ALCON RESEARCH, LTD. (f/k/a ALCON MANUFACTURING, LTD.), ALCON LABORATORIES, INC., and KYOWA HAKKO KIRIN CO., LTD., Plaintiffs, vs. APOTEX INC. and APOTEX CORP., Defendants.

1:06-cv-1642-RLY-TAB (Consolidated)

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF INDIANA, INDIANAPOLIS DIVISION

790 F. Supp. 2d 868*; *2011 U.S. Dist. LEXIS 55144

May 23, 2011, Decided
May 23, 2011, Filed

SUBSEQUENT HISTORY: Motion granted by *Alcon Research, Ltd. v. Apotex Inc., 2012 U.S. App. LEXIS 1521 (Fed. Cir., Jan. 25, 2012)*

PRIOR HISTORY: *Alcon Mfg. v. Apotex, Inc., 2008 U.S. Dist. LEXIS 96630 (S.D. Ind., Nov. 26, 2008)*

COUNSEL: [1]** For ALCON RESEARCH, LTD., ALCON LABORATORIES, INC., KYOWA HAKKO KIRIN CO., LTD., Plaintiffs: Adam L. Perlman, Bruce Roger Genderson, Christopher J. Mandernach, Daniel P. Shanahan, Jessamyn S. Berniker, Shelley J. Webb, Thomas H. L. Selby, PRO HAC VICE, WILLIAMS & CONNOLLY LLP, Washington, DC; Deborah Pollack-Milgate, BARNES & THORNBURG, Indianapolis, IN; Donald E. Knebel, Paul B. Hunt, Todd G. Vare, BARNES & THORNBURG LLP, Indianapolis, IN.

For APOTEX INC., APOTEX CORP., Defendants: Abram B. Gregory, Gayle A. Reindl, TAFT STETTINIUS & HOLLISTER LLP, Indianapolis, IN; Brian J. Sodikoff, Craig M. Kuchii, Martin S. Masar, III, Robert B. Breisblatt, Thomas J. Maas, PRO HAC VICE, KATTEN MUCHIN ROSENMAN LLP., Chicago, IL.

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For KYOWA HAKKO KIRIN CO., LTD., ALCON RESEARCH, LTD., ALCON LABORATORIES, INC., Counter **[**2]** Defendants: Christopher J. Mandernach, Shelley J. Webb, Thomas H. L. Selby, PRO HAC VICE, WILLIAMS & CONNOLLY LLP, Washington, DC; Jessamyn S. Berniker, WILLIAMS & CONNOLLY LLP, Washington, DC.

For APOTEX INC., APOTEX CORP., Counter Claimants: Brian J. Sodikoff, Craig M. Kuchii, Martin S. Masar, III, Robert B. Breisblatt, Thomas J. Maas, PRO HAC VICE, KATTEN MUCHIN ROSENMAN LLP., Chicago, IL.

JUDGES: RICHARD L. YOUNG, CHIEF JUDGE.

OPINION BY: RICHARD L. YOUNG

OPINION

[*873] FINDINGS OF FACT AND CONCLUSIONS OF LAW

Plaintiffs, Alcon Research, Ltd. (f/k/a Alcon Manufacturing, Ltd.), Alcon Laboratories, Inc. (collectively "Alcon"), and Kyowa Hakko Kirin Co. Ltd. (f/k/a Kyowa Hakko Kogyo Co. Ltd.) ("Kyowa") (collectively "Plaintiffs"), filed suit against the Defendants, Apotex, Inc. and Apotex Corp. (collectively "Apotex" or "Defendants"), for infringement of *United States Patent No. 5,641,805 ("the '805 patent")*. The parties tried this case before the court from April 26, 2010, through May 7, 2010. Following the trial, the parties filed proposed findings of fact and conclusions of law. The parties presented their final arguments to the court on August 3, 2010.

Being duly advised, the court finds that Plaintiffs have proven, by **[**3]** a preponderance of the evidence, that the Defendants' generic equivalent of Plaintiffs' patented allergy topical ocular medication, Patanol®;, infringed claims 1-8 of the *'805 patent*. The court finds that Defendants have failed to prove by clear and convincing evidence that claims 1-8 of the *'805 patent* are invalid as obvious under *35 U.S.C. § 103*, as anticipated under *35 U.S.C. § 102*, and for lack of written description under *35 U.S.C. § 112*. The court further finds that Defendants have failed to prove by clear and convincing evidence that the *'805 patent* is unenforceable due to inequitable conduct.

The court now issues its findings of fact and conclusions of law pursuant to *Federal Rule of Civil Procedure 52(a)*:

FINDINGS OF FACT[1]

> 1 Citations to the trial transcript will be "[witness name] Tr." followed by "[transcript page: line];" citations to the deposition testimony submitted by the parties will be "[witness name] Dep." followed by "[dep. page: line]"; citations to the trial exhibits will be "TX" followed by the exhibit number; citations to Plaintiffs' demonstrative exhibits will be "AA" followed by the exhibit number; citations to the parties' pre-trial stipulations, Docket Nos. **[**4]** 173, 179, and 204, which are part of the trial record, will be "[Docket No.], Stipulation" followed by the paragraph number; and citations to any other document on the court's docket will be "[Docket No.]" followed by the title of the document.

I. The Parties

1. Alcon Research, Ltd. (f/k/a Alcon Manufacturing, Ltd.) is a corporation organized and existing under the laws of the State of Delaware, having its corporate offices and principal place of business at 6201 South Freeway, Fort Worth, Texas 76134. (Docket # 173, Stipulation ¶ 1).

2. Alcon Laboratories, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its corporate offices and principal place of business at 6201 South Freeway, Fort Worth, Texas 76134. (Docket # 173, Stipulation ¶ 2).

3. Kyowa Hakko Kirin Co., Ltd. (f/k/a Kyowa Hakko Kogyo Co., Ltd.) is a corporation organized and existing under the laws of Japan, having its principal place of business at 1-6-1 Ohtemachi, Chiyoda-ku, Tokyo 100-8185, Japan. (Docket # 173, Stipulation ¶ 3).

4. Apotex, Inc. is a corporation organized and existing under the laws of Canada, having its principal place of business at 150 Signet Dr., Weston, Ontario **[**5]** M9L 1T9. (Docket # 173, Stipulation ¶ 4).

5. Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 2400 North Commerce **[*874]** Parkway, Suite 400, Weston, Florida 33326. (Docket # 173, Stipulation ¶ 5).

6. Alcon Laboratories, Inc. holds the approved New Drug Application ("ANDA"), # 20-688, for Patanol®; ophthalmic solution. The NDA was approved on December 18, 1996. (Docket # 173, Stipulation ¶ 6).

7. On June 6, 1995, Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co. filed United States Patent Application # 08/469,729 (the "'729 application"), naming John Yanni, Stella Robertson, Eiji Hayakawa, and Masashi Nakakura as inventors. (Docket # 173, Stipulation ¶ 7).

8. The '729 application issued on June 24, 1997, as the *'805 patent*, entitled "Topical Ophthalmic Formulations for Treating Allergic Eye Diseases." Alcon Laboratories, Inc. and Kyowa Hakko Kogyo Co. Ltd.,

were the original assignees of the *'805 patent*. (Docket # 173, Stipulation ¶ 7).

9. Alcon Laboratories, Inc.'s interest in the *'805 patent* has been subsequently assigned to Alcon Research, Ltd. Alcon Laboratories, Inc. sells drug products covered by the *'805 patent* **[**6]** under the trademark Patanol®; pursuant to an ANDA held by Alcon Laboratories, Inc. and approved by the Food and Drug Administration ("FDA"). (Docket # 173, Stipulation ¶ 8).

10. Kyowa Hakko Kogyo Co., Ltd.'s interest in the *'805 patent* has been subsequently assigned to Kyowa Hakko Kirin Co., Ltd. (Docket # 173, Stipulation ¶ 9).

11. Patanol® is approved for the treatment of the signs and symptoms of allergic conjunctivitis. TX 131 at NDA000008; NDA000029 (showing approved indications on Patanol®'s label). The active ingredient of Patanol® is olopatadine hydrochloride. The concentration of Patanol®is 1 mg/mL, or 0.1% w/v. (Docket # 173, Stipulation ¶ 10).

12. Apotex is the owner of ANDA # 78-350, which was submitted to the FDA under *section 505(j) of the Federal Food, Drug and Cosmetic Act* ("FDCA"), and seeks approval to engage in the commercial manufacture, use, and sale of a generic olopatadine hydrochloride product ("Apotex's product") prior to the expiration of the *'805 patent*. (Docket # 173, Stipulation ¶ 13).

13. By letter dated October 2, 2006 (the "Notice Letter"), Apotex notified Plaintiffs that Apotex had submitted ANDA # 78-350 to the FDA. (Answer ¶ 16). In the Notice Letter, **[**7]** Apotex notified Plaintiffs that, as part of its ANDA, it had filed a certification of the type described in *section 505(j)(2)(A)(vii)(IV) of the FDCA* ("Paragraph IV" certification). (Answer ¶ 18); TX 131 at ANDA000043 (Paragraph IV certification statement).

14. On November 15, 2006, Plaintiffs brought suit against Apotex, asserting infringement of the *'805 patent*, arising out of Apotex's filing of ANDA # 78-350. (Docket # 1, Complaint).

15. Jurisdiction and venue are proper in this district pursuant to *28 U.S.C. §§ 1331, 1338(a), 1391*, and *1400(b)*. (Docket # 21, Answer ¶ 8; Docket # 35, Entry on Defendants' Motion to Transfer at 3 (no dispute between parties that the Southern District of Indiana is a proper venue)).

II. The Science of Allergy and the Invