of infringement of the '149, '976, '463, and '258 patents. (Civil Action No. 2:09–cv–00344).

H. Procedural Posture

1. The Sandoz Action: Civil Action No. 2:09–cv–97

66. On April 7, 2009, Allergan filed suit against Sandoz for infringement of the '149 and '976 patents.

67. On October 15, 2009, Allergan moved to consolidate *Allergan, Inc. v. Sandoz Inc.*, C.A. No. 2:09–cv–97 (TJW) with *Allergan, Inc. v. Hi–Tech Pharmacal Co., Inc.*, C.A. No. 2:09–cv–182 (TJW), for pretrial and trial purposes. Neither Sandoz nor Hi–Tech opposed this motion.

68. On October 22, 2009, the Court ordered the cases consolidated.

2. The Alcon Action: Civil Action No. 2:09–cv–348

69. On November 6, 2009, Allergan filed suit against Alcon for infringement of the '149, '976, and '463 patents.

70. On January 13, 2010, Allergan moved to consolidate *Allergan, Inc. v. Hi–Tech Pharmacal Co., Inc.*, C.A. No. 2:09–cv–182 (TJW) with *Allergan, Inc. v. Alcon Laboratories, Inc., et al.*, C.A. No. 2:09–cv–348 (TJW), for pretrial and trial purposes. Neither Sandoz, HiTech nor Alcon opposed this motion.

71. On January 19, 2010, the Court ordered the cases consolidated.

3. The Apotex Action: Civil Action No. 2:10–cv–0200

72. On June 15, 2010, Allergan filed suit against Apotex for infringement of the '149, '976, '463, and '258 patents.

73. On September 2, 2010, Allergan moved to consolidate *Allergan, Inc. v. Apotex Corp. and Apotex, Inc.*, C.A. No. 2:10–CV–200 with *Allergan, Inc. v. Sandoz Inc.*, C.A. No. 2:09–cv–97 (TJW) for pretrial and trial purposes.

74. On September 9, 2010, the Court ordered the cases consolidated.

4. The Watson Action: Civil Action No. 2:10–cv–00344

75. On September 2, 2010, Allergan filed suit against Watson for infringement of the '149, '976, '463, and '258 patents.

76. On March 1, 2011, Allergan and Watson jointly moved to consolidate *Allergan, Inc. v. Watson Laboratories, Inc.*, C.A. No. 2:10–cv–00344 (TJW) with *Allergan, Inc. v. Sandoz Inc.*, C.A. No. 2:09–cv–97 (TJW) for pretrial and trial purposes.

77. On March 2, 2011, the Court ordered the cases consolidated.

5. The Court's Claim Construction, Summary Judgment, and Parties' Stipulation

78. The Court held a *Markman* hearing in this consolidated matter on January 28, 2011. Following the hearing, the court issued an order construing the disputed claim terms of the patents-in-suit.[8]

79. The Court granted Defendants' Motion for Partial Summary Judgment of Noninfringement with respect to claims 1–3 of the '149 patent. (*See* D.I. 218.)

80. Defendants have stipulated that each of their proposed products described in their respective ANDAs (ANDA No. 91–087 for Sandoz; ANDA No. 91–574 for Alcon; ANDA No. 91–442 for Apotex; ANDA No. 201949 for Watson) meet all of the limitations of claim 4 of the '149 patent, claim 1 of the '976 patent, claims 1–6 of the '463 patent, and claims 1–9 of the '258 patent. (D.I. 234.)

I. Parties' Contentions

81. Allergan contends that Sandoz, Alcon, Apotex, and Watson are each infringing each of the claims of each of the Patents–in–Suit under 35 U.S.C. § 271 either literally or under the doctrine of equivalents, by Sandoz's, Alcon, Apotex and Watson's filing of ANDA Nos. 91–087, 91–574, 91–442, and 201949, respectively, seeking to market generic copies of Allergan's COMBIGAN® product that practice the inventions of the patents-in-suit. (D.I. 233 at 12–16.) Allergan also contends that the asserted claims of patents-in-suit are valid. (*Id.*)

82. Defendants contend that the patents-in-suit are invalid for anticipation in view of U.S. Patent No. 5,502,052 to DeSantis ("DeSantis") and obviousness over DeSantis when viewed by a person of ordinary skill in the art. (*Id.*) Defendants also contend that claims 1–3 of the '149 patent are invalid under 35 U.S.C. § 112, first paragraph, for lacking written description and for failing to satisfy the enablement requirement. (*Id.*)

J. U.S. Patent No. 5,502,052 ("DeSantis")

83. U.S. Patent No. 5,502,052 to DeSantis ("DeSantis") (DTX 123), issued on March 26, 1996, which is more than one year before the April 19, 2002 priority date of the patents–in–suit.

84. DeSantis describes combinations of an alpha$_2$-adrenergic agonist and a beta-blocker for controlling the IOP in patients with glaucoma or ocular hypertension. (DTX 123 at col. 1, ll. 12–24 and col. 3, ll. 3–6; *see also* Tr. Trial Tr. Day 2(AM) at 20: 7–17 (Tanna); 29:9–30:3 (Tanna); Trial Tr. Day 2(PM) at 68:2–6; 94:2–10 (Laskar); Trial Tr. Day 3(PM) at 53:3–6 and 11–14 (Noecker).)

85. DeSantis describes the alpha$_2$-agonists that can be used in the combination products in broad terms, stating:

> The alpha–2 agonists which can be employed in the compositions of the present invention include all pharmaceutically acceptable compounds which have alpha–2 agonist activity and are effective in controlling intraocular pressure.

(*Id.* at col. 3, ll. 17–21; *see also* Trial Tr. Day 3(AM) at 24:15–22 (Tanna).)

86. DeSantis identifies a number of alpha$_2$-agonists that may be used in the claimed combination, including "all pharmaceutically acceptable compounds which have alpha$_2$-agonist activity and are effective in controlling intraocular pressure," (DTX 123 at col. 3, ll. 18–21; *see also* Trial Tr. Day 2(AM) at 24:15–22 (Tanna)), which includes "clonidine derivatives or 'cloni-

8. The Court fully adopts and incorporates herein by reference, the above-mentioned claim construction order entered in this case. (D.I. 151.)

dine-like' drugs," further described as follows:

> In addition to the 2–(arylimino) imidazolidines identified above, other groups or classes of alpha–2 agonists which may be utilized in the present invention include 2–(arylimino) oxazolidines; 2–(arylmethylene) imidazolidines; 2–(arylimino) pyrrolidines; arylalkylaminoguanidines, such as aryl-imidazoquinazolines and pheny-lacetylguanidines; and 2–(phenylimino) diazocyclopentenes. All of these groups of drugs may be referred to as being clonidine derivatives or "clonidine-like" drugs. A comprehensive discussion of the properties of clonidine and clonidine-like compounds is presented in a publication by Timmermans et al. titled "Structure-Activity Relationships in Clonidine–Like Imidazolidines and Related Compounds" (pages 1–97, published in 1980 by Gustav Fischer Verlag, of Stuttgart and New York). The entire contents of that publication are hereby incorporated in the present specification by reference. As indicated by Timmermans *et al.*, the molecular structure of clonidine consists of three parts: an aromatic (i.e., aryl) portion, a bridge, and an imidazolidine moiety. Timmermans *et al.* disclose many compounds which have been produced by modifying one or two of these three parts, but which retain one of the three parts intact. For purposes of the present specification, all such compounds are defined as being "clonidine derivatives."

(*Id.* at col. 4, ll. 34–57.)

87. Timmermans (DTX 124), which was published in 1980 and cited above, discloses "UK–14,304–18 (tartrate)," which is brimonidine tartrate. (*See* Timmermans at 28–9; *see also* Trial Tr. Day 2(AM) 20:21–22:6 (Tanna) and 41:25–43:23; Trial Tr. Day 2(PM) at 70:2–7; 70:11–25; 71:1–14; 71:21–72:1 (Laskar).) Allergan's expert, Dr. Robert Noecker, confirmed that Timmermans discloses brimonidine and its tartrate salt. (Trial Tr. Day 3(PM) at 53:19–54:9 and 64:8–65:1 (Noecker).)

88. By April 2001, brimonidine was a known alpha$_2$-agonist that had been shown useful for lowering IOP at a concentration of 0.2%. (*See* Serle 1993 (DTX 193); *see also* Trial Tr. Day 2(AM) at 22:12–24:14 (Tanna); Trial Tr. Day 2(PM) at 73:18–25; 74:9–10 (Laskar); Trial Tr. Day 1(AM) at 146:18–19(Beck); Trial Tr. Day 1(PM) at 74:14–75:10 (Batoosingh).)

89. By April 2001, a person of ordinary skill in the art would have considered brimonidine to be one of the best alpha$_2$-agonist for treating glaucoma or ocular hypertension. (*See* Trial Tr. Day 1(PM) at 105:23–106:6 (Batoosingh); *see also* Trial Tr. Day 2(AM) at 22:12–24:14 (Tanna); Trial Tr. Day 1(AM) at 146:18–19 (Beck).)

90. DeSantis gives the preferred amount of alpha$_2$-agonist in the combinations as an amount of about 0.02 to 2.0 percent by weight ("wt. %"). (*See* DTX 123 at col. 4, ll. 58–61; *see also* Trial Tr. Day 2(AM) at 25:8–26:9 (Tanna); Trial Tr. Day 2(PM) at 79:21–24 (Laskar).)

91. DeSantis also states that the "preferred beta-blockers include timolol,. . . ." (*Id.* at col. 5, l. 34; *see also* Trial Tr. Day 2(AM) at 26:10–27:5 (Tanna); Trial Tr. Day 2(PM) at 81:17–82:4 (Laskar).)

92. The preferred amount of the beta-blocker in the combinations is stated to be an amount of about 0.01 to 3.0 wt. %. (*See id.* at col. 5, ll. 37–40; *see also* Trial Tr. Day 2(AM) at 28:11–29:3 (Tanna); Trial Tr. Day 2(PM) at 82:8–12 (Laskar).)

93. As discussed by Defendants' expert, Dr. Tanna, DeSantis also discloses beta-blockers that may be utilized in the disclosed invention include all pharmaceutically acceptable compounds that are capable of reducing the production of aqueous humor when applied topically. (DTX

123 at col. 4, ll. 62–65; *see* Trial Tr. Day 2(AM) at 27:24–28:10 (Tanna).)

94. Timolol is listed in the title of DeSantis. (DTX 123 at p. 1; *see also* Tr. Trial Tr. Day 2(AM) at 26:10–27:5 (Tanna); Trial Tr. Day 2(AM) at 81:23–25 (Laskar).)

95. Timolol is the only claimed beta-blocker in DeSantis. (DTX 123 at col. 6, ll. 42–48; *see also* Trial Tr. Day 2(AM) at 26:10–27:5 (Tanna); Trial Tr. Day 2(PM) at 82:1–4 (Laskar).)

96. DeSantis discusses "formulatory ingredients" such as "benzalkonium chloride" that "will typically be employed in an amount of from about 0.001% to 1.0% by weight (wt.%)." (*Id.* at col. 5, l. 41–col. 6, l. 1; *see also* Trial Tr. Day 2(AM) at 31:17–32:14 (Tanna); Trial Tr. Day 2(PM) at 87:11–15 (Laskar).)

97. DeSantis states BAK is an example of a suitable antimicrobial preservative that can be used with the disclosed anti-glaucoma single composition:

> In addition to the above described principal active ingredients, the anti-glaucoma compositions of the present invention may further comprise various formulation ingredients, such as antimicrobial preservatives and tonicity agents. Examples of suitable antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, ONAMER M and other agents equally well known to those skilled in the art.

(DTX 123 at col. 5, ll. 41–48; *see also* Trial Tr. Day 2(AM) at 31:17–32:14 (Tanna); Trial Tr. Day 2(PM) at 87:11–15 (Laskar).)

98. DeSantis states that the compositions typically include the preservative in an amount of from about 0.001 % to about 1.0% by weight. (*See* DTX 123 at col. 6, ll. 1–6; *see also* Trial Tr. Day 2(AM) at 31:17–32:14 (Tanna); Trial Tr. Day 2(PM) at 87:11–15 (Laskar).)

K. The Development of Combigan®

99. After nine years of formulation development and clinical trials, Allergan brought Combigan®, a fixed combination glaucoma medication comprising 0.2% brimonidine and 0.5% timolol, to the market. (D.I. 238, Trial Tr. Day 1(AM) at 135:8–24; PTX–24.) The development of the product is described below.

1. Formulation Challenges in Developing Combigan®

100. Drug formulation is a challenging and unpredictable endeavor, and the formulation of ophthalmic drugs is even more complex than normal drug formulation. (D.I. 238, Trial Tr. Day 1(AM) at 133:4–23, 134:5–24 (Beck); D.I. 242, Trial Tr. Day 3(AM) at 64:9–65:3 (Noecker).) This is because ophthalmic drugs are generally formulated as aqueous solutions, stability is more of a challenge than it would be for drugs formulated as tablets or other dosage forms. Also, the surface area of the eye is very small, and the residence time for an eye drop is very short. (*Id.*) With the small surface area and the short residence time, it is a challenge to design an aqueous drug that can quickly pass through the hydrophobic corneal membrane to reach the site of action in the eye. (*Id.*) Many of these difficulties were acknowledged by Defendants' formulation expert, Dr. Laskar. (*See, e.g.*, D.I. 241, Trial Tr. Day 2(PM) at 53:21–55:25 (Laskar) (discussing the importance of the selection of buffering systems, tonicity agents, viscosity agents, pH, and preservative for an ophthalmic formulation).)

101. Formulating a fixed combination ophthalmic drug adds yet another layer of complexity on top of the considerations already described. As described in an article appearing in *Review of Ophthalmology:*

> For many reasons, not every possible pair of glaucoma drugs can be combined

> in one bottle; many stars must be aligned for such a combination to be feasible. For instance, both drugs must be soluble at the same pH or one of the drugs could end up in clump of powder at the bottom of the bottle. More importantly, the two drugs to be combined must have comparable dosing frequency and timing.

(PTX–122; *see also* D.I. 238, Trial Tr., Day 1(AM) at 137:4–138:23 (Beck).)

102. At trial, the difficulties involved in fixed combination ophthalmological formulations were conceded by Defendants' formulation expert, Dr. Laskar. (*See, e.g.,* D.I. 241, Trial Tr. Day 2(PM) at 34:12–35:3 (Laskar)) (discussing "significant formulation challenges that he faced in developing combination product due to the fact that 'the active ingredients were incompatible' "); D.I. 243, Trial Tr. Day 3(PM) at 124:3–125:1 (Laskar) (discussing potential reactivity between active ingredients); *id.* at 123:2–6, 11–17; 126:3–6 (acknowledging that "[y]ou can't predict how that—what's going to happen when you put two salts together in an aqueous solution until you actually do so").

103. Formulating brimonidine tartrate and timolol maleate into a fixed combination presented many challenges to Allergan's formulators. A fixed combination formulation of these two compounds required combining two different active ingredients that had two different salts, and that had previously been formulated at two different pH values, with two different buffer systems, and with two different concentrations of preservative. As discussed more fully below, each of these differences presented its own set of challenges.

104. First, the use of two different active ingredients posed challenges to the formulators because these ingredients "have two different physical chemical characteristics, so each of these two separate active ingredients will demand a different formulation, and somehow we have to accommodate the demands of both actives in a single formulation." (D.I. 238, Trial Tr. Day 1(AM) at 137:2–12 (Beck).) The formulators did not know how the two would behave together in a single formulation. (*Id.* at 144:2–6.)

105. Further, Defendants' expert, Dr. Laskar, acknowledged that reactivity can occur between brimonidine and timolol because the secondary amines in brimonidine can act as nucleophiles that attack the electron-poor carbon-nitrogen double bonds present in timolol. (D.I. 243, Trial Tr. Day 3(PM) at 124:3–125:1 (Laskar).)

106. Second, the use of active ingredients with two different salts presented additional challenges. As Mr. Beck explained, "[i]f the salt forms dissociate from the active ingredients, which they often do in solution and pH dependent, they too can have reactivities with the active ingredients, for example." (D.I. 238, Trial Tr. Day 1(AM) at 137:16–25 (Beck).) Dr. Laskar also agreed that "there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound in dosage forms." (D.I. 243, Trial Tr. Day 3(PM) at 123:2–6, 11–17; 126:3–6 (Laskar); DTX–274.)

107. Third, the pH differences between previous formulations of brimonidine tartrate and timolol maleate presented an additional challenge to the inventors. Brimonidine tartrate had previously been formulated at a pH in the range of 6.3 to 6.5 in Allergan's Alphagan® product, and timolol maleate had been formulated at a pH of 7.0 in Timoptic®. (JTX–9I at AGN_COMBI0000683; PTX–74 at AGN_COMBI0478511; D.I. 238, Trial Tr. Day 1(AM) at 139:5–8 (Beck).) Because pH is measured on a logarithmic scale, this difference of up to 0.7 pH units is significant. (D.I. 238, Trial Tr. Day 1(AM) at

139:2–21 (Beck)); (D.I. 241, Trial Tr. Day 2(PM) at 139:16–140:14 (Laskar).)

108. The importance of pH to an ophthalmic formulation was a fact agreed to by numerous witnesses—both Allergan's and Defendants'—at trial. Mr. Beck explained that pH is important because it affects solubility, stability, and bioavailability. (D.I. 238, Trial Tr. Day 1(AM) at 139:22–140:5) (Beck.) Dr. Laskar explained that the pH of an ophthalmic formulation is important to the "stability, comfort, and bioavailability." (D.I. 241, Trial Tr. Day 2(PM) at 59:13–18 (Laskar); *id.* at 54:13–55:13 ("Q: As to pH adjusting agents, is that a specific concern with regard to ophthalmic products or drugs? A: Absolutely.").) Dr. Tanna also agreed that "pH can have a significant effect on an active ingredient." (D.I. 241, Trial Tr. Day 2(PM) at 14:7–10 (Tanna).)

109. Fourth, brimonidine and timolol had previously been formulated with different buffer systems, presenting yet another challenge to the inventors. Alphagan® had been formulated with a citric acid buffer system, and Timoptic® used a phosphate buffer system. (JTX–9I at AGN_COMBI0000683; PTX–74 at AGN_COMBI0478511; D.I. 241, Trial Tr. Day 2(PM) at 134:12–135:2 (Laskar)). The buffer system affects the isotonicity of a formulation, and adjusting the buffers to achieve the appropriate isotonicity is not a routine matter. (Chang Deposition Tr. at 107:19–24; D.I. 241, Trial Tr. Day 2(PM) at 136:2–7, 13–17 (Laskar).)

110. Finally, brimonidine and timolol had previously been formulated with two different concentrations of the BAK preservative. Alphagan® contained 50 ppm BAK, but Timoptic® contained 100 ppm, twice the concentration in Alphagan®. (JTX–9I at AGN_COMBI0000683; PTX–74 at AGN_COMBI0478511.) When asked whether he would agree that "the formulators of Timoptic used the .01% BAK, because they believed that that was necessary for that formulation," Dr. Laskar acknowledged that he "would agree that they had some reason to do so." (D.I. 241, Trial Tr. Day 2(PM) at 135:20–136:1 (Laskar)).

111. In light of all these challenges, the path to the final formulation that resulted in the Combigan® product was anything but straightforward. In addition to the brimonidine tartrate and timolol maleate that are included in the final formulation, Allergan investigated several other active ingredients for use in the combination, including levobunolol as an alternate beta blocker. (D.I. 238, Trial Tr. Day 1(AM) at 146:7–21 (Beck).)

112. Once brimonidine and timolol were selected as the active ingredients, the inventors also tried a number of different vehicles for the formulation, many of which ultimately turned out to be failures.

113. Early in the formulation process, Allergan was investigating at least two possible vehicles for its formulation. One was formulated in Synergel, a viscous polymeric substance, as the delivery vehicle. (PTX–26; D.I. 238, Trial Tr. Day 1(AM) at 148:22–150:21 (Beck).) The other contained Purite®, a mild preservative with few detrimental effects on the eye, and the preservative that was used with Alphagan® P. (PTX–26; D.I. 238, Trial Tr. Day 1(AM) at 147:3–148:2) (Beck); (PTX–75 at AGN_COMBI0478533.) Although Allergan had estimated its probability of success with both of these formulations as "good," both ended up failing, demonstrating the unpredictability of the art. (PTX–26; D.I. 238, Trial Tr. Day 1(AM) at 147:3–150:21 (Beck).)

114. Allergan inventor Mr. Beck explained that he was attempting to use the Synergel vehicle to improve the residence time on the eye in an attempt to increase the penetration across the cornea. (D.I.

238, Trial Tr. Day 1(AM) at 149:1–150:13 (Beck).) In practice, however, the Synergel formulation proved too viscous because it did not allow for sterile filtration. (*Id.* at 150:24–152:12; PTX–24 at AGN_COMBI0145291–293.)

115. Like the Synergel formulation, the inventors also had problems with the Purite® formulation. The inventors were attempting to use the Purite® preservative as a replacement for the commonly-used benzalkonium chloride ("BAK") preservative, which is known to be toxic to the eye. (D.I. 238, Trial Tr. Day 1(AM) at 147:16–148:5 (Beck); PTX–24 at AGN_COMBI0145296.) But they discovered that the Purite® degraded the timolol too quickly to make a stable formulation and were forced to abandon the attempt. (D.I. 238, Trial Tr. Day 1(PM) at 3:25–7:15 (Beck); PTX–35; PTX–128.)

116. The Allergan formulators also tried a carboxymethylcellulose ("CMC") vehicle for the formulation because it was thought to increase the comfort of an eye drop, but found that it was not compatible with the benzalkonium chloride ("BAK") preservative. Because CMC has a negative charge and BAK has a positive charge, they can form a complex that makes sterile filtering difficult. (D.I. 238, Trial Tr. Day 1(AM) at 153:6–20 (Beck); D.I. 239, Trial Tr. Day 1(PM) at 8:11–25 (Beck); PTX–159.)

117. Even after settling on an appropriate vehicle and preservative for the brimonidine and timolol formulation, the inventors faced further hurdles with the formulation. In the course of stability studies on the formulation, Allergan found novel degradants—which can be caused by breaking down of the active ingredients, impurities, or complexation of the active ingredient with something else in the formulation—that they did not expect to see. (D.I. 239, Trial Tr. Day 1(PM) at 9:1–10:6 (Beck).) Mr. Beck explained that "the monotherapy formulations did not have these degradants. These were new degradants as a result of the combination of the two active ingredients in the formulation." (*Id.* at 10:7–17.)

118. As a result of the unexpected degradants, Allergan was required to conduct toxicology studies to determine whether the degradants would compromise the safety of the formulation. (*Id.* at 10:18–12:12 ("We didn't know whether or not these degradants could compromise safety in the products. So we were obligated to conduct studies to ensure that they were safe. And this would be before we would go into human clinical studies."); PTX–126.)

119. After force-degrading the formulation for seven months to obtain sufficient quantities of the degradants to perform a study, Allergan ran a one-month toxicology study in rabbits to evaluate the safety of the degradants, and submitted that study to the FDA. (D.I. 239, Trial Tr. Day 1(PM) at 12:13–13:25 (Beck); JTX–9H.) Although Allergan ultimately determined that the degradants did not compromise the safety of the products, there was no way of knowing the potential safety ramifications of the degradants without running the study. (D.I. 239, Trial Tr. Day 1(PM) at 13:14–25 (Beck).)

120. Furthermore, because of the difficulties involved in combining two active ingredients that had been formulated at different pH values, the inventors did several studies to select the appropriate pH for the formulation. (D.I. 239, Trial Tr. Day 1(PM) at 15:18–18:17 (Beck); PTX–38 at AGN_COMBI0171458; PTX–89.) They could not simply choose either the pH of Alphagan® (6.3) or Timoptic® (7.0), but rather had to run the experiments to determine the appropriate pH for the combination. (D.I. 239, Trial Tr. Day 1(PM) at 15:24–16–5) (Beck) ("Q: Why didn't you

just pick the pH that was the closest to the pH of the eye? A: We couldn't do that. Again, pH has a significant impact of stability of a product and aqueous environment. And it has an impact on the molecule's ability to penetrate the cornea."); *see also* D.I. 241, Trial Tr. Day 2(PM) at 54:23–55:23 (Laskar) (discussing the critical nature of pH to an ophthalmic formulation); D.I. 241, Trial Tr. Day 2(PM) at 14:7–10 (Tanna) ("Q. So you would agree with me, Dr. Tanna, that a pH can have a significant effect on an active ingredient? A. Yes, it can."). The inventors eventually settled on a final target pH of 6.9 for the formulation. (PTX–100; JTX–9 at AGN_COMBI0055391.)

121. The different preservative concentrations of Alphagan® (50 ppm BAK) and Timoptic® (100 ppm BAK) also required the inventors to perform a number of different tests to determine the optimum pH for the combination formulation. Because BAK is known to be toxic to cells, Allergan's inventors generally "want to formulate the product at the lowest [concentration] of BAK that [they] can." (D.I. 239, Trial Tr. Day 1(PM) at 19:19–20:2 (Beck).) However, because BAK is also able to increase the uptake of an active ingredient, the inventors were concerned that reducing the BAK concentration would negatively impact the uptake of timolol into the eye, adversely affecting its efficacy. (*Id.* at 21:19–24:7.) Therefore, in addition to performing several titration to failure studies to determine how much BAK was needed to properly preserve the formulation, they also performed tests to ensure that a reduced concentration of BAK would not have a negative impact on the uptake of the active ingredients. (*Id.* at 19:11–24:7; PTX–101; PTX–61.)

122. Ultimately, the Allergan formulators spent nearly a year developing the formulation of Combigan®. (D.I. 238, Trial Tr. Day 1(AM) at 135:8–24 (Beck); D.I. 239, Trial Tr. Day 1(PM) at 24:4–7 (Beck).) Far from Defendants' characterizations as a "routine" exercise, this process was complex, difficult, and unpredictable. This is consistent with the unpredictable arts. *See Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed.Cir.2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

123. Defendants argue that this evidence of formulation challenges is a red herring and nothing more than general formulation practices employed by a person of ordinary skill in the art as of 2002. The Court disagrees and finds that this is nothing more than unsupported attorney argument. To be sure, Dr. Tanna admitted that he did not consider any formulation difficulties faced by the inventors in his obviousness analysis and does not consider himself to have expertise in the area of formulation. (D.I. 240, Trial Tr. Day 2(AM) at 120:3–7 (Tanna) ("Q: So I take it you did not take into consideration any formulation difficulties the formulators in this case may have faced when rendering your obviousness opinion? A: Correct. I—I did not."); D.I. 240, Trial Tr. Day 2(AM) at 119:14–120:2 (Tanna).) Likewise, Dr. Laskar admitted at trial he did not take into account any information about the actual formulation work done by the inventors. (D.I. 241, Trial Tr. Day 2(PM) at 144:12–18; 145:17–20 (Laskar).) Moreover, Dr. Laskar agreed that formulation difficulties are an important part of obviousness considerations, and admitted to applying for his own combination patent where there were formulation challenges overcome in making the combination. (D.I. 241, Trial Tr. Day 2(PM) at 160:10–19 (Laskar).) The Court finds it disingenuous to blindly assert that formulations challenges only apply to some patents and

not others, especially when Defendants' experts did not even consider the formulation challenges overcome by Allergan.

124. The final formulation of Combigan® developed by Mr. Beck and his team is as follows:

Table 3.3.2.1 Quantitative Composition of Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution (Formula 9262X)

Ingredient	Concentration (% w/v)	Concentration (mg/mL)	Amount (g) for a 300-L batch
Brimonidine Tartrate	0.20	2.0	600.0
Timolol Maleate	0.68[a]	6.8	2040.0
Benzalkonium Chloride (use 10% w/v stock solution)	0.005	0.05	149g[b]
Dibasic Sodium Phosphate Heptahydrate	2.15	21.5	6450.0
Monobasic Sodium Phosphate Monohydrate	0.43	4.3	1290.0
Hydrochloric Acid, 1N	Adjust pH to 6.8 – 7.0 if needed		
Sodium Hydroxide, 1N	Adjust pH to 6.8 – 7.0 if needed		
Purified Water	q.s. ad 100%	q.s. ad 1 mL	q.s. ad 300 L

[a] 0.68% timolol maleate corresponds to 0.5% timolol free-base.

[b] Added as weight of 10% w/v stock solution.

(JTX–9 at AGN_COMBI0055391.)

125. Because the final formula is disclosed and claimed in the patents-in-suit, the patent inherently discloses all of the drug formulation challenges presented at trial even though the specifications of the patent may not specifically discuss these formulation challenges. That is, the claims are not directed to a general abstract combination of two drugs, but instead are directed to a specific formulation that was determined only after overcoming the inherent formulation challenges. Thus, Defendants assertion that the patents-in-suit do not set forth any difficulties in development of the fixed combination product is a self-serving view of what the patents-in-suit disclose. Again, both Dr. Tanna and Dr. Laskar admitted that they did not consider or take into account any information about the actual formulation work done by the inventors. (D.I. 240, Trial Tr. Day 2(AM) at 120:3–7 (Tanna); D.I. 241, Trial Tr. Day 2(PM) at 144:12–18; 145:17–20 (Laskar).) Moreover, Dr. Laskar agreed that formulation difficulties are an important part of obviousness considerations, and admitted to applying for his own combination patent where there were formulation challenges overcome in making the combination. (D.I. 241, Trial Tr. Day 2(PM) at 160:10–19 (Laskar).)

2. Clinical Challenges in Developing Combigan®: Reducing Brimonidine Therapy from Three to Two Times a Day Without Loss of Efficacy

126. In addition to the significant formulation challenges that the inventors of the four patents-in-suit faced, there was also a unique clinical challenge in the development of Combigan®. According to Ms. Amy Batoosingh, the clinical lead for the project and an inventor on the patents-in-suit, reducing the dose of brimonidine from three times a day to twice a day without losing efficacy was the key clinical challenge on the product:

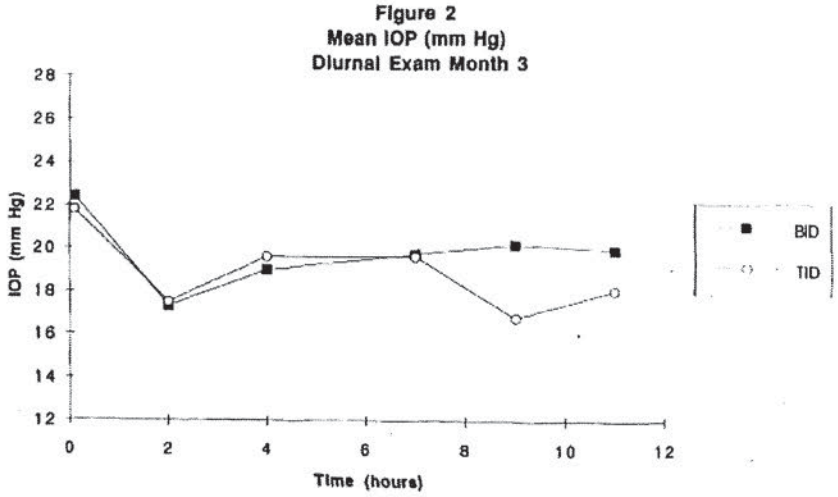
> Q. From the clinical perspective that you brought to the project, what were the challenges in developing a brimonidine combination product?

> A. The—I suppose there were—you know, the key challenge was the fact that we were taking Brimonidine, which we knew was a three-times-a-day drug, and trying to combine it with something that was likely a once- or twice-a-day drug.

(D.I. 239, Trial Tr. Day 1(PM) at 94:5–12 (Batoosingh); *see also* JTX–9 at AGN_COMBI0000684 (Alphagan®'s "recommended dose is one drop of ALPHGAN® in the affected eye(s) three times daily, approximately 8 hours apart"); PTX–74 at AGN_COMBI0478516 (noting that, for timolol, "[t]he usual starting dose is one drop of 0.25 percent TIMOPTIC in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) twice a day."); *id.* ("Dosages above one drop of 0.5 percent TIMOPTIC twice a day generally have not been shown to produce further reduction in intraocular pressure".).)

127. As fully set forth below, Allergan had little reason to believe that it would be successful in reducing the dosing of brimonidine from three to two times a day. Even putting aside the FDA's historic reluctance to approve fixed combinations, Allergan had already tried and failed to convince the FDA that brimonidine could be given twice a day with multiple products. (D.I. 238, Trial Tr. Day 1(AM) at 58:13–59:9 (Whitcup) ("And so the hurdle rate we knew for a combination glaucoma product was fairly substantial. You know, as—as you noted, Alphagan was a three-times-a-day drug, and the FDA made it quite clear that unless we were able to show a reasonable IOP control over the course of the day going from three times a day to twice a day, that they would not approve the drug."); PTX–75.)

128. The reason for Allergan's prior failures was the significant difference in the IOP-lowering effect of brimonidine dosed BID compared to brimonidine dosed TID. In support of its NDA for Alphagan® and its request for BID dosing of the drug, Allergan submitted, among other things, clinical study A342–119–7831, which compared the IOP lowering effect of BID brimonidine with TID brimonidine. (PTX–134.) That study showed that at hour nine, two hours after the TID group received their second dose of brimonidine and nine hours after the first (and only) dose of brimonidine was administered to the BID group, there was approximately a 3.25 mm Hg difference in IOP lowering effect between the two groups:



(PTX–134 at AGN_COMBI0676465; *see also id.* at AGN_COMBI0676405–406 (showing that the mean change in IOP was –2.07 for the BID group and –5.31 for the TID group at hour 9, a difference that was statistically significant with a p value of <0.001).)

129. This phenomenon is known as the "afternoon trough" of IOP with BID dosing of Alphagan®, so named because the effect of the drug has largely worn off-i.e., it is at its "trough." (D.I. 239, Trial Tr. Day 1(PM) at 77:13–7 (Batoosingh); *id.* at 78:3–7.) The added effect of the third dose in the afternoon is known as the "afternoon peak" of TID dosing, so named because the effect of that afternoon dose is at its "peak." (*Id.* at 79:6–23 (Batoosingh).) By way of example, the "morning trough" with both BID and TID dosing occurs at hour zero in the above graph, and the "morning peak" with both BID and TID dosing occurs at hour two. (*Id.* at 77:9–78:21 (Batoosingh).)

130. Ms. Batoosingh testified that the difference at hour 9 between the two treatments was "not only numerically significant; it's also clinically relevant and statistically significant." (D.I. 239, Trial Tr. Day 1(PM) at 79:24–80:8 (Batoosingh).) Moreover, two hours later, the difference between the BID and TID dosed groups was still "[a]bout 1–1/2 millimeters of mercury, and it was still statistically significant and clinically relevant." (D.I. 239, Trial Tr. Day 1(PM) at 80:16–19 (Batoosingh); *see also* PTX–134 at AGN_COMBI067645; *id.* at AGN_COMBI0676405–406 (showing that the mean change in IOP was –2.51 for the BID group and –4.01 for the TID group at hour 11, a difference that was statistically significant with a p value of 0.020).)

131. The results from Allergan's clinical study A342–119–7831 were published both in an abstract by Rosenthal (DTX–138), and in a full length article by Walters (DTX–137).

132. While the Rosenthal abstract notes only that the BID and TID regimens have no statistically significant difference at the morning trough,[9] the article by Wal-

9. Defendants focus on the abstract's conclusion, which states: "Dosing of brimonidine 0.2% TID offered no clinically significant advantage over BID dosing. Brimonidine 0.2% was effective in the lowering of elevated IOP and was well-tolerated in patients with open-angle glaucoma or ocular hypertension."

ters provides more information. As the Walters paper states:

> In the three times daily group, an additional mean decrease in IOP of 3.5 mm Hg was observed at hour 9 after the morning dosing (2 hours following the afternoon dosing). However, this additional IOP decrease diminished to within 1.5 mm Hg for the twice daily group by hour 11 (evening).

(DTX–137 at DEFS(B/T) 000346.)

133. Thus, one of ordinary skill in the art would have been aware as of the date the Walters paper was published, November 1996, that there was a significant decrease in efficacy when brimonidine was dosed BID versus when it was dosed TID. (*See* D.I. 239, Trial Tr. Day 1(PM) at 125:1–6 (Batoosingh); *id.* at 126:13–127:6.) Indeed, Defendants' expert Dr. Tanna agreed. (D.I. 241, Trial Tr. Day 2(PM) at 5:10–19 ("Q. So isn't it true that one of skill in the art would look at Walters and see that there was a statistically significant decrease in IOP at 9.0 hours after morning dosing on the three-times-a-day brimonidine? A. Yes. And it is overall, in my opinion, that three-times-a-day Brimonidine is more effective than twice-a-day Brimonidine.").)

134. Based at least in part on the data from clinical study A342–119–7831, the FDA rejected Allergan's efforts to achieve approval of BID dosing of brimonidine. Instead, in 1996, the FDA approved Alphagan® 0.2% only for TID dosing, despite the fact that Allergan's Phase III clinical trials were conducted on patients receiving only BID dosing of brimonidine. (PTX–75; D.I. 239, Trial Tr. Day 1(PM) at 87:12–24.) (Batoosingh). The third afternoon dose was believed so important that, in a "very unusual" move, the FDA granted approval to Alphagan® 0.2% for TID dosing despite the fact that, to that point, Allergan had not conducted Phase 3 safety or efficacy clinical trials on Alphagan® 0.2% dosed TID. (*Id.* at 88:4–20) (Batoosingh). ("Q. In your experience, is that unusual? A. Very.") According to Ms. Batoosingh, that has not happened before or since in her experience with the FDA in ophthalmic products. (*Id.*)

135. Allergan tried again with Alphagan® P 0.15% to achieve BID dosing for brimonidine. The FDA rejected those efforts as well. (D.I. 239, Trial Tr. Day 1(PM) at 92:15–20 (Batoosingh) ("Q. In connection with Alphagan P, did Allergan try to get twice-a-day approval for—or twice daily dosing with the product? A. Yes, we did. Q. Did FDA accept that? A. No, they did not.").)

136. With Combigan®, the inventors again aimed for the goal of BID dosing for a brimonidine product. Expectations, however, were not high. (PTX–41 at AGN_COMBI0415218 ("expectations were not high for U.S. approval of Combigan").) Combining brimonidine with timolol gave the inventors little hope that their efforts to reduce the dose of brimonidine to twice-a-day without loss of efficacy would be successful. As Ms. Batoosingh testified:

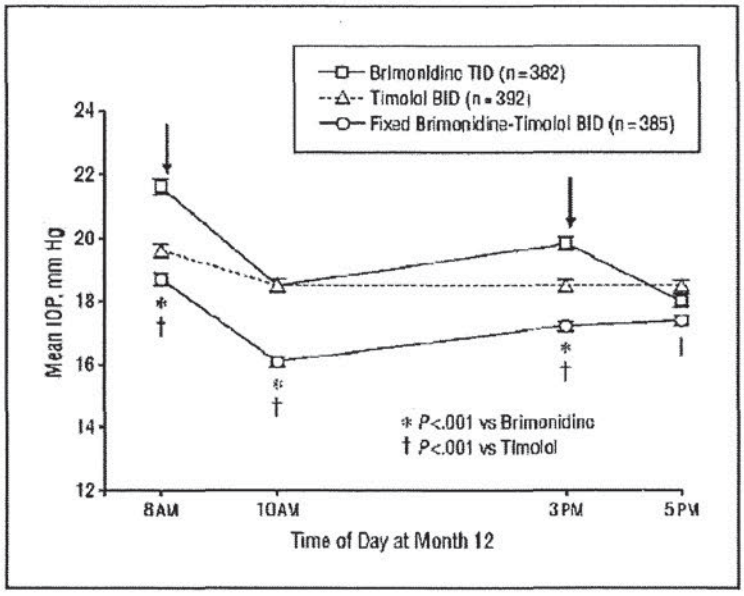
> Q. Did the prospect of combining Brimonidine with Timolol give you hope that you could overcome that challenge?
> A. No.
> Q. Why not?

(DTX–138.) As explained by Ms. Batoosingh, at the time of the abstract's publication the morning trough and peak IOP measurements were thought to be the most important. (D.I. 239, Trial Tr. Day 1(PM) at 83:1–21 (Batoosingh).) Accordingly, if two therapies had no difference at those time points, it was a common view that the two therapies were, clinically, the same. (*Id.*) The FDA rejected this viewpoint in the consideration of Alphagan® and Alphagan® P, and, as explained by Dr. Noecker, it is now accepted that IOP control throughout the day is critical to the preservation of sight. (D.I. 242, Trial Tr. Day 3(AM) at 147:1–148:9 (Noecker).)

A. Because there wasn't anything that said that made sense.

(D.I. 239, Trial Tr. Day 1(PM) at 94:22–95:2 (Batoosingh); *see also id.* at 98: 3–8 (Batoosingh) ("There was nothing that said, when you dose Timolol in the same bottle as Brimonidine, eight hours later, you're going to be able to eliminate that peak effect of Alphagan dosed three times a day.").)

137. Despite this challenge and the past record of failure, Allergan was able to demonstrate that the dosing for brimonidine could be reduced from the three-times-a-day required for Alphagan® and Alphagan® P to a more convenient two-times-a-day dosing for Combigan® while maintaining equal efficacy to the three times a day dosing. (D.I. 238, Trial Tr. Day 1(AM) at 92:5–11 (Whitcup); PTX–100 at COMBI0551262.) Specifically, Allergan was surprisingly able to eliminate the afternoon trough in IOP lowering that had been shown to occur when brimonidine was dosed only twice a day. (*See, e.g.*, PTX–77.) In the two pivotal clinical trials on Combigan®, numbered 190342–012T and 190342–013T (the "012T study" and "013T study," respectively) Allergan was able to show that Combigan® dosed BID showed numerically better and statistically equivalent IOP lowering compared to brimonidine monotherapy dosed TID:



(PTX 77 at AGN_COMBI0481543.) As Ms. Batoosingh testified,

Q. And what did you see when you combined them with respect to that afternoon third dose that was your concern?

A. We were able to—by putting the two drugs into the same bottle, we were able to improve the IOP effect so much so that it eliminated that difference that we saw with BID dose Alphagan when it was compared with Alphagan three times a day. The IOP lowering of Combigan throughout the entire day was greater for the earlier time points and the same at that peak Alphagan midday dose time point.

(D.I. 239, Trial Tr. Day 1(PM) at 96:16–97:1.)

138. The fact that Combigan® was able to eliminate the significant difference that had previously been observed and reported for twice a day brimonidine versus three times a day brimonidine was surprising to the inventors, to Allergan, and to the industry. As Ms. Batoosingh testified:

> Q. Ms. Batoosingh, based on your experience as a working clinical trial sand your work with Alphagan and Alphagan P, were you surprised by the result with Combigan in achieved in the IOP lowering?
>
> A. I was very surprised.

(D.I. 239, Trial Tr. Day 1 (PM at 97:23–98:2.))

139. Similarly, Allergan's expert, Dr. Noecker testified that one of skill in the art would have found the magnitude of the efficacy effect shown with Combigan® to be "rather striking." (D.I. 243, Trial Tr. Day 3(PM) at 23:5–18) (testifying that one of skill in the art would have expected a "neutral effect" from the addition of timolol to BID brimonidine, and that "We suspect (sic) that it might have some positive effect, but that magnitude is really what's rather striking. It really eliminated that—that difference we saw in those other studies, which was the TID dose three-times-a-day dosing, and twice-a-day dosing.")

140. In addition to these surprising efficacy results, clinical trials demonstrated that combining brimonidine and timolol resulted in an unexpected reduction in side effects. First, in the two pivotal clinical studies conducted on Combigan®, the 012T and 013T studies, Allergan and the inventors saw a statistically significant reduction in ocular allergy as compared with brimonidine monotherapy. (JTX–9 at AGN_COMBI0007714; *id.* at AGN_COMBI0060050.)

141. The reduction in allergy was not due to the reduction in brimonidine dosing from TID to BID because the dose reduction was not shown to significantly reduce the allergy rate. (PTX–123.) Instead, the significant allergy reduction, which came as a surprise to the inventors, appears to be attributable to combining brimonidine and timolol into a single, fixed-combination formulation. A clinical study comparing Combigan® to brimonidine 0.2% monotherapy dosed twice a day showed that Combigan® still led to a 50% lower incidence of ocular allergy, comparable to the allergy reduction for Combigan® compared to brimonidine dosed three times a day. (PTX–123 at AGN_COMBI0644507–508; D.I. 243, Trial Tr. Day 3(PM) at 35:23–36:14 (Noecker).)

142. Additionally, patients treated with Combigan® had significantly fewer incidences of nervous system side effects when taking Combigan® compared to brimonidine. For example, they experienced less somnolence (i.e., sleepiness) and oral dryness. (PTX–9 at AGN_COMBI0007714; *id.* at AGN_COMBI0060050.) Given that glaucoma is a disease that primarily affects the elderly, this reduction in side effects provides meaningful benefits to a vulnerable patient population.

143. Allergan demonstrated the significant reduction in somnolence and oral dryness as compared with adjunctive therapy using brimonidine TID and timolol BID in clinical trials 190342–023T and 190342–024T. Specifically, the 024T study, which examined patients greater than 40 years old, the patients most likely to suffer from glaucoma, found an over two fold greater risk of sleepiness in patients treated with the adjunctive therapy as compared to the fixed combination. (PTX–9 at AGN_COMBI0022630.) The 024T study also showed a significant reduction in dry mouth from 20.6% in patients treated with

the adjunctive therapy to 14.8% in patients treated with the fixed combination therapy. (*Id.*)

144. As a result, the FDA approved Combigan® in 2007, after "roughly a decade of work" and five clinical trials. (D.I. 238, Trial Tr. Day 1(AM) at 58:20–25.) When the FDA finally approved the New Drug Application ("NDA") for Combigan® in October of 2007, after several rounds of clinical studies, it was the first fixed combination glaucoma product approved in over nine years. (PTX–92; PTX–129 at AGN_COMBI0672990 (noting that, as of mid–2005, "no new agent of this type has entered the market in 7 years").)

145. FDA approval of Combigan® was a complete surprise to those in the industry. (PTX–118 at AGN_COMBI0642729 ("The approval came as a surprise to us and the Street, all of whom downplayed the potential approvability of this drug"); PTX–119 at AGN_COMBI0642734 ("Combigan Approval Is a Welcome Surprise from the Pipeline"); PTX–120 at AGN_COMBI0642741 ("Combigan Finally Approved In The U.S.; This Is An Upside Surprise"); PTX–121 at AGN_COMBI0642748 ("In a surprising move, the FDA has approved Combigan, the first combination beta-blocker alpha-blocker approved by the FDA for glaucoma."); PTX–127; D.I. 238, Trial Tr. Day 1(AM) at 94:20–96:22 (Whitcup).)

146. Dr. Noecker confirmed the surprise of the industry:

> Q. And as an ophthalmologist, were you surprised when Combigan was approved?
>
> A. I was shocked.

(D.I. 242, Trial Tr. Day 3(AM) at 79:22–24.) The Court found Dr. Noecker to be a very credible witness whose testimony was well supported by the evidence presented at trial.

III. CONCLUSIONS OF LAW

147. The Court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this Court and the parties are subject to personal jurisdiction for purposes of this action, in this Court. (D.I. 233 at 16.)

148. After having considered the entire record in this case and the applicable law, the Court concludes that: (1) each of the Defendants infringe claim 4 of the '149 Patent, claim 1 of the '976 patent, claims 1–6 of the '463 Patent, and claims 1–9 of the '258 Patent; and (2) the patents-in-suit are not invalid.

A. Infringement

1. There Is No Dispute that Defendants Infringe Claim 4 of the '149 Patent, Claim 1 of the '976 Patent, Claims 1–6 of the '463 Patent, and Claims 1–9 of the '258 Patent

[1] 149. Infringement is a question of fact, *e.g., Scanner Techs. Corp. v. ICOS Vision Sys. Corp.*, 528 F.3d 1365, 1382 (Fed.Cir.2008), and must be proven by the preponderance of the evidence, *e.g., Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1310 (Fed.Cir. 2005).

150. As noted above, Sandoz, Alcon, Apotex, and Watson have each stipulated that the products described in each of their ANDAs, ANDA Nos. 91–087, 91–574, 91–442, and 201949, respectively, including use of the product, would meet each and every limitation of claim 4 of the '149 patent, claim 1 of the '976 patent, claims 1–6 of the '463 patent, and claims 1–9 of the '258 patent.[10] (D.I. 234.) Thus, there

10. Allergan also alleged that each of the Defendants infringed claims 1–3 of the '149 patent. The Court informed the parties on July 20, 2011, that it would grant Defendants' motion for summary judgment of non-infringement of those claims. (D.I. 218.)

is no dispute between the parties that each of the Defendants infringes each of the asserted claims pursuant to 35 U.S.C. § 271(e)(2). (*Id.*)

151. Accordingly, the Court concludes that each of the Defendants infringe claim 4 of the '149 Patent, claim 1 of the '976 patent, claims 1–6 of the '463 Patent, and claims 1–9 of the '258 Patent.

B. Validity over the Prior Art

152. Patents are presumed valid, and the accused infringer has the burden of proof to prove invalidity by clear and convincing evidence. 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, —— U.S. ——, 131 S.Ct. 2238, 2242, 180 L.Ed.2d 131 (2011). The Court concludes that defendants have failed to prove by clear and convincing evidence that the patents-in-suit are invalid as being anticipated or obvious.

153. Defendants' presented two bases for the invalidity of all the asserted claims over the prior art at trial. These were: (1) anticipation by U.S. Patent No. 5,502,052 to DeSantis [11] ("DeSantis") and (2) obviousness over DeSantis when viewed by a person of ordinary skill in the art. (D.I. 240, Trial Tr. Day 2(AM) at 11:11–16 (Tanna); *id.* at 12:21–13:15 (Tanna); D.I. 241, Trial Tr. Day 2(PM) at 77:22–78:8 (Laskar).)

154. Allergan disputes that DeSantis anticipates or renders obvious any of the claims of the patents-in-suit. With respect to obviousness specifically, Allergan asserts that one of skill in the art would not have reason reading DeSantis to develop the claimed combination methods and compositions, particularly given the unpredictable nature of the field, the factors that teach away from a fixed combination of brimonidine and timolol, and the presence of several secondary considerations of non-obviousness.

155. In support of their assertions, Defendants presented the opinions of Dr. Tanna and Dr. Laskar. Dr. Tanna opined only as to the '149 and '976 patents, i.e., the "method of treating" patents, while Dr. Laskar opined only as to the '258 and '463 patent. (D.I. 240, Trial Tr. Day 2(AM) at 105:9–21 (Tanna); D.I. 241, Trial Tr. Day 2(PM) at 46:4–7 (Laskar).)

156. At trial, Dr. Tanna admitted that he did not consider any formulation difficulties faced by the inventors in his obviousness analysis and does not consider himself to have expertise in the area of formulation. (D.I. 240, Trial Tr. Day 2(AM) at 120:3–7 (Tanna) ("Q: So I take it you did not take into consideration any formulation difficulties the formulators in this case may have faced when rendering your obviousness opinion? A: Correct. I—I did not."); D.I. 240, Trial Tr. Day 2(AM) at 119:14–120:2 (Tanna).)

157. As for Dr. Laskar, while he had formulation expertise, he admitted at trial he did not take into account any information about the actual formulation work done by the inventors. (D.I. 241, Trial Tr. Day 2(PM) at 144:12–18; 145:17–20 (Laskar).) Dr. Laskar admitted to not even asking for the inventors' laboratory notebooks, but instead looked at the patent and assumed that this was the starting formulation. (D.I. 241, Trial Tr. Day 2(PM) at 144:19–23; 145:17–20 (Laskar).) Despite adopting this approach, Dr. Laskar agreed that formulation difficulties are an important part of obviousness considerations, and admitted to applying for his own combination patent where there were formulation challenges overcome in making the

11. DeSantis qualifies as prior art to the patents-in-suit under 35 U.S.C. § 102(b), and is statutory prior art to the patents-in-suit.

combination. (D.I. 241, Trial Tr. Day 2(PM) at 160:10–19 (Laskar).)

158. For Allergan, Dr. Noecker testified on the issue of validity as to all four patents-in-suit. (D.I. 242, Trial Tr. Day 3(AM) at 90:6–14 (Noecker).) While not a formulator per se, Dr. Noecker testified that he was very familiar with the issues faced by formulators, as he collaborates with them frequently. (D.I. 242, Trial Tr. Day 3(AM) at 62:9–14 (Noecker); *id.* at 64:9–65:9.) Dr. Noecker also testified that he had worked on ophthalmic formulations in the past. (D.I. 242, Trial Tr. Day 3(AM) at 62:15–20 (Noecker).) Again, the Court found Dr. Noecker to be a very credible witness whose testimony was well supported by the evidence presented at trial.

1. The Applicable Level of Ordinary Skill in the Art

159. Dr. Noecker opined that a person of ordinary skill in the art is "a person engaged in developing pharmaceutical formulations and treatment methods for the eye, or is a specialist in treating diseases of the eye such as an optometrist or ophthalmologist who also has experience either in developing ophthalmic pharmaceutical formulations or in designing and running clinical trials on such formulations. This person may also work in collaboration with other scientists and/or clinicians who have experience developing ophthalmic pharmaceutical formulations, running clinical trials related to such formulations, and/or treating patients using such formulations." (D.I. 242, Trial Tr. Day 3(AM) at 90:15–91:17 (Noecker).)

160. Defendants' experts' definition was as follows:

> A POSITA of ophthalmology and ophthalmic formulations for the patents-in-suit would have a Ph.D. degree in pharmaceutical chemistry, pharmacology, biological sciences, anatomy, or toxicology, a medical degree, M.D., or an optometry degree, O.D.
>
> It can also be a medical doctor who concentrates on ophthalmology and who administers and/or prescribes medications for the treatment of glaucoma or ocular hypertension.
>
> A POSITA of ophthalmology and ophthalmic formulations for the patents-in-suit may instead have a M.S. degree in pharmaceutical chemistry, pharmacology, biological sciences, anatomy, or toxicology, along with significant laboratory and/or industrial experience.
>
> A POSITA of ophthalmology and ophthalmic formulations for the patents-in-suit may also have obtained skill in the art through significant actual experience in the field, such as publishing in the area of glaucoma or through specialized training, such as postgraduate training or residency training.

(D.I. 240, Trial Tr. Day 2(AM) at 46:6–47:4.)

161. It is unclear whether Defendants' definition excludes inventors Beck, Pratt, and Batoosingh from its ambit of the person of ordinary skill. While not a fatal flaw, the Court nonetheless adopts Allergan's definition for purposes of clarity. *Neupak, Inc. v. Ideal Mfg. and Sales Corp.*, 41 Fed.Appx. 435, 440 (Fed.Cir. 2002) (noting that although obviousness is determined from the perspective of a hypothetical person of ordinary skill in the art, the inventors' perspective is nonetheless relevant).

162. Other than Defendants' economic expert Dr. Hay, each of the parties' experts qualifies as a person of ordinary skill in the art under either party's definition.

2. Defendants' Anticipation Defenses Pursuant to 35 U.S.C. § 102

a. The Legal Standard for Anticipation

[2] 163. A patent is invalid as "anticipated" under 35 U.S.C. § 102 if a single prior art reference discloses each element of the claimed invention. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed.Cir.2005); *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed.Cir.1999). The standard for anticipation is one of strict identity. Federal Circuit decisions have repeatedly emphasized that anticipation is established only if all the elements of an invention, as stated in a patent claim, are identically set forth in a single prior art reference. *See, e.g., Xerox Corp. v. 3Com Corp.*, 458 F.3d 1310, 1322 (Fed.Cir. 2006) ("[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention."); *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1335 (Fed.Cir.2002) ("As we have repeatedly stated, anticipation requires that each limitation of a claim must be found in a single reference.") Disclosure of each element of the patent claim in the single prior art document is not enough; to establish anticipation the single prior art document must disclose of all elements of a claimed invention "arranged as in the claim." *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed.Cir. 2001); *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed.Cir.1983).

[3–5] 164. To invalidate a patent by anticipation, a prior art reference must disclose each and every limitation of the claim. However, a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. *In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1371 (Fed.Cir.2007); *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1375 (Fed.Cir.2006); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed.Cir.2003). If a limitation is not explicitly disclosed in an allegedly anticipating prior art reference, the defendants bear the burden of showing that the limitation is inherently disclosed by the reference. *Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1052 (Fed.Cir.1994). To establish inherency, the anticipatory feature or result must be consistent, necessary, and inevitable, not simply possible or probable, and it should be clear that it would be so recognized by persons of ordinary skill. *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 1000 (Fed.Cir.2006); *In re Robertson*, 169 F.3d 743, 745 (Fed.Cir. 1999). That is, inherency may not be established by probabilities or possibilities, and the mere fact that a certain thing may result from a given set of circumstances is not sufficient to show inherency. *In re Robertson*, 169 F.3d at 745.

[6, 7] 165. To anticipate, the identical subject matter must not only be disclosed by the single prior art reference, but also the disclosure must be sufficiently enabling to place the information in the possession of the public. "An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art and that such existence was recognized by persons of ordinary skill in the field of the invention." *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed.Cir.1995). Furthermore, anticipation requires enablement, whereby the reference "must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation." *Elan Pharmaceuticals, Inc. v. Mayo Foundation*, 346 F.3d 1051, 1054–55 (Fed.Cir.2003). A prior art reference that does not enable a person of ordinary

skill in the art to practice the claimed invention does not anticipate the patent claims. *Helifix Ltd. v. Blok–Lok, Ltd.*, 208 F.3d 1339 (Fed.Cir.2000).

166. "It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus." *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d at 999. "There may be many species encompassed within a genus that are not disclosed by a mere disclosure of the genus." *Id.*

167. Although a patent's specific claims may be subsumed in a prior art reference's generalized disclosure, this is not literal identity. *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1572 (Fed.Cir. 1992). A patent claim to a functionally defined chemical composition is not anticipated by a prior art reference that discloses a broad range of possible compositions. *Ultradent Products, Inc. v. Life–Like Cosmetics, Inc.*, 127 F.3d 1065 (Fed. Cir.1997). The burden is on Defendants to show that the prior art reference "would describe to one of skill in the art the tested combinations, or other combinations meeting the limitations of the claims, from among the many possible candidates." *Id.* at 1071.

[8] 168. Typically, testimony concerning anticipation must be testimony from one skilled in the art and must identify each claim element, state the witnesses' interpretation of the claim element, and explain in detail how each claim element is disclosed in the prior art reference. The testimony is insufficient if it is merely conclusory. *Koito Mfg. Co., Ltd. v. Turn–Key–Tech, LLC*, 381 F.3d 1142, 1151–52 (Fed.Cir.2004) (reversing a finding of anticipation even though the challenger entered a prior art reference into evidence, but otherwise failed to provide any testimony or other evidence that would demonstrate to the fact finder how that reference met the limitations of the claims of the asserted patent or how the reference enabled one of ordinary skill in the art to practice the claimed invention).

[9] 169. Evidence of secondary considerations, such as unexpected results or commercial success, is irrelevant to the 35 U.S.C. § 102 analysis. *See In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A.1973).

b. DeSantis Does Not Anticipate the Asserted Claims

[10] 170. "[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention." *Xerox Corp. v. 3Com Corp.*, 458 F.3d 1310, 1322 (Fed.Cir. 2006). In the context of a prior art reference that discloses a broad genus of possibilities, that prior art reference does not typically anticipate every species found in the genus. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed.Cir.2006). Moreover, a prior art reference that discloses a range of possible values for a property of a claimed invention does not disclose any particular value in that range. *Id.* at 999–1000. Thus, in *Atofina* a prior art reference that disclosed a temperature range of 100° C to 500° C did not expressly or inherently anticipate a claimed range of 330° C to 450° C. *Id.* at 999.

171. Defendants contend that each of the claims of the patents-in-suit is invalid under 35 U.S.C. § 102(b), because the subject matter recited in those claims was described either explicitly or inherently by DeSantis more than one year prior to the effective filing date of the patents-in-suit. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed.Cir.2005); *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed.Cir.1999); *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed.Cir.2003). Defendants further con-

tend that a person of ordinary skill in the art would have immediately envisaged 0.2% brimonidine tartrate as the alpha$_2$-agonist of choice in DeSantis. *In re Petering*, 49 C.C.P.A. 993, 301 F.2d 676, 681 (1962). In addition, Defendants contend that a person of ordinary skill in the art would have immediately envisaged 0.5% as the concentration of timolol maleate in DeSantis and the 0.01% and 0.005% concentrations of BAK. (*Id.*)

172. Allergan responds that DeSantis fails to anticipate any of the claims of the patents-in-suit, either expressly or inherently. The Court agrees with Allergan and finds that numerous elements of the claims are missing from the reference. Specifically, DeSantis fails to describe a fixed combination of brimonidine and timolol, and fails to disclose a method of treating glaucoma using such a combination. (D.I. 242, Trial Tr. Day 3(AM) at 96:11–15 (Noecker).) It also fails to disclose a method of reducing brimonidine treatment from three times a day to twice a day by using a fixed combination, and fails to disclose the specific concentrations of brimonidine (i.e., 0.2%), timolol (0.5%) and BAK (a range of 0.001% to 0.01% and the specific concentration of 0.005%) identified in the claims of the patents-in-suit.

173. At best, DeSantis discloses a very large genus of potential fixed combinations of alpha-agonists and beta-blockers, listing all known beta-blockers and alpha-agonists for theoretical use. (D.I. 242, Trial Tr. Day 3(AM) Tr. 96:6–9, 17–19 (Noecker).) "It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus. There may be many species encompassed within a genus that are not disclosed by a mere disclosure of the genus." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d at 999.

174. On its face, DeSantis identifies 56 different beta-blockers. (DTX–123 at 5:21–33.) Dr. Noecker testified that the 56 beta-blockers listed in DeSantis were a comprehensive list of all the beta-blockers. (D.I. 242, Trial Tr. Day 4(AM) at 98: 12–18 (Noecker); D.I. 243, Trial Tr. Day 3(PM) 74:23–24 (Laskar).) DeSantis discloses that the "most preferred" beta-blocker disclosed is betaxolol. (DTX–123 at 5:33.) The only examples disclosed in DeSantis is a formulation combining apraclonidine and betaxolol. (DTX–123 at 6:21–28; D.I. 241, Trial Tr. Day 2(PM) 156:3–8 (Laskar).) And while for reasons that are unclear, DeSantis includes timolol in its lone claim and its title, timolol is the only beta-blocker in the patent that is called out for criticism: "At least one beta-blocker, timolol, has increasingly become associated with serious pulmonary side effects attributable to its effect on beta–2 receptors in pulmonary tissue." (DTX–123 at 1:64–67; D.I. 243, Trial Tr. Day 3(PM) at 128:21–129:18 (Laskar).)

175. Given the lengthy list of beta-blockers in DeSantis, the Court finds that it does not point a person of skill to any particular beta-blocker, except betaxolol, which is included in a formulation in the patent. Indeed, Dr. Laskar was unable to opine whether a person of skill in the art would look at DeSantis and go immediately to betaxolol rather than timolol based on the difference in side effects between the two compounds. (D.I. 243, Trial Tr. Day 3(PM) at 128:9–17 (Laskar).)

176. With respect to alpha-agonists, DeSantis states that clonidine and its derivatives are the "preferred" alpha-agonists, and then goes on to disclose seventeen specific clonidine derivatives, singling out apraclonidine (p-amino clonidine) as "particularly well-suited." (DTX–123 at 3:21–4:40.) The experts agree that brimonidine is not one of the alpha-agonists listed in DeSantis specification. (D.I. 240, Trial

Day 2(AM) at 109:9–10 (Tanna); D.I. 242, Trial Day 3(AM) at 99:7–11 (Noecker).)

177. Instead, Defendants rely on DeSantis's incorporation by reference of a book chapter by Timmermans, which itself discloses approximately 197 alpha-agonists, but again does not disclose brimonidine by name. (DTX–124 at 21–41; D.I. 242, Trial Day 3(AM) at 100:3–6; 102:21–25.) In addition, DeSantis incorporates three other patents' listing of alpha-agonists. (DTX–123 at 2:24–28; D.I. 244, Trial Tr. Day 4 at 4:19–6:6.) The alpha-agonists disclosed by DeSantis constitute all potential alpha-agonists. (D.I. 242, Trial Day 3(AM) at 108:3–13 (Noecker).)

178. The discussion of alpha-agonists in Timmermans relates to the *cardiovascular* effects of alpha-agonists, and relates to *intravenous* administration of those drugs. (DTX–124 at 21, 29; D.I. 242, Trial Day 3(AM) at 100:7–10 (Noecker).) Arterial pressure is a different system than intraocular pressure and chronic glaucoma treatments are not administered via an IV. (D.I. 242, Trial Day 3(AM) at 100:7–10, 101:7–9, 106:13–16 (Noecker); *id.* at 101:21–102:2 (Noecker); D.I. 240, Trial Tr. Day 2(AM) at 128:9–15 (Tanna).) Timmermans does not refer anywhere to the topical administration of brimonidine to lower intraocular pressure, and suggests that brimonidine has much poorer activity than clonidine or apraclonidine in the cardiovascular applications it discusses. (DTX–124 at 21; D.I. 242, Trial Day 3(AM) at 106:13–16 (Noecker).) Neither DeSantis itself nor the Timmermans reference that it incorporates highlight that brimonidine should be selected as an alpha-agonist in a combination glaucoma drug among the numerous possibilities. (D.I. 242, Trial Day 3(AM) at 108:14–20 (Noecker).)

179. Moreover, because brimonidine was considered a "far from perfect" drug, due to its systemic side effects and potential for allergy, a person of skill in the art would be motivated to "do better." (D.I. 242, Trial Day 3(AM) at 109:1–7 (Noecker).) For example, in making a species of the genus of DeSantis, a person of skill might try an alpha-agonist with a longer half-life than brimonidine, a decreased likelihood of oxidization, and less central nervous system effects. (D.I. 242, Trial Day 3(AM) at 109:8–18 (Noecker).) Neither DeSantis nor Timmermans disclose the use of brimonidine in a glaucoma treatment, let alone a fixed combination treatment with timolol. Dr. Tanna's opinion that "a practitioner would have envisioned" brimonidine as the "go-to alpha–2 agonist" from simply reading DeSantis is unsupported by the evidence. (D.I. 240, Trial Day 2(AM) at 23:12–16 (Tanna).)

180. DeSantis further identifies nine different preservatives for possible use in the disclosed formulations. (PTX–123 at 5:45–48; D.I. 242, Trial Day 3(AM) at 109:23–110:4 (Noecker).) One of the preservatives listed is BAK, but also listed are chlorobutanol, sorbic acid and edetate disodium, all of which are less toxic than BAK. (D.I. 242, Trial Day 3(AM) at 110:22–111:3 (Noecker).)

181. For each of the ingredients it discusses, beta-blockers, alpha-agonists, and preservatives, DeSantis discloses a wide range of possible concentrations that can be used. DeSantis discloses a range of alpha-agonists of 0.02% to 2.0% by weight. (DTX–123 at 4:58–61; D.I. 242, Trial Day 3(AM) at 114:9–23 (Noecker).) Dr. Noecker explained that this range was all inclusive for glaucoma medications because at the high end the alpha-agonists will cause allergy and at the low end they will be "subtherapeutic." (D.I. 242, Trial Day 3(AM) at 114:14–20 (Noecker).) DeSantis discloses a range for beta-blockers of 0.01% to 3.0% by weight (DTX–123 at 5:36–39), above which "people's hearts would be stopping." (D.I. 242, Trial Day

3(AM) at 113:11–22 (Noecker).) DeSantis' range for preservatives, 0.001% to 1.0% by weight, is also a wide range, the high end of which would cause extensive cytotoxicity on the ocular surface by BAK. (DTX–123 at 5:48–6:1; D.I. 242, Trial Day 3(AM) at 115:18–22 (Noecker).)

182. These ranges teach nothing more than there are a lot of possibilities—they are broad but shallow in terms of differentiation or preference. (D.I. 242, Trial Day 3(AM) at 112:3–11 (Noecker).) Nowhere in the specification or the claims does DeSantis disclose a preferred concentration for an alpha-agonist, beta-blocker or preservative.

183. The specific concentration of 0.2% brimonidine is not disclosed in DeSantis and is not inherent in DeSantis. As discussed above, brimonidine is not listed in the DeSantis reference. Alphagan®, which was 0.2% brimonidine, had been on the market since 1996. (D.I. 242, Trial Day 3(AM) at 135:15–17 (Noecker).) Alphagan® P 0.15% had come on the market in 2001. (D.I. 242, Trial Day 3(AM) at 137:16–25 (Noecker).) Alphagan® P 0.15% was shown to work as well as 0.2% but with a significantly less side effect profile and was therefore the favored concentration at the time. (D.I. 242, Trial Day 3(AM) at 138:1–13 (Noecker).) Developing a combination drug with 0.2% brimonidine when 0.15% was available was "a step backwards." (D.I. 242, Trial Day 3(AM) at 138:20–139:3 (Noecker).) Even if one were to select brimonidine as a potential alpha-agonist for use in a fixed combination formulation based on DeSantis, which, as explained above, one would not, a person of skill in the art at the time of the invention would have selected brimonidine as formulated in Alphagan® P 0.15% rather than brimonidine as formulated in the inferior Alphagan® product.

184. Similarly, the specific concentration of timolol is not disclosed in DeSantis and is not inherent in DeSantis. The sole example in DeSantis does not use timolol. Looking at the label for Timoptic® ophthalmic solution, two concentrations are listed: 0.25% and 0.5%. (DTX–134 at DEFS(B/T) 000250 "Dosage and Administration"; D.I. 242, Trial Day 3(AM) at 134:10–15 (Noecker).) The basic understanding is that less medicine is better and Dr. Noecker explained that he was trained to start dosing at 0.25% Timoptic®. (D.I. 242, Trial Day 3(AM) at 134:17–135:2 (Noecker).) Even if one were to select timolol as a potential beta-blocker for use in a fixed combination formulation based on DeSantis, which, as explained above, one would not, a person of skill in the art at the time of the invention would have at least started with 0.25% timolol.

185. Notably, it is undisputed that Timoptic® had been on the market since 1978, in the 0.5% and 0.25% concentrations. (D.I. 240, Trial Tr. Day 2(AM) at 27:12–16 (Tanna); *id.* at 52:22–53:1 (Tanna).) Despite this, DeSantis fails to specifically identify either of these two concentrations for use in its claimed invention or anywhere else in the specification. This confirms that DeSantis is simply a laundry list of possibilities, and not a specific disclosure of any particular combination. *Ultradent Products, Inc. v. Life–Like Cosmetics, Inc.*, 127 F.3d 1065, 1071 (Fed.Cir. 1997) (explaining that there were many possible compositions that could have been made within the range of disclosures made by a prior art patent, which incorporated another patent by reference).

186. Indeed, simply taking the eighteen alpha-agonists, fifty-six beta-blockers, and nine preservatives that are disclosed on the face of DeSantis, DeSantis discloses 9,072 possible combinations of the named beta-blockers, alpha-agonists, and types of preservative identified on the face of the reference. (D.I. 242, Trial Day 3(AM) at

116:24–117:17 (Noecker).) Including just three possible concentrations of each alpha-agonist, beta-blocker, and preservative from the large ranges identified in DeSantis, which is the typical number of concentrations tested in a Phase II clinical trial, the number of possible combinations grows to 244,944. (D.I. 242, Trial Day 3(AM) at 117:18–118:2; 118:12–15 (Noecker).) None of those 244,944 possible combinations includes brimonidine. (D.I. 242, Trial Day 3(AM) at 118:16–19 (Noecker).) If one then includes the 197 possible alpha-agonists disclosed by Timmermans, the number of possible combinations grows to 99,288. (D.I. 242, Trial Day 3(AM) at 119:9–12 (Noecker).) Accounting for three possible concentrations, that number grows to 2,680,776 possible combinations of alpha-agonist, beta-blocker, and preservative that, according to Defendants, are "anticipated" by DeSantis. (D.I. 242, Trial Day 3(AM) at 119:13–17 (Noecker).)

187. One of ordinary skill in the art would thus not read DeSantis' disclosure of an enormous genus of potential fixed combinations to anticipate a brimonidine and timolol combination. (D.I. 242, Trial Day 3(AM) at 123:4–12 (Noecker).) Indeed, as a testament to the difficulties in developing combination drugs, the only claimed combination in DeSantis, apraclonidine and betaxolol, was never marketed or approved anywhere in the world. (D.I. 242, Trial Day 3(AM) at 119:18–25 (Noecker); D.I. 240, Trial Tr. Day 2(AM) at 131:22–24 (Tanna).)

188. Moreover, there is nothing in DeSantis or Timmermans disclosing the therapeutic effect of any of the tens of thousands of combinations for the treatment of glaucoma or ocular hypertension. Indeed, there is no clinical data in DeSantis whatsoever, either for the claimed apraclonidine/timolol combination, the disclosed apraclonidine/betaxolol combination or any other combination of alpha-agonist and beta-blocker. (D.I. 242, Trial Day 3(AM) at 112:12–15 (Noecker).)

189. Specific to claim 4 of the '149 patent, nothing in DeSantis discloses that reducing the dose of brimonidine from three times a day to two times a day through a fixed composition of brimonidine and timolol can maintain the efficacy of the brimonidine treatment. (D.I. 242, Trial Day 3(AM) at 127:10–21 (Noecker).) Dr. Tanna directed the court to two portions of the DeSantis reference that allegedly disclose this claim element: column 2 lines 41–48 and column 6 lines 34–40. (D.I. 240, Trial Day 2(AM) at 35:5–8 (Tanna).) The first reference in column 2 simply states the goal of achieving greater IOP lowering with the combination as compared to the individual ingredients. (DTX–123 at 2:41–48.) The second reference is preceded by the sentence: "The frequency and amount of the dosage will be determined by the clinician based on various clinical factors." (DTX–123 at 6:35–37.) Such clinical factors presumably include FDA-approved dosing regimens. Moreover, nothing in DeSantis teaches a *reduction* of dosing, as is specifically claimed in claim 4 of the '149 patent. (D.I. 240, Trial Day 2(AM) 138:13–14 (Tanna) ("Q: Where do you see the word reduced, Dr. Tanna? A: I don't see the word reduced."); *id.* at 138:24–139:4 (Tanna) ("Q: Where, Dr. Tanna, do you see a discussion anywhere in DeSantis regarding reducing the dosage of an alpha–2 agonist from three times a day to two times a day? A: Literally seeing those words together, I don't see them together.").)

190. Thus, DeSantis does not disclose a fixed composition of 0.2% brimonidine and 0.5% timolol, as required by independent claim 1 of the '976 patent, independent claims 1 and 7 of the '258 patent, independent claim 4 of the '149 patent, and independent claims 1 and 4 of the '463 patent.

(D.I. 242, Trial Day 3(AM) at 120:20–121:3; 121:24–122:11 (Noecker).) DeSantis does not disclose a fixed composition of 0.2% brimonidine and 0.5% timolol with a specific BAK concentration, as required by claims 2, 3, 8, and 9 of the '258 patent and claims 2, 3, 5, and 6 of the '463 patent. (D.I. 242, Trial Day 3(AM) at 124:7–17; 125:1–10 (Noecker).) DeSantis does not disclose a method of reducing the dose of brimonidine from three times a day to two times a day without losing efficacy in the treatment of glaucoma. (D.I. 242, Trial Day 3(AM) at 127:10–21 (Noecker).)

191. For all of these reasons, the Court is not persuaded that Defendants have established by clear and convincing evidence that the patents-in-suit are anticipated by DeSantis.

3. Defendants' Obviousness Defenses Pursuant to 35 U.S.C. § 103

a. The Legal Standard for Obviousness

[11] 192. A determination of obviousness is a legal determination based on four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), *cited in KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 1734, 167 L.Ed.2d 705 (2007).

[12] 193. When the patented invention is a combination of known elements, the Court must "determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue" by considering the teachings of multiple references, the effects of demands known to the design community or present in the marketplace, and the background knowledge possessed by a person having ordinary skill in the art. *KSR*, 127 S.Ct. at 1740–41.

194. "[K]nowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed [invention]." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed.Cir.2008) (concluding that the district court correctly dismissed an expert's vague and conclusory obviousness testimony, which did not offer any motivation for one skilled in the art to combine the particular references he cited in order to practice the claimed invention); *see also Graham*, 383 U.S. at 36, 86 S.Ct. 684 (discussing the "importance of guarding against hindsight ... and resist[ing] the temptation to read into the prior art the teachings of the invention in issue" when considering the obviousness of a patent).

195. Additionally, "[t]wo ingredients might be therapeutically effective when use separately as part of an overall treatment regimen, yet be incompatible or ineffective when combined in a single solution." *In re Brimonidine*, 643 F.3d 1366 (Fed.Cir. May 19, 2011) at Section B.2 (pinpoint cite unavailable); *see also Pozen Inc. v. Par Pharmaceutical, Inc., et al.*, C.A. No. 6:08–cv–00437, Slip Opinion at 4, 40.

[13] 196. Secondary considerations that provide evidence of non-obviousness include copying, commercial success, failure of others, long-felt need, general skepticism of those in the art, and unexpected results. *See KSR*, 127 S.Ct. at 1734. "As (the Federal Circuit) has repeatedly explained, this evidence is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness." *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed.Cir.2008) (citing *Catalina Lighting, Inc. v. Lamps Plus,*

Inc., 295 F.3d 1277, 1288 (Fed.Cir.2002) ("Objective indicia may often be the most probative and cogent evidence of nonobviousness in the record.")).

[14] 197. "[A] presumption arises that the patented invention is commercially successful 'when a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent.'" *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1376 (Fed.Cir. 2000). A prima facie case of nexus is made when the patentee shows both that there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310–1311 (Fed.Cir.2010). Once the patentee demonstrates a prima facie nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger. *Id.*

198. In an unpredictable art, such as the chemical arts, results are more likely to be unexpected and, thus, nonobvious. *See Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed.Cir.2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."); *see also Sanofi–Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085–90 (Fed.Cir.2008) (upholding nonobviousness finding of a chemical patent because of evidence that the patented result was unexpected and unpredictable).

[15] 199. If there is no proof that there were a finite number of identified and predictable solutions in the prior art at the time of the patented invention, this cuts against a finding of obviousness. *See Ortho–McNeil*, 520 F.3d at 1364 ("*KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness.... (T)his clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness."); *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1380 (Fed.Cir.2008) (affirming finding that the patents were not obvious when "(t)he district court gave lengthy consideration to the multiple paths that would have faced a person of ordinary skill in the art who recognized" the problem solved by the patents).

[16] 200. Obviousness is analyzed from the perspective of one of skill in the art at the time of the invention—the use of hindsight is not permitted. *See KSR*, 127 S.Ct. at 1742 (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness); *see also Ortho–McNeil*, 520 F.3d at 1364 ("In retrospect, (the inventor's) pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted.").

201. The field of ophthalmic drug formulation is an unpredictable art, and the Defendants have not shown that, for any of the patents-in-suit, there were an identified number of predictable solutions for the inventors. In fact, the evidence of record demonstrates the many reasons why one of skill would have been led away from the claimed inventions and does not provide any reasonable expectation of success in making the inventions. Defendants' arguments in support of obviousness are grounded in hindsight, and do not properly consider all the evidence about the development of the inventions.

202. Allergan also presented strong evidence of secondary considerations.

203. Defendants have not met their burden to provide clear and convincing evidence that the asserted claims of the patents-in-suit are invalid under 35 U.S.C. § 103.

b. DeSantis when viewed by One of Ordinary Skill in the Art Does Not Render the Asserted Claims Obvious

[17] 204. Defendants contend that the claims of the patents-in-suit are obvious based on the teachings of DeSantis alone, and combined with what was known by a person of ordinary skill in the art prior to April 2002 regarding the concentrations of brimonidine, timolol, and BAK in the commercial products Alphagan® and Timoptic®. The commercial product Alphagan®, available since 1996, was 0.2% brimonidine tartrate preserved in 0.005% BAK. The commercial product Timoptic®, available since 1978, was 0.5% timolol maleate preserved in 0.01% BAK. Thus, Defendants argue that a person of ordinary skill in the art would have considered the concentrations of brimonidine, timolol, and BAK recited in the claims of the patents-in-suit could be achieved through routine optimization by a person of ordinary skill in the art at the time. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341 (Fed.Cir.2009).

205. Defendants also contend that DeSantis in view of the commercial products Alphagan® (*See, e.g.*, Alphagan PDR) and Timoptic® (*See, e.g.*, Timoptic PDR) teach each and every limitation of the claims of the patents-in-suit.

206. Defendants also argue that articles of manufacture with instructions how to use the composition contained within the articles were well known to a person of ordinary skill in the prior art, especially in view of the commercial products of 0.2% brimonidine and 0.5% timolol, both available prior to April 2002.

207. Defendants also contend that a person of ordinary skill in the art would have reasonably expected successful reduction in the number of doses of medication administered while maintaining the same or enhanced efficacy based on, for example, the prior art Timpilo®'s and Cosopt®'s success in reducing the daily dose while maintaining or enhancing efficacy.

208. Defendants also argue that a person of ordinary skill in the art in April 2002 would have been motivated to combine DeSantis with what was known about the commercial products Alphagan® and Timoptic® to arrive at the claimed invention based on the teachings in DeSantis that some patients required more than one glaucoma medication to achieve adequate lowering of IOP, the known problem of patient compliance with multiple glaucoma medications, and the solution to both problems of putting two glaucoma medications in a single composition administered twice daily.

209. Defendants also contend that a person of ordinary skill in the art in April 2002 would have been motivated to combine DeSantis with what was known about the commercial products of Alphagan® and Timoptic® to arrive at the claimed invention based on: 1) the known IOP lowering effects of both 0.2% brimonidine and 0.5% timolol; 2) the known successful concomitant use of 0.2% brimonidine and 0.5% timolol BID that showed a greater IOP-lowering than either brimonidine or timolol used alone as monotherapy; and 3) the known compliance problem for patients taking more than one glaucoma medication. Defendants also argue that a person of ordinary skill in the art would have had a reasonable expectation of success because of the multiple, fixed combination glaucoma medications known prior to April 2002 and the fixed combination glaucoma medications that included 0.5% timolol as

one of the active ingredients known prior to April 2002. *See id.* at 407.

210. Defendants also argue that the claims of the patents-in-suit were a common sense solution to a known problem as set out in *KSR:*

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421, 127 S.Ct. 1727. That is, Defendants contend that the known problems of greater IOP-lowering and patient compliance were solved by the common sense, predictable solution of fixed combinations. Defendants argue that 0.2% brimonidine was the best known alpha$_2$-agonist for treating glaucoma and ocular hypertension prior to April 2002 and 0.5% timolol was the best known beta-blocker for treating glaucoma and ocular hypertension prior to April 2002. Defendants then note that 0.5% timolol was successfully used in fixed combination glaucoma products prior to April 2002 (*e.g.,* Timpilo®, Cosopt®, Xalacom®). Thus, Defendants conclude that putting 0.2% brimonidine and 0.5% timolol into a single bottle for the treatment of glaucoma and ocular hypertension was simply a matter of selecting from a finite number of identified, common sense, predictable solutions that was well within a person of ordinary skill in the art's technical grasp. For these reasons, the claims of the patents-in-suit would have at least been obvious to try.

211. Allergan disputes that DeSantis renders obvious any of the claims of the patents-in-suit. Allergan contends that one of skill in the art would not have reason reading DeSantis to develop the claimed combination methods and compositions, particularly given the unpredictable nature of the field, the factors that teach away from a fixed combination of brimonidine and timolol, and the presence of several secondary considerations of non-obviousness. The Court agrees with Allergan.

212. In their testimony, Defendants' experts discussed a number of references at trial that are not part of any combination and thus, per the Court's ruling on Allergan's motion *in limine,* cannot be asserted as part of a combination now. Though the references cannot be asserted as part of any obviousness combination, Defendants relied on them at trial as evidence of what a person of ordinary skill in the art allegedly would have known. These additional references are: Cantor (DTX–145), Physicians' Desk Reference for Timoptic and Brimonidine (DTX–134 and 129), Rosenthal (DTX–138), Netland (DTX–192), Soderstrom (DTX–164), Diestelhorst (DTX–156), Strohmeier (DTX–152), Sall (DTX–168A), Stewart (DTX–144), Larsson (DTX–167), Baudoin (DTX–204), Airaksinen (DTX–155), Clineschmidt (DTX–148), Boyle (DTX–200), and Hutzelmann (DTX–201). In addition, Defendants rely on anecdotal evidence of the use in the prior art of BID–BID concomitant therapy of brimonidine and timolol and TID–BID concomitant therapy of brimonidine and timolol. (D.I. 240, Trial Tr. Day 2(AM) at 71:7–11 (Tanna).)

213. Based on the above, Defendants appear to argue that DeSantis, including the material incorporated by reference from Timmerman's, renders all the asserted claims obvious because DeSantis discloses the general concept of making a fixed combination of an alpha–2–adrenergic agonist and a beta–blocker and the ref-

erences listed in previous paragraph would motivate or provide a reason for the person of ordinary skill in the art to make the claimed fixed combination of brimonidine and timolol and the methods of treating glaucoma with a "reasonable expectation of success" in doing so.

214. In considering Defendants' contentions, the court applies the law of obviousness as required by the Supreme Court and the Federal Circuit. Defendants' reliance on *KSR*'s "obvious to try" concept is misplaced. This is because in an unpredictable art, such as the chemical arts, results are more likely to be unexpected and, thus, nonobvious. *See Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed.Cir.2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."). If there is no proof that there were a finite number of identified and predictable solutions in the prior art at the time of the patented invention, this cuts against a finding of obviousness. *See Ortho–McNeil*, 520 F.3d at 1364 ("*KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness.... [T]his clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness.").

215. This unpredictability is no less true when the asserted combination of prior art includes two previously marketed products, in this case, the prior approved products Alphagan® 0.2% and Timoptic® 0.5%. "This fact alone does not establish that it would have been obvious to combine the two in a single formulation. Two ingredients might be therapeutically effective when used separately as part of an overall treatment regiment, yet be incompatible or ineffective when combined in a single solution." *In re Brimonidine*, 643 F.3d 1366 (Fed.Cir.2011) at Section B.2 (pinpoint cite unavailable).

216. The volume of references relied upon by Defendants also counsels against a finding of obviousness. Any suggestion to combine references "becomes less plausible when the necessary elements can only be found in a large number of references." *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, No. IP 02–0512–C–B/S, 2004 WL 1724632, at *34 (S.D.Ind. July 29, 2004).

217. As with their anticipation argument, many of the references relied on by Defendants were before the Patent and Trademark Office during prosecution. These are: DeSantis (for the '258 patent), Sall, (for all patents), Larsson (for all patents), Goni (for all patents), Clineschmidt (for the '258 patent), Airaksinen (for the '258 patent), Diestelhorst (for the '258 patent), Strohmeier (for the '258 patent), Alphagan® (for all patents), Timoptic® (for all patents), and Cosopt® (for the '258 patent). (*See* JTX–1; JTX–2; JTX–3; JTX–4; D.I. 242, Trial Tr. Day 3(AM) at 129:3–132:9 (Noecker).) Moreover, each of the patents-in-suit discloses, and discusses in its specification, the prior existing regimen of concomitant use of brimonidine and timolol in the unfixed combination. (JTX–1 at 1:7–12 ("The invention relates to the topical ophthalmic use of brimonidine in combination with timolol when indicated for treatment of glaucoma or ocular hypertension. Such combinations or formulations are available for separate use in the ophthalmic art and have been combined in serial application during the course of treatment of glaucoma.")).

218. In light of the above underlying law, the Court finds that Defendants have

failed to meet their burden to establish the obviousness of the asserted claims.

219. As discussed above, Defendants' main reference, DeSantis, suffers from numerous flaws as a prior art reference in relation to Combigan. These include:

- Tens of thousands, if not millions, of possible combinations (D.I. 242, Trial Tr. Day 3(AM) at 116:24–117:17; 117:18–118:2; 118:12–15; 119:13–17 (Noecker).)
- No discussion of potential incompatibility of different actives and different formulations (*Id.* at 112:3–11 (Noecker).)
- No clinical data on any particular combination (*Id.* at 112:12–15 (Noecker).)
- No discussion of the particular problems associated with brimonidine therapy, including the "afternoon trough" issue (D.I. 240, Trial Tr. Day 2(AM) at 109:9–10 (Tanna); D.I. 242, Trial Tr. Day 3(AM) at 99:7–11 (Noecker); DTX–124 at 21, 29; D.I. 242, Trial Tr. Day 3(AM) at 100:7–10 (Noecker).)
- No discussion of dose reduction by using a combination therapy (D.I. 242, Trial Tr. Day 3(AM) at 127:10–21 (Noecker); D.I. 240, Trial Tr. Day 2(AM) 138:13–14; 138:24–139:4 (Tanna).)
- While listing timolol, a specific caution against using timolol because of deleterious side effects (DTX–123 at 1:64–67; D.I. 243, Trial Tr. Day 3(PM) at 128:21–129:18 (Laskar).)

220. From this flawed disclosure, Defendants would have the Court find that, because brimonidine 0.2% and timolol 0.5% were on the market as of the relevant "critical date" for the patents-in-suit, a person of skill in the art, reading DeSantis would combine those two actives at those two concentrations to yield the claimed invention. The Court rejects Defendants' argument. As an initial matter, even as to concentrations of the two active ingredients, at the relevant time, the preferred concentration of Alphagan® was 0.15%, not 0.2%, and the starting point for timolol therapy was 0.25%, not 0.5%. (D.I. 242, Trial Tr. Day 3(AM) at 133:16–135:2; 137:16–138:13 (Noecker); D.I. 243, Trial Tr. Day 3(PM) at 79:17–80:4 (Noecker).) To say, as Defendants do, that 0.2% brimonidine and 0.5% timolol are the "obvious" choice presented by DeSantis upon reading by the person of ordinary skill is hindsight, the use of which is forbidden in the obviousness analysis. *See Grain Processing Corp. v. Am. Maize–Prods. Co.*, 840 F.2d 902, 907 (Fed.Cir.1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.' ").

221. Moreover, DeSantis's failure to provide any clinical data on the effectiveness of the purported combination and failure to discuss brimonidine specifically (beyond merely listing it by incorporating Timmerman's) is fatal to Defendants' argument. The problems faced by the inventors and solved by the claimed inventions were unique to brimonidine therapy, which had previously been approved in the United States only for three times a day use because of the "afternoon trough." (D.I. 239, Trial Tr. Day 1(PM) at 75:14–20; 77:13–17; 78:3–7; 90:16–91:10 (Batoosingh).) And while the claims do not require an FDA-approved product, certainly a person of ordinary skill in the art would be acutely aware of the FDA-approved label of brimonidine and the problems that it entailed for those trying to develop a fixed combination brimonidine product. (*See* D.I. 240, Trial Tr. Day 2(AM) at 55:17–56:4 (Tanna).) *See In re Cyclobenzaprine*, 794 F.Supp.2d 517, 536–37 (D.Del.

2011) (relying on FDA standards to support a motivation to combine); *Pozen Inc. v. Par Pharmaceutical, Inc., et al.*, C.A. No. 6:08–cv–00437, Slip Opinion at 4, 40.

222. In addition, DeSantis simply does not address the formulation difficulties that exist in making fixed combinations in the ophthalmic arts, the "most difficult" task in all of ophthalmological product development. (D.I. 238, Trial Tr. Day 1(AM) at 65:19–23) (Whitcup); D.I. 242, Trial Tr. Day 3(AM) at 64:9–65:3 (Noecker) (referring to therapeutic eye drops as "the trickiest thing to get right"). As Dr. Laskar conceded with respect to his own patent application, even putting aside any clinical challenges, such formulation difficulties by themselves can make patentable the combination of two previously known active ingredients into a fixed combination product. (D.I. 241, Trial Tr. Day 2(PM) 157:18–160:19) (Laskar) (agreeing that, with respect to his patent application on a combination product for acne treatment, he "believed at the time that [his] ability to combine those two monotherapies was new and novel and patentable"). DeSantis contains no discussion of such potential difficulties, and Defendants' experts failed to consider them. (D.I. 241, Trial Tr. Day 2(PM) at 145:17–20; 144:12–18; 145:11–13 (Laskar); D.I. 240, Trial Tr. Day 2(AM) at 120:3–7 (Tanna).)

223. The additional references relied upon by Defendants' experts do not cure these problems with DeSantis and simply demonstrate that Defendants position relies on hindsight. Each reference is discussed below.

224. Dr. Tanna relies on Cantor (DTX 145) for the position that a person of skill in the art would know that timolol was "the current medical management benchmark" for efficacy and safety. (D.I. 240, Trial Tr. Day 2(AM) at 51:2–5 (Tanna).) As Dr. Noecker explained, the FDA required, and still requires, any new glaucoma medication to be compared against timolol, even though timolol is not considered the "gold standard," nor was it at the time of the inventions of the patents-in-suit. (D.I. 242, Trial Tr. Day 3(AM) at 142:9–18 (Noecker).) Cantor does not suggest or motivate one of skill to combine timolol with brimonidine or that a fixed combination of brimonidine and timolol would reduce the dose of brimonidine from three times a day to twice a day without losing efficacy. (*Id.* at 142:19–22; 144:10–19 (Noecker).) In fact, Cantor does not even consider the afternoon dose in its study when it looks at the twice a day brimonidine versus three times a day brimonidine morning doses. (*Id.* at 143:4–11; 143:17–144:1 (Noecker).) It thus does not address at the problem faced by the inventors here.

225. Next, Dr. Tanna cites to the Rosenthal, et al. abstract (DTX–138), which compared the efficacy of brimonidine twice a day to brimonidine three times a day. (D.I. 240, Trial Tr. Day 2(AM) 57:15–58:2 (Tanna).) Ms. Batoosingh testified about this abstract, explaining that it presents data for the morning trough only and not the afternoon dose of brimonidine. (D.I. 239, Trial Tr. Day 1(PM) 82:8–17 (Batoosingh).) Dr. Noecker confirmed that the abstract contains no clinical data and speaks only to measurements done in the morning and does not address the difference between the different dosing regimens. (D.I. 242, Trial Tr. Day 3(AM) at 145:19–146:4 (Noecker).) Rosenthal does not mention timolol at all and does not teach that one of skill could avoid the afternoon dose of brimonidine and maintain efficacy if it were combined with timolol in a fixed combination. (*Id.* at 148:21–149:4 (Noecker).) Defendants' focus on the abstract's conclusion is misplaced for the reasons noted above.

226. Dr. Tanna next relies on a series of references for the proposition that, due to patient compliance issues, one of skill in the art would have been motivated to create a fixed combination glaucoma drug. (DTX–192, DTX–164, DTX–156, DTX–152.) This argument fails for multiple reasons. While not dispositive, the FDA does not consider increase in compliance in its safety and benefit analysis, so a person of skill in the art would not be motivated by increased compliance in developing a new glaucoma treatment for patients. As Dr. Whitcup testified:

> Q. So—but we heard from opposing counsel in opening how the whole purpose of a combination drug is patient compliance, that you're going to only have to use two drops instead of as many as five.
>
> Why—why isn't that good enough for the FDA?
>
> A. The FDA's current feeling is that the compliance piece has never been proven in a study, and compliance to date has had no impact on how they approve drugs.

(D.I. 238, Trial Tr. Day 1(AM) at 83:18–84:1 (Whitcup).) As explained by Ms. Batoosingh, and not genuinely contested by defendants, the FDA's perspective is something a person of skill in the art would take into account when developing a product such as Combigan®. (D.I. 239, Trial Tr. Day 1(PM) at 73:19–22 (Batoosingh).) Indeed, consistent with FDA's point of view, fixed combinations have drawbacks because they are fixed and therefore give ophthalmologists less flexibility. (D.I. 242, Trial Day 3(AM) at 79:7–18 (Noecker); D.I. 239, Trial Tr. Day 1(PM) at 66:8–16 (Batoosingh).)

227. Moreover, these references all suffer from the same flaw: none of them teach one of skill whether it is even possible to combine brimonidine with timolol in a fixed combination, let alone brimonidine at 0.2% and timolol at 0.5%, nor reduce the dosing of brimonidine from TID to BID. For example, Dr. Tanna cites to a fixed combination of timolol and pilocarpine, disclosed in the Soderstrom reference (DTX–164) and called Timpilo®, as an alleged example of how poor compliance issues were solved by a fixed combination drug. (D.I. 240, Trial Tr. Day 2(AM) at 62:15–24 (Tanna).) The Soderstrom paper makes no mention of brimonidine or a brimonidine and timolol combination, and actually shows that a fixed combination of pilocarpine and timolol is less effective than its individual components in lowering IOP in the afternoon, the opposite of what was needed for brimonidine. (DTX–164 at Table 3; D.I. 242, Trial Tr. Day 3(AM) at 150:8–15 (Noecker).) In addition, the Timpilo® product was a "lousy drug" (D.I. 242, Trial Tr. Day 3(AM) at 87:6–7 (Noecker)), in part because it was distributed as a dual-chamber product that the patient had to mix themselves. (*Id.* at 87:9–88:4 (Noecker); D.I. 241, Trial Tr. Day 2(PM) at 13:16–23 (Tanna).) Finally, as discussed above, while patient compliance may have created a need for fixed combination products, it did not motivate a person of skill in the art to develop fixed combinations with a reasonable expectation of success, because the FDA did not consider improving patient compliance as a factor in its approval decision. (D.I. 238, Trial Tr. Day 1(AM) at 83:18–84:1 (Whitcup).) Thus, this reference would not motivate a person of skill in the art to develop a fixed combination of pilocarpine and timolol, let alone a 0.2% brimonidine and 0.5% timolol combination product dosed BID.

228. Dr. Tanna also cites to a publication by Diestelhorst which studied a fixed combination of latanoprost and timolol. (DTX–156; D.I. 240, Trial Tr. Day 2(AM) at 64:1–9 (Tanna).) This reference fares no better than Soderstrom. The data in

Diestelhorst, which looks at the IOP lowering of fixed combinations of latanoprost and timolol versus latanoprost, merely shows mean IOP lowering, so no data is available regarding the afternoon dose. (D.I. 242, Trial Tr. Day 3(AM) at 153:4–6; 16–23 (Noecker).) The results showed that the studied combinations worked less well or only marginally better than latanoprost alone. (DTX–156 at Table 2, Figure 2; D.I. 242, Trial Tr. Day 3(AM) at 154:15–17 (Noecker).) Thus, Diestelhorst teaches a person of skill nothing about brimonidine and nothing about reducing the dose of brimonidine from three to two times a day when combined with timolol. (D.I. 242, Trial Tr. Day 3(AM) at 155:2–12 (Noecker).)

229. Dr. Tanna next cites to an article by Strohmeier, reporting on Cosopt® (dorzolamide and timolol fixed combination) for the proposition that fixed combination products solve problems of patient compliance. (DTX–152; D.I. 240, Trial Tr. Day 2(AM) at 164:25–65:10 (Tanna).) This reference suffers from the same flaws. Because patient compliance is not a factor considered by the FDA in deciding whether to approve drugs for use, the need to improve patient compliance did not create a motivation to persons of skill in the art or an expectation of success in developing a fixed combination drug. (D.I. 238, Trial Tr. Day 1(AM) at 83:18–84:1 (Whitcup).) In addition, the data reported in Strohmeier teaches that the combination of dorzolamide and timolol had worse IOP lowering during hour 8, which is the afternoon measurement, than its components (D.I. 242, Trial Tr. Day 3(AM) at 156:6–11; 156:22–157:1 (Noecker)), and had no safety gains (*id.* at 158:15–19 (Noecker)). The Strohmeier paper presents no motivation to develop a combination drug, let alone a combination of brimonidine, which is not mentioned, and timolol, particularly where the afternoon time point presented an acute problem.

230. Dr. Tanna then cites to three references in support of the existence of twice a day brimonidine being dosed with twice a day timolol: an abstract by Sall (DTX–168A), a retrospective study by Stewart (DTX–144), and a paper by Larsson (DTX–167), two of which (Larsson and Sall) were before the PTO during prosecution of all the patents-in-suit. (D.I. 242, Trial Tr. Day 3(AM) at 129:3–132:9 (Noecker).) As Dr. Tanna admitted, the fact that drugs were given concomitantly teaches nothing about whether these same drugs can be combined in a fixed combination. (D.I. 241, Trial Tr. Day 2(PM) at 18:4–14 (Tanna) ("Q: But this [concomitant use in Larsson] doesn't tell anyone of skill in the art whether one would be able to successfully combine these two drugs in the same bottle, correct? A: That is correct."); *see also* D.I. 238, Trial Tr. Day 1(AM) at 52:1–9 (Beck).) Moreover, none of these studies teach a person of skill whether brimonidine twice a day and timolol twice a day would be effective at treating chronic glaucoma due to the very limited study designs and data.

231. The Sall study compared Cosopt® with twice a day brimonidine and twice a day timolol dosed concomitantly. (D.I. 242, Trial Tr. Day 3(AM) at 159:13–17 (Noecker).) Dr. Tanna admits that the comparison of brimonidine to dorzolamide is an "apples to oranges" comparison. (D.I. 243, Trial Tr. Day 3(PM) at 154:5–10 (Tanna).) Nevertheless, he relies upon Cosopt® references in his obviousness analysis. In Sall, IOP measurements were taken in the morning, so no data exists regarding the afternoon trough. (DTX–168 at S822; D.I. 242, Trial Tr. Day 3(AM) at 159:23–160:9; 160:13–17 (Noecker).) Sall thus does not provide any clear teaching that brimonidine and timolol, each administered twice a day, would be effective for treating glaucoma throughout the day. Additionally, Sall does not teach or sug-

gest a fixed combination of brimonidine and timolol, does not teach or suggest whether such a combination could be made, and does not teach whether such a combination would be effective for treating glaucoma or ocular hypertension throughout the day. (D.I. 242, Trial Tr. Day 3(AM) at 160:18–161:1 (Noecker).)

232. Stewart is a retrospective study looking at the safety and efficacy of latanoprost compared to brimonidine or dorzolamide when added to multiple beta-blockers. (D.I. 240, Trial Tr. Day 2(AM) at 69:2–7 (Tanna); D.I. 242, Trial Tr. Day 3(AM) at 161:18–24 (Noecker).) The conclusion of the study was that "latanoprost, when added to beta-blockers, compares favorably in ocular hypotensive efficacy and is similar in safety to brimonidine and dorzolamide." (DTX–144 at DEFS(B/T)000428.) Stewart does not teach anything about combining brimonidine and timolol into a fixed combination, but instead focuses on latanoprost. (D.I. 242, Trial Tr. Day 3(AM) at 163:18–22 (Noecker).)

233. Larsson is a two-day study of the concomitant administration of brimonidine and timolol. (DTX–167.) This reference fails to teach that even the long-term adjunctive use of brimonidine and timolol would be effective for the treatment of chronic glaucoma or ocular hypertension, much less that their use in a fixed combination would be effective for the treatment of glaucoma or ocular hypertension. (D.I. 242, Trial Tr. Day 3(AM) at 165:24–166:17 (Noecker).) Larsson looked at healthy volunteers, so it is not as informative about IOP lowering in glaucoma patients as other studies. (*Id.* at 164:13–165:5 (Noecker); D.I. 241, Trial Tr. Day 2(PM) at 18:15–19 (Tanna).) The study did not test any fixed combinations (D.I. 241, Trial Tr. Day 2(PM) at 18:11–14 (Tanna)) and applied only three doses over the course of two days. (D.I. 242, Trial Tr. Day 3(AM) at 165:12–23 (Noecker); D.I. 241, Trial Tr. Day 2(PM) at 18:20–22 (Tanna).) As Dr. Noecker explained, the point of the study was looking at the mechanism of action, not IOP lowering, let alone IOP lowering for effective glaucoma treatment. (D.I. 242, Trial Tr. Day 3(AM) at 167:1–5 (Noecker).)

234. Dr. Tanna then relies on four references and combination products to support that a person of ordinary skill in the art would have expected that a fixed combination would be more or similarly effective than either of the monotherapies: Airaksinen (DTX–155), Clineschmidt (DTX–148); Boyle (DTX–200); and Hutzelmann (DTX–201). None of these studies contain data regarding the afternoon dose and trough because all of these studies measured IOP lowering at hours 0 and 2 only. (D.I. 243, Trial Tr. Day 3(PM) at 5:5–12; 7:7–14; 11:14–22; 13:10–15 (Noecker).) In addition, these studies look at combination products with active ingredients very different from brimonidine. Dr. Tanna described such a comparison as "apples-to-oranges." (D.I. 243, Trial Tr. Day 3(PM) at 154:5–10 (Tanna); *see also* D.I. 238, Trial Tr. Day 1(AM) at 52:11–15 (Beck).)

235. The Airaksinen study examined the IOP lowering of Timpilo® (pilocarpine and timolol) and its component drugs. (DTX–155; D.I. 243, Trial Tr. Day 3(PM) at 4:5–8 (Noecker).) The data depicted in Airaksinen show poor pressure control over the course of 42 days and report for the morning dose only. (DTX–155 at DEFS(B/T)000204; D.I. 243, Trial Tr. Day 3(PM) at 4:25; 5:5–12; 6:8–10 (Noecker).) Dr. Noecker's conclusion on this paper was that "it might give you pause about combination drugs in general." (D.I. 243, Trial Tr. Day 3(PM) at 6:16–17 (Noecker).)

236. The Clineschmidt article compares Cosopt® to the timolol (twice a day) and dorzolamide (three times a day) monother-

apies. (DTX–148; D.I. 243, Trial Tr. Day 3(PM) at 6:22–7:1 (Noecker).) Clineschmidt measures IOP at 8 am, when the dose is administered, and then two hours post dose. (D.I. 243, Trial Tr. Day 3(PM) at 7:7–11 (Noecker).) What this limited data does show is that in the morning, in the best case scenario, the timolol/dorzolamide combination will result in about a 1.4 to 2 mm Hg decrease in pressure compared to the dorzolamide. (*Id.* at 8:12–24 (Noecker).) With the understanding that a dorzolamide/timolol combination does not teach any information on a brimonidine/timolol combination, (*id.* at 9:25–10:1 (Noecker)), if one were to draw a comparison, the magnitude of the IOP lowering resulting from the dorzolamide/timolol combination is insufficient to adequately compensate for the mid-day dose of brimonidine missing in a brimonidine/timolol combination. (*Id.* at 9:25–10:18 (Noecker).)

237. The Boyle paper also looks at Cosopt® (dorzolamide/timolol combination) compared to the individual ingredients with IOP measures at hours 0 and 2 only. (DTX–200; D.I. 243, Trial Tr. Day 3(PM) at 10:24–11:4; 14–17 (Noecker).) Again, Cosopt® does not teach a person of skill anything about a combination of brimonidine and timolol because dorzolamide and brimonidine are different drugs. (D.I. 243, Trial Tr. Day 3(PM) at 11:5–10 (Noecker); *see also* D.I. 238, Trial Tr. Day 1(AM) at 52:11–15 (Beck).) However, if one was to draw a comparison between the data, Table 2 shows that the dorzolamide/timolol combination has insufficient IOP lowering as compared to the dorzolamide to make up the lowering required when removing one dose of brimonidine in the afternoon. (D.I. 243, Trial Tr. Day 3(PM) at 11:18–23 (Noecker).)

238. The Hutzelmann paper also looks at Cosopt and its component ingredients at hours 0 and 2 from dosing. (DTX–201; D.I. 243, Trial Tr. Day 3(PM) at 13:3–6; 10–12 (Noecker).) Table 2 shows the change at month 3 between the concomitant and combination therapies and the pressure reductions are the same. (DTX–201 Table 2; D.I. 243, Trial Tr. Day 3(PM) at 13:20–25 (Noecker) ("Right. So in terms of efficacy, it's neutral for the morning.").) The only thing a person of skill would conclude from this paper is that timolol in a fixed combination "doesn't seem like it's going to solve efficacy problems." (D.I. 243, Trial Tr. Day 3(PM) at 14:6–9 (Noecker).)

239. In sum, none of these references would motivate a person of skill in the art to develop a single composition drug of 0.2% brimonidine and 0.5% timolol for the treatment of glaucoma with any reasonable expectation of success. First, because virtually all of the references teach combination drugs with different active ingredients than Combigan®, they teach nothing about whether one of skill can successfully combine brimonidine and timolol in a fixed combination. (*See, e.g.*, D.I. 238, Trial Tr. Day 1(AM) at 52:11–15 (Beck).) Second, there is no information that there is a benefit to doing so. (D.I. 243, Trial Tr. Day 3(PM) at 14:17–15:3 (Noecker).) Lastly, these references do not provide a motivation to one of skill in the art to make a fixed combination of 0.2% brimonidine and 0.5% timolol to reduce the dose of brimonidine from three times a day to two times a day without losing efficacy. (*Id.* at 15:4–15 (Noecker).) Specifically, with respect to claim 4 of the '149 patent, Dr. Noecker explained that the prior art does not address the key time point, the afternoon trough, so there is no reason to believe that the addition of timolol to the brimonidine would allow the reduced dosing interval with losing efficacy. (*Id.* at 18:14–20 (Noecker).)

240. Furthermore, none of the references relied on by Defendants' experts

provide any argument that there would have been a reasonable expectation of success in making a fixed combination of 0.2% brimonidine and 0.5% timolol, or in using such a combination to treat glaucoma with twice a day administration. Moreover, the failure of any of these references to discuss potential formulation difficulties with the brimonidine/timolol combination further demonstrates that they do not render the claims obvious.

c. Numerous Factors, Evidence, and Considerations Demonstrate Non-Obviousness in Light of the Prior Art

241. For all of the reasons set forth above, none of the references cited by Defendants discloses or suggests a combination ophthalmic product consisting of brimonidine and timolol as claimed in the patents-in-suit. The mere existence in the art of fixed combination products with other constituents, and the available information about the concomitant or adjunctive administration of brimonidine and timolol does not provide a substantial reason for one of ordinary skill in the art to create a fixed combination product of brimonidine and timolol as claimed in the patents-in-suit. In particular, one of skill in the art would not expect that, simply because two active ingredients are effective and marketed separately, they could or should be put together in a single, workable formulation that is safe and therapeutically effective for glaucoma treatment. (*See* D.I. 238, Trial Tr. Day 1(AM) at 58:13–59:9 (Whitcup).) Moreover, given the significant difference in efficacy between brimonidine BID and brimonidine TID at hours 9 and 11, one of skill in the art would not have expected that adding timolol to brimonidine would enable a reduction in the dose of brimonidine from three to two times a day without loss of efficacy.

242. This is particularly true given the nature of the field, factors that teach away from the invention, and several secondary considerations of non-obviousness.

i. Formulation of Ophthalmic Medications is a Challenging and Unpredictable Art

243. As discussed above, the formulation of ophthalmic products is a challenging and unpredictable field. Dr. Noecker testified that he believes that these products are among the most difficult to formulate:

> [T]herapeutic eye drops are probably the trickiest thing to get right. And the problem is that you have to have the drug behaving in the bottle, so being stable in the bottle for a period of time in a water environment. Then usually to get through the eye, you need to have a different set of favorable properties to get delivered across the cornea, typically, or some other routes, but typically across the cornea. So that's a different set of properties, kind of going back to what we heard earlier, about lipophilicity and hydrophilicity. And then the biggest problem is the window of delivery. It's there, you blink a bunch, and the eye is gone. So you have about a minute to get this right and get it into the eye.

(D.I. 242, Trial Tr. Day 3(AM) at 64:9–65:3 (Noecker); *see also* D.I. 241, Trial Tr. Day 2(PM) at 39:23–24 (Laskar) (explaining that "ophthalmic formulations are a subset with special requirements and special considerations").)

244. There are numerous important considerations for formulation of an ophthalmic medication. For example, the drug must be soluble and remain physically stable in solution so that it does not precipitate, comfortable enough to be used in the eye, adequately preserved to prevent microbial growth, and sufficiently bioavailable to pass across the hydrophobic corneal membrane. (*See, e.g.*, D.I. 238,

Trial Tr. Day 1(AM) at 134:5–24 (Beck); D.I. 241, Trial Tr. Day 2(PM) at 54:13–55:13 (Laskar).) In making a formulation, these considerations can compete with each other, and there are trade-offs that must be made.

245. In designing a formulation with two active drugs, the formulation challenges are magnified because, in addition to considering each of the drugs on its own, the formulator must also consider how the two active drugs may interact with each other and with other components of the formulation, as well as how to create a formulation that will work for the different physical and chemical properties of the two drugs. (*See, e.g.*, D.I. 238, Trial Tr. Day 1(AM) at 137:2–12; 137:16–25; 144:2–6 (Beck); D.I. 243, Trial Tr. Day 3(PM) at 124:7–125:1; 123:2–6; 123:11–17; 126:3–6 (Laskar).)

246. These trade-offs and challenges can cause a fixed combination formulation to fail, and there are numerous examples of failed attempts at combination products. For example, Allergan itself has attempted to formulate combinations of Betagan® (also known as levobunolol) and pilocarpine and Betagan® and Propine® (also known as dipivifrin), but neither resulted in a successful product. (D.I. 239, Trial Tr., Day 1(PM) at 66:17–69:1 (Batoosingh); *id.* at 72:12–22 (Batoosingh).)

247. The Betagan®/pilocarpine product failed because, at the pH required to make the formulation stable, "the bioavailability was insufficient in order to pursue the formulation." (*Id.* at 71:6–21; PTX–179.) Because of the bioavailability issues, Allergan "didn't succeed in formulating it so that [they] could test it in people." (D.I. 239, Trial Tr., Day 1(PM) at 68:19–69:1 (Batoosingh); *see also* PTX–169 at AGN_COMBI0676851–857.)

248. Allergan's attempt to make a fixed combination of Betagan® and Propine also failed. Although Allergan submitted this product to the FDA, it was not approved "[b]ecause the IOP lowering did not outweigh the risks of putting the two drugs into the same bottle." (D.I. 239, Trial Tr., Day 1(PM) at 72:12–22 (Batoosingh).)

249. Even Defendants' expert, Dr. Laskar, was forced under cross-examination to admit to his own failure in the ophthalmic combination product realm. (D.I. 241, Trial Tr. Day 2(PM) at 131:14–25 (Laskar).) Like Allergan's failures with levobunolol, Dr. Laskar's own failure amply demonstrates that the art of making a fixed combination ophthalmic product is highly unpredictable.

250. As discussed above, the inventors faced numerous of challenges in combining brimonidine and timolol into a fixed combination product. In making this combination, they had to find a way to put together two products with (1) different active ingredients, (2) different salts, (3) different pHs, (4) different buffer systems, and (5) different preservative concentrations into one bottle. As Mr. Beck explained, "[w]hen I am working with two different active ingredients, I have no idea how those two are going to behave in a formulation. So from my perspective, I needed to start and try to devise the optimal formulation for the two active ingredients." (D.I. 238, Trial Tr., Day 1(AM) at 144:2–6 (Beck).) The art of reaching such an optimal formulation is unpredictable, as evidenced by the inventors' failures along the way to arriving at the final formulation.

251. As discussed above, the inventors of the patents-in-suit experienced several failures before arriving at the final formulation of Combigan®, including their attempt to use the Purite® preservative, and their attempts to use Synergel and CMC as vehicles for the formulation. They had estimated that these attempts had a good probability of success, but, instead, they unexpectedly failed. (*See* PTX–26.)

252. The inventors also did not predict the appearance of degradants in the brimonidine/timolol formulation. The degradants, which had not appeared in the individual formulations, were a result of combining the two active ingredients into one bottle. Neither the formation of these degradants, nor their potential effect on the safety of the formulation, were predictable. (D.I. 239, Trial Tr. Day 1(PM) at 9:9–10:17; 12:4–13:25 (Beck).)

253. The proper pH of the formulation was also something the inventors had to test, and could not simply predict based on the pHs of the previously marketed formulations of brimonidine (Alphagan®, with a pH of 6.3 to 6.5) and timolol (Timoptic®, with a pH of 7). Indeed, the inventors ran numerous experiments to determine the effects of various pHs on the solubility of brimonidine and on the preservative ability of BAK. (*See, e.g.*, D.I. 239, Trial Tr. Day 1(PM) at 14:2–18:24 (Beck); PTX–38 at AGN_COMBI0171458; PTX–89.)

254. Finally, the BAK concentration of the final formulation was also the subject of significant testing. The inventors could not simply choose the pH of one of Alphagan® or Timoptic®, but rather tested various potential BAK concentrations before arriving at the final formulation. The appropriate concentration was not predictable. Indeed, marketed ophthalmic formulations have widely varying concentrations of BAK. (*See, e.g.*, D.I. 239, Trial Tr. Day 1(PM) at 18:25–24:7 (Beck); PTX–101; PTX–61.)

255. Rather than addressing these significant formulation hurdles faced by the inventors, Defendants' experts chose simply to ignore them. Dr. Laskar admitted that his opinion was based only on the patent itself and that he had never seen nor asked to see the laboratory notebooks that detailed the work done by the inventors. (D.I. 241, Trial Tr. Day 2(PM) at 145:17–20 (Laskar) ("Q: So your opinion on whether the formulators did or did not have any formulation issues is based solely on the patent; is that right? A: Yes, it is."); *id.* at 144:12–18; 145:11–13.) Dr. Tanna also admitted that he "did not take any formulation difficulties the formulators in this case may have faced into account when rendering [his] obviousness opinion." (D.I. 240, Trial Tr. Day 2(AM) at 120:3–7 (Tanna).)

256. Even though they ignored the specific hurdles faced by Allergan's inventors, however, Defendants' experts acknowledged that ophthalmic formulation is an art full of complexity and unpredictability. (D.I. 241, Trial Tr. Day 2 at 18:4–14 (Tanna); *id.* at 54:13–55:13 (Laskar); D.I. 243, Trial Tr. Day 3(PM) at 124:7–125:1; 123:2–6, 11–17; 126:3–6.)

257. Because of the difficulties in formulating a fixed combination of brimonidine and timolol, one of ordinary skill in the art would be taught away from making the fixed combination disclosed and claimed in the patents-in-suit.

ii. The Evidence and Art Teach Away from Combining Brimonidine and Timolol

258. In addition to the evidence listed above with respect to specific prior art references, there are several factors that teach away from making combinations of the prior art identified by Defendants.

259. First, the available information about brimonidine and timolol would have taught one of skill in the art away from making a fixed-combination of those two drugs. The product insert for Alphagan® itself teaches away from combining 0.2% brimonidine with beta-blockers like timolol. With respect to "drug interactions," the product insert for Alphagan® states:

> However, since alpha-agonists, as a class, may reduce pulse and blood

> pressure, caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

(DTX–129 at DEFS(B/T) 000233; *see also* D.I. 242, Trial Tr. Day 3(AM) at 137:2–6 (Noecker) ("Q. And what does this [DTX–129] tell you in regards to whether one would be motivated to try to combine Timolol with Alphagan in a combination drug? A. It would teach away from that or certainly not be your first choice.").)

260. In addition to the explicit caution on the label, one of skill in the art would be concerned that combining brimonidine and timolol, both problematic glaucoma medications with significant side effects, would exacerbate those negative side effects. (*See* D.I. 242, Trial Tr. Day 3(AM) at 74:2–6 (Noecker); *id.* at 74:17–75:20 (Noecker); *id.* at 137:7–15 (Noecker).) In particular, one of skill in the art would have been concerned that combining brimonidine, a medication known to cause somnolence, with timolol, a medication known to decrease blood pressure, heart rate, and respiratory rate, would exacerbate those side effects, particularly in the elderly. (*Id.* at 137:7–15 (Noecker) ("Q. Why is that a—why is—why is it a hazard? What—what do you understand to be the interaction problem? A. What you worry about is that the side effects will be additive. So, basically, having, you know, one drop—drop that can have an effect on blood pressure, which we certainly know beta-blockers do, and then the alpha-agonists on top of that may make some people hypotensive, make them dizzy, et cetera.").)

261. Furthermore, given the introduction of Alphagan® P 0.15% in 2001, one of skill in the art in 2002 would have been concerned with using any product that contained 0.2% brimonidine to treat patients. The clinical data for Alphagan® P 0.15% showed that "it worked just as well [as Alphagan® 0.2%], but this side effect profile is significant less, both for eye problems as well as systemic problems," and for that reason clinicians like Dr. Noecker were converting their patients from Alphagan® 0.2% to Alphagan® 0.15%. (*Id.* at 138:6–13.) Accordingly, as Dr. Noecker testified, clinicians looked at the 0.2% brimonidine in Combigan® "as almost a step backwards." (D.I. 242, Trial Tr. Day 3(AM) at 138:1–139:3 (Noecker).) Moreover, even during the clinical trials, physicians were skeptical about whether the fixed combination product that ultimately became Combigan® would be a worthwhile drug. (*Id.* at 140:1–6. (Noecker) ("Q. Were you skeptical whether this combination would turn out to be any good? A. I—I think my words are less kind than skeptical. Q. What words did you have? A. Dog of a drug.").)

262. Second, a difference in the dosing intervals for the components of a fixed combination glaucoma product, which is often based on the disparate half-lives of the products, makes formulating fixed combination products especially difficult, and would also teach away from making such products.

263. With respect to Combigan® specifically, one of skill in the art would have been aware that brimonidine and timolol have different half-lives, and thus different dosing regimens. (*See* D.I. 242, Trial Tr. Day 3(AM) at 73:12–74:1 (Noecker); *id.* at 74:17–75:2 (Noecker).) As fully described above, one of skill in the art would have been aware of the FDA's repeated refusal to approve brimonidine for anything other than three times a day dosing, despite multiple efforts by Allergan to achieve BID dosing. One of skill in the art would have been very concerned about the significant difference in efficacy between brimonidine BID and brimonidine TID at hours 9 and 11, both of which were statisti-

cally and clinically significant. (*See* PTX–134 at AGN_COMBI0676465; *id.* at AGN_COMBI0676405–406; D.I. 239, Trial Tr. Day 1(PM) at 79:24–80:8 (Batoosingh); *id.* at 80:16–19 (Batoosingh); *id.* at 125:1–6 (Batoosingh); *id.* at 126:13–127:6; D.I. 241, Trial Tr. Day 2(PM) at 5:10–19 (Tanna).) This afternoon trough effect would have taught a person of skill in the art away from making a fixed-combination product with brimonidine dosed BID.

264. Each of these factors taught away from creating a combination product comprising brimonidine 0.2% and timolol.

iii. Secondary Considerations Demonstrate Non–Obviousness

265. Objective considerations—including unexpected results, long felt need, commercial success and copying—also compel the conclusion that the claims of the Patents-in-Suit were not obvious. Those considerations will be discussed below.

(i) Unexpected Results

266. Allergan's clinical studies of Combigan® demonstrated unexpected results related both to efficacy and safety of Combigan®, which embodied the asserted claims of the patents-in-suit.

267. Defendants repeatedly criticize Allergan's unexpected results analysis for not comparing the claims of the patents-in-suit to the closest prior art. Defendants' arguments are misplaced. Indeed, Defendants' expert, Dr. Tanna, admitted that the alleged "prior art" to which he compared the claims for unexpected results was not prior art at all. (D.I. 241, Trial Tr. Day 2(PM) at 19:6–8 (Tanna) ("Q. Now, neither the 19T study nor the 507T study are prior art to the patents-at-issue; is that correct? A. That is correct.").) Moreover, Allergan's analysis of unexpected results compares the results of the claimed invention with treatment regimens that are set out in the claims themselves (e.g., TID brimonidine versus the fixed combination, as in Claim 4 of the '149 patent) and treatment regimens (e.g., brimonidine monotherapy) that were undertaken to secure FDA approval of Combigan®. The comparisons made by Allergan are appropriate.

268. Although Combigan® provides only two doses of 0.2% brimonidine daily, it surprisingly does not suffer from the afternoon trough in IOP lowering that was previously observed with 0.2% brimonidine dosed twice-a-day. As discussed extensively above, one of the clinical trials performed to secure the approval of Alphagan® 0.2% showed that there was a statistically and clinically significant difference in IOP lowering at hours 9 and 11 when dosing brimonidine BID as compared with brimonidine TID. The results that study, which were available to one of ordinary skill in the art through the Walters publication (DTX–137), show that at hour 9 of the study—i.e., nine hours after the morning dose of brimonidine for both the BID and TID groups and two hours after the brimonidine for the TID group—the group that received brimonidine 0.2% TID had a mean IOP that was a 3.25 to 3.5 mm Hg lower than the group that received brimonidine BID. Two hours later, at hour 11 of the study, that difference was still approximately 1.5 mm Hg. (*See* DTX–137; PTX–134.)

269. A person of ordinary skill in the art would not have expected that combining brimonidine with timolol would eliminate that afternoon trough. (*See* D.I. 239, Trial Tr. Day 1(PM) at 94:22–95:2 (Batoosingh); D.I. 243, Trial Tr. Day 3(PM) at 9:20–10:18 (Noecker).) Indeed, the evidence shows that one of skill would have expected the opposite—that the addition of timolol would fall short of making up the 3.25 mm Hg reduction in IOP lowering effect between BID and TID brimonidine

at hour 9. (D.I. 243, Trial Tr. Day 3(PM) at 9:20–10:18 (Noecker).)

270. Surprisingly, however, the pooled results for the two pivotal clinical trials on Combigan®, the 12T and 13T clinical studies showed that Combigan® unexpectedly reduces the afternoon trough seen with brimonidine monotherapy dosed BID. (PTX–77 at AGN_COMBI0481544; D.I. 243, Trial Tr. Day 3(PM) at 22:8–23:18 (Noecker) ("Q. Is this something that you as one of skill in the art would have found surprising in 2002? A. Yes."); *id.* at 23:14–18 (Noecker) ("We suspect that it might have some positive effect, but that magnitude is really what's rather striking. It really eliminated that—that difference we saw in those other studies . . .").) Those results were reported in Sherwood, et al., Twice–Daily 0.2% Brimonidine—0.5% Timolol Fixed–Combination Therapy vs Monotherapy With Timolol or Brimonidine in Patients With Glaucoma or Ocular Hypertension, Arch Ophthalmol, 2006 (the "Sherwood paper"). (PTX–77 at AGN_COMBI0481544.)

271. Defendants offered little evidence at trial to counter the strong showing by Allergan that the elimination of the afternoon trough was a goal that was unlikely to be achieved. Indeed, none of the prior art relied upon by defendants addresses the issue at all.

272. In addition to the unexpected results related to efficacy, treatment with Combigan® also unexpectedly resulted in dramatically reduced ocular side effects, and in particular, reduced incidence of allergy and allergic conjunctivitis, as compared to brimonidine monotherapy. (D.I. 243, Trial Tr. Day 3(PM) at 26:19–24 (Noecker) ("Q. In your experience, Dr. Noecker, are allergies common with brimonidine as a monotherapy? A. Over time, yes. We don't see them right away, but the longer the patients are on the drug, they—they tend to occur. The original Alphagan, why clinicians grew not to love it is because the rate would approach 25 percent, and over a longer period of time, probably a little bit higher than that." . . . "Q. Okay. In your experience, are allergies as common with Combigan, which also has .2 percent Brimonidine? A. No, it's dramatically less. Q. Was that surprising to you as one of skill in the art? A. Definitely.").)

273. During the pivotal clinical trials done on Combigan®, study numbers 190342–012T and 190342–013T (the "012T study" and "013T study," respectively), Allergan surprisingly observed a statistically significant reduction in the symptoms of allergic conjunctivitis in patients taking Combigan® compared to patients taking brimonidine alone. (JTX–9A at AGN_COMBI0007714; JTX–9B at AGN_COMBI0060050.) In the 012T study, the incidence of allergic conjunctivitis was 5.7% in the Combigan® group compared to 14.0% in the brimonidine group, and the incidence of conjunctival folliculosis, a symptom of ocular allergy, was 4.2% in the Combigan® group compared to 8.6% in the brimonidine group. (JTX–9A at AGN_COMBI0007714.) Both of those differences were statistically significant. (*Id.*) Similarly, the 013T study revealed that the incidence of conjunctival folliculosis was 1.0% in the Combigan® group compared to 4.6% in the brimonidine group. (JTX–9B at AGN_COMBI00060050.) That difference was also statistically significant. (*Id.*) Additionally, patients in both the 012T and 013T studies experienced statistically significantly lower incidences of eye pruritus (itching), another symptom of ocular allergy. (JTX–9A at AGN_COMBI0007714; JTX–9B at AGN_COMBI00060050.) The patents-in-suit also report the data from the 013T study, which, as set forth above, shows a statistically significantly lower percentage of patients experienced ocular adverse events on Combigan® than did patients

taking brimonidine monotherapy. (JTX–1 at 7:6–11.) The patents-in-suit also explicitly report that, in the 013T study, the incidence of patients who discontinued treatment due to adverse events was statistically significantly lower in the Combigan® group (3.6%) compared to the Brimonidine group (14.3%). (JTX–1 at 7:38–42.)

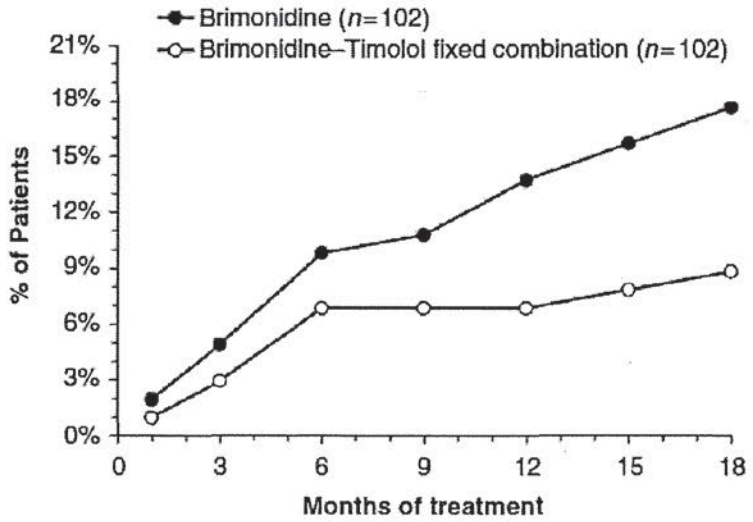
274. Moreover, the fact that treatment with Combigan® twice a day exposes patients to one less dose of brimonidine compared to brimonidine administered three times a day (either adjunctively or as monotherapy) does not explain the unexpected reduction in ocular side effects because allergic side effects are caused "in that two minute period where there's drug on the eye.". (D.I. 243, Trial Tr. Day 3(PM) at 28:8–30:6 (Noecker).) Dr. Noecker testified:

> Q. Now, the people getting the combination therapy were only getting Brimonidine two times a day versus three times a day for those in the Brimonidine monotherapy.
>
> Were these results surprising nonetheless to you as one of skill in the art?
>
> A. Yes. And I think it's—I think it's—part of it is why allergy occurs with Brimonidine, and I can explain that.

(*Id.*; *see also* D.I. 243, Trial Tr. Day 3(PM) at 30:7–12) (Noecker) (results were "surprising" until "we figured out why"), 31:24–32:2 (Noecker) (results were "not predicted at all"..)

275. A clinical study reported by Motolko provides further support. That study compared the incidence of ocular allergy in glaucoma patients receiving Combigan® BID versus patients receiving treatment with 0.2% brimonidine BID. Despite the fact that patients in both groups were receiving two doses of brimonidine per day, Motolko found a 50% lower incidence of ocular allergy in the Combigan® group. (PTX–123.)

276. Motolko summarizes the incidence of ocular allergy suffered by participants in the study in the following graph, which appears as Figure 1:



(PTX–123 at AGN_COMBI0644507.) As Dr. Noecker explained, the Motolko data show "that the—the rate of allergy in patients who are only getting Brimonidine is—is much, much higher than those who are getting Combigan." (D.I. 243, Trial Tr. Day 3(PM) at 36:2–11 (Noecker).)

277. That patients receiving Combigan® BID had significantly reduced allergy was surprising to one of skill in the art in the 2001–2002 timeframe. (D.I. 243, Trial Tr. Day 3(PM) at 36:12–14 (Noecker) ("Q. And was that something that was a surprise to a person of ordinary skill in the art in 2001/2002? A. Definitely, until we figured it out.").)

278. Importantly, the 12T and 13T clinical studies were twelve month studies, and the clinical study reported in Motolko was an eighteen month study. By contrast, the clinical study on which Defendants attempt to rely, the 507T clinical study and the publication of that study by Goni (DTX–23), was a twelve week study. As multiple witnesses testified, a twelve week study would be insufficient to observe any differences between groups in ocular allergy. (*See* D.I. 243, Trial Tr. Day 3(PM) at 35:8–36:21 (Noecker); D.I. 239, Trial Tr. Day 1(PM) at 131:19–132:8 (Batoosingh) (noting that Goni reports a twelve week study and stating that "for those who know Alphagan really, really well, the allergy that's associated with Alphagan often doesn't appear until, on average, five to nine months after a patient has initiated therapy.").)

279. In addition to a reduction in ocular side effects, the 012T and 013T clinical studies showed that patients taking Combigan® experienced fewer nervous system side effects than patients on brimonidine monotherapy, including that patients treated with Combigan® experienced statistically significantly lower incidences of oral dryness when compared to patients who were treated with brimonidine alone. (JTX–9A at AGN_COMBI0007714; JTX–9B at AGN_COMBI0060050.)

280. Clinical trial 190342–019T (the "019T study") also showed that, when patients taking Combigan® twice a day were compared to patients on a regimen of brimonidine 0.2% three times a day concurrently with timolol 0.5% dosed twice a day, the patients taking Combigan® experienced a statistically significantly reduced number of nervous system side effects, including somnolence, depression, dizziness, ataxia, insomnia, and incoordination. (JTX–9C at AGN_COMBI0003524.) Indeed, while 3.0% of patients taking the concurrent brimonidine-timolol regimen experienced nervous system side effects, no patients in the Combigan® group reported any nervous system side effects. (*Id.* at AGN_COMBI0003524.) The incidence of oral dryness in patients taking Combigan® was also approximately 50% lower than in patients on adjunctive therapy. (*Id.* at AGN_COMBI0003524.)

281. Nervous system side effects, in particular somnolence and dry mouth, are clinically significant. (D.I. 238, Trial Tr. Day 1(AM) at 84:12–22 (Whitcup).) The literature has reported that patients with glaucoma were six times more likely to have been involved in one or more motor vehicle crashes than were age-matched control individuals without glaucoma. (JTX–9E at AGN_COMBI0022644.) As Dr. Noecker explained, the somnolence associated with brimonidine is dose-related; "So they take their 7:00 a.m. drop and about a half an hour later, they get really sleepy and fall into their cereal." (D.I. 243, Trial Tr. Day 3(PM) at 36:19–37:9 (Noecker).) Additionally, dry mouth is a clinically significant side effect because it is related to cavities. (D.I. 238, Trial Tr. Day 1(AM) at 84:20–22 (Whitcup).)

282. Additional clinical studies, study numbers 190342–023T and 190342–024T

(the "023T study" and the "024T study," respectively), compared the incidence of sleepiness and dry mouth as primary and secondary endpoints, respectively, in patients receiving Combigan® compared to patients receiving concurrent therapy with brimonidine tartrate 0.2% TID and timolol 0.5% BID. (JTX–9D; JTX–9E.) The 023T and 024T studies demonstrated that Combigan® dosed BID caused statistically significantly less sleepiness and dry mouth compared to adjunctive therapy with brimonidine dosed TID and timolol dosed BID.

283. In the 023T study, which was done in healthy adult subjects, the proportion of current severity of sleepiness responders in the group treated with Combigan® (24.2%) was numerically lower than the responders in the group treated with adjunctive therapy (30.0%). (JTX–9D at AGN_COMBI0130812.) Additionally, for the secondary endpoint, the proportion of dry mouth responders was statistically significantly lower in the group treated with Combigan® (20.3%) than in the group treated with adjunctive therapy (30.0%). (*Id.*)

284. Similarly, in the 024T study, which was done in patients with glaucoma or ocular hypertension, there was a statistically significant difference between the Combigan® and adjunctive therapy groups in the proportion of current severity of sleepiness responders, with 9.2% responders in the Combigan® treatment group and 19.3% responders in the adjunctive therapy group. (JTX–9E at AGN_COMBI0022630.) In fact, there was a greater than two fold risk for sleepiness with adjunctive therapy compared to Combigan® treatment, which correlated to a two-fold decrease relative risk of severe car accidents. (*Id.;* D.I. 238 Trial Tr. Day 1(AM) at 87:18–23 (Whitcup).) Similarly, for the secondary endpoint, the proportion of current severity of dry mouth responders, there was a statistically significant difference between the Combigan® and adjunctive therapy groups, with 14.8% responders in the Combigan® treatment group and 20.6% responders in the adjunctive therapy group. (JTX–9E at AGN_COMBI0022630.) This result was surprising both to Allergan and to those in the industry. (D.I. 243, Trial. Tr. Day 3(PM) at 37:10–12, 39:18–24) (Noecker) ("Q. Okay. Do you see that high rate of somnolence with Combigan. A. Surprisingly, no.... Q. Okay. And you said that was a surprise. Why was that a surprise? A. Because we—it was something we've never observed with using these drugs for patients who happen to be on both drugs together. And it hadn't been reported in any other situation. So it was—it was unique.") (D.I. 238, Trial Tr. Day 1(AM) at 87:24–88:10 (Whitcup) ("Q. What was your reaction, if you had one, to the results of the 24T study? A. I think I screamed for about a minute when I heard this on the phone initially, because sleepiness is—is tough to document. So we knew that you really had to have substantial decrease.").)

285. After the 24T study was submitted to the FDA, the FDA finally approved Combigan®. (PTX–92; D.I. 238, Trial Tr. Day 1(AM) at 88:11–89:5 (Whitcup) ("Q. What was your reaction to finally receiving this letter from the FDA on Combigan? A. Well, out of the, you know, multiple projects, this is probably the—the toughest one that I had to work through. So when you finally get a drug that you can get available to patients, it makes everyone feel good. So I think people were very happy and proud.").)

(ii) Long Felt Need

286. As of April 2001, there was a long felt need for a fixed combination product to treat glaucoma. (D.I. 243, Trial Tr. Day 3(PM) at 40:12–41:6 (Noecker).) The inventions disclosed and claimed in the pat-

ents-in-suit provided a long awaited fixed combination alternative for the treatment of glaucoma, and the unexpected FDA approval of Combigan® satisfied the long-felt need for such a product. That there continues to be a need for more products, according to Dr. Noecker (D.I. 243, Trial Tr. Day 3(PM) at 40:12–23; 72:4–73:18 (Noecker)), does not mean that the long-felt need was not satisfied by Combigan®, contrary to Defendants' strained arguments at trial.

(iii) FDA Approval

287. Courts have noted that FDA approval may be relevant to secondary considerations of non-obviousness. See, e.g., *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 803 F.Supp.2d 397, 2011 WL 996794 FN 11 (E.D.Va. Mar. 17, 2011) (noting that FDA approval and associated documents had no relevance in claim construction because they were not in existence at the time of the patent filing, but noting that it may be relevant in an obviousness analysis). For example, the Court in *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litigation* considered FDA approval in the context of evaluating the asserted failure of others to solve the purported problem. 2010 WL 3766530, *1–2 (D.Del. Sept. 21, 2010) (citing *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.* 367 F.3d 1381, 1385 (Fed.Cir.2004) (denying motion in limine to exclude defendant's unsuccessful attempts to obtain FDA approval and finding that the FDA evidence was relevant to secondary consideration of failure of others)).

288. The FDA is and has been hostile to the approval of fixed combination drugs. (*See* 130; D.I. 238, Trial Tr. Day 1(AM) at 58:13–59:9 (Whitcup).) That hostility would have been known to one of ordinary skill in the art. (*Id.*; D.I. 242, Trial Tr. Day 3(AM) at 79:22–24 (Noecker) ("Q. And as an ophthalmologist, were you surprised when Combigan was approved? A. I was shocked."); *see also id.* at 80:18–20 (Noecker).) Moreover, the FDA's hostility is evidenced by the fact that there are only two FDA approved and marketed combination products for treating glaucoma—Combigan® and Cosopt®—despite many attempts to create such combinations and get them approved, and despite the existence of combination products that are effective and approved for use elsewhere. (*See* D.I. 242, Trial Tr. Day 3(AM) at 78:9–16 (Noecker); *id.* at 86:23–87:5; *id.* at 88:13–22; *id.* at 89:14–23.)

289. Defendants and their experts referred to at least six "combination products" that have been approved outside the United States, including Timpilo® (timolol and pilocarpine), ProBeta® (levobunolol and dipivefrin), Betoptic® Pilo (betaxolol and pilocarpine), Xalcom®/Xalacom® (latanoprost and timolol), Ganfort® (bimatoprost and timolol) and DuoTrav® (travoprost and timolol), but even Defendants admit none of those are available to doctors and patients in the United States. (D.I. 241, Trial Tr. Day 2(PM) at 10:2–11:10 (Tanna); *id.* at 15:21–16:3.) With respect to both Timpilo® and Betoptic® Pilo, neither is a fixed combination product that is stable for shelf-life, as both must be mixed by either the patient or pharmacist and then used within a period of a few weeks. (D.I. 241, Trial Tr. Day 2(PM) at 13:16–15:5 (Tanna); *id.* at 29:18–23 (Tanna); D.I. 242, Trial Tr. Day 3(AM) at 87:6–89:13 (Noecker).)

290. The Court concludes that in this case the difficulty in getting FDA approval for the claimed combination drug is a further secondary consideration of non-obviousness. This is because the FDA has not approved any fixed combination drug containing a prostaglandin analog. Prostaglandin analogs are the most common first-line therapy for glaucoma. (D.I. 242, Trial Tr. Day 3(AM) at 81:20–82:18

(Noecker) (noting that prostaglandin analogs are the typical first line therapy); D.I. 241, Trial Tr. Day 2(PM) at 9:21–23 (Tanna) (same).) When a prostaglandin analog alone is insufficient to lower intraocular pressure, the most common adjunctive therapies add Alphagan® P, a beta-blocker (like timolol), a CAI (like Azopt®), or one of the two available combination drugs. (D.I. 242, Trial Tr. Day 3(AM) at 83:25–84:14 (Noecker) (discussing common adjunctive therapies).) Despite these common adjunctive therapies with prostaglandin analogs, no party presented evidence of any fixed combination drugs on the market in the United States combining a prostaglandin analog and any other product. While, as described above, several companies have tried to make fixed combinations of a prostaglandin analog and a beta-blocker, none of those fixed combinations are FDA approved. Thus, the difficulty of securing FDA approval of a combination treatment would have been known to a person of skill in the art; and, while the claims do not require FDA approval, would have cautioned the person of ordinary skill in the art that successful therapeutically effective combinations could readily be made.

(iv) Commercial Success

291. The Court finds that the evidence of commercial success is ambiguous. In order to determine whether a product is a "commercial success," the relevant market must be defined, which Allergan did not fully develop. Allergan's commercial success analysis is also lacking because Allergan relied on Combigan® gross sales figures without considering Allergan's development costs and any rebates, discounts, coupons and charge-backs that were used to achieve the gross sales. The Combigan P & L statement upon which Allergan's fact witness relied to for his gross sales data and marketing expenditures was less than clear. For example, it appears that the Combigan P & L statement failed to report expenses such as distribution costs once the product was launched and legal and marketing costs during the ten years prior to launch. At best, Allergan's fact witness testified to gross sales figures. Sales figures alone are not compelling evidence of commercial success. *See Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed.Appx. 978, 983 (Fed.Cir.2010); *see also In re Huang*, 100 F.3d 135, 140 (Fed.Cir.1996) ("[E]vidence related solely to the number of units sold provides a very weak showing of commercial success, if any.").

292. However, the Court is not concluding that there was not any commercial success or that the drug was a complete failure as proposed by Defendants. This would fly in the face of common sense as Defendants' employees testified by deposition that they believe Combigan® is a commercial success, as each chose to make a generic copy of Combigan® based on studying the marketplace for the product. (*See, e.g.*, Tremonte Deposition Tr. (Sandoz) at 27:24–28:4 ("Q. And why did Sandoz choose to develop a generic version of Combigan? A. The portfolio group assessed the product, felt like Allergan would be able to grow the market, and Sandoz felt that we could make the product in our facility."); Mittleberg Deposition Tr. (Sandoz) at 37:3–10 (Q. Do you know why Sandoz chose to develop the brimonidine/timolol combination product? A. Probably because it was felt that it would be a profitable product, and since we are a profit-making organization, we felt that—I would assume, and I would say, that it followed that we would pick a product like that.); Krishnan Deposition Tr. (Apotex) at 210:12–18 ("Q. And it shows that Brimonidine/Timolol is ranked a must win. Correct? A. Correct. Q. So is it your understanding that Brimonidine/Timolol was a must-win product? A. Yeah, based

on what it says in the list, yes, it was designated as a must win.").)

293. Thus, the Court concludes that Allergan's evidence of commercial success is ambiguous, and neither supports nor contradicts a finding that the patents-in-suit were not obvious. Notwithstanding, Allergan has provided sufficient evidence of other secondary considerations that support a finding that the patents-in-suit were not obvious.

(v) Copying Is of Little Significance in Hatch–Waxman Litigations

294. Where the law prohibits significant changes, copying of the innovator product is not evidence of non-obviousness. The FDA regulations for ophthalmics do not allow significant changes from the branded product. *See* 21 C.F.R. § 314.127(a)(8)(ii)(C). Because the Defendants were required to follow the FDA regulations on ophthalmics, this is not evidence of non-obviousness. *See, e.g., Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1325 (Fed.Cir.2003).

d. Defendants Have Failed to Establish that the Patents–In–Suit are Obvious in Light of the Prior Art

295. In sum, the Court is not persuaded that Defendants have established by clear and convincing evidence that the patents-in-suit are obvious in light of the prior art. The Court finds that there are significant differences between the prior art and the claimed inventions, such that a person of ordinary skill in the art would not have been motivated to create a fixed combination composition of 0.2% brimonidine and 0.5% timolol, In addition, there exist a number of secondary considerations that severely undermine the defendants' claims of obviousness. Accordingly, the court concludes that the patents-in-suit are not invalid as obvious under 35 U.S.C. § 103.

4. Validity Under Section 112

296. The Court declines to reach Defendants' counterclaims of invalidity under 35 U.S.C. § 112 with respect to claims 1–3 of the '149 patent. As stated during the trial, those claims were mooted by the Court's grant of summary judgment of non-infringement of those claims at Defendants' request. (*See* D.I. 243, Trial Tr. Day 3(PM) at 80:20–24 ("Well, you know, this Court granted a summary judgment as to Claims 1 through 3. I don't think they're relevant at this stage. I think we mooted those, Counsel, at your request. I took them out of the case.").)

297. Moreover, in their claim construction briefing, Defendants argued that the specification supported the Court's construction of the claims. (D.I. 123 at 24, 27–28.) They should not be heard to complain now that the construction adopted by the Court at their own request renders the claims invalid under Section 112. *New Hampshire v. Maine*, 532 U.S. 742, 750–51, 121 S.Ct. 1808, 149 L.Ed.2d 968 (2001) (discussing factors informing judicial estoppel). Accordingly, the Court concludes that Defendants are judicially estopped from arguing that the claims are invalid under Section 112 as failing to meet the requirements for written description and enablement.

IV. CONCLUSION

The statements above constitute the Court's findings of fact and conclusions of law in accordance with Rule 52(a) of the Federal Rules of Civil Procedure. For the reasons stated above, the court concludes that: (1) each of the Defendants infringe claim 4 of the '149 Patent, claim 1 of the '976 patent, claims 1–6 of the '463 Patent, and claims 1–9 of the '258 Patent; and (2) the patents-in-suit are not invalid. The Court will enter a judgment and injunction

consistent with these findings of fact and conclusions of law.

John WHITE, Plaintiff

v.

STRYKER CORPORATION, et al., Defendants.

Civil Action No. 3:10–CV–544–H.

United States District Court, W.D. Kentucky, at Louisville.

March 25, 2011.

Background: Patient brought products liability action in state court against manufacturer of hip-replacement system, certain components of which failed after system was implanted in patient. Action was removed to federal court. Manufacturer moved to dismiss for failure to state a claim upon which relief could be granted, alleging that patient's claims were preempted by the Medical Device Amendments (MDA) because they sought to impose requirements that differed from the requirements established by the Food and Drug Administration (FDA) for the system, which was a Class III medical device.

Holding: The District Court, John G. Heyburn, II, J., held that patient did not plausibly allege that system violated any FDA standard, and thus MDA preempted patient's claims.

Motion granted.

1. Health ⇐107
Sales ⇐427
States ⇐18.65

The MDA does not preempt state-law claims that are premised on a violation of Food and Drug Administration (FDA) regulations. Medical Device Amendments of 1976, § 2(a), 21 U.S.C.A. § 360k(a).

2. Products Liability ⇐226, 310
States ⇐18.65

When facing preemption under the MDA, a plausible state-law medical-device product liability cause of action requires a showing that the alleged violation of state law parallels a violation of federal law, which requires some greater specificity in the pleadings than in a typical products liability case. Medical Device Amendments of 1976, § 2(a), 21 U.S.C.A. § 360k(a).

3. Products Liability ⇐227, 310
Sales ⇐427
States ⇐18.15, 18.65

Patient who received implant of hip-replacement system, components of which subsequently failed, did not plausibly allege that system, a Class III medical device, violated any Food and Drug Administration (FDA) standard, and thus MDA preempted patient's state-law product liability, negligence, and warranty claims against manufacturer; patient generally purported to limit claims to circumstances involving noncompliance with FDA standard, but identified no particular design flaw, manufacturing impropriety, or product defect, and asserted no specific violation of standard established by FDA premarket approval process or generally applicable FDA manufacturing standard. Medical Device Amendments of 1976, §§ 2(a)(1)(C), 2(a), 21 U.S.C.A. §§ 360c(a)(1)(C), 360k(a).

Martin H. Kinney, Jr., Dolt, Thompson, Shepherd & Kinney PSC, Louisville, KY, for Plaintiff.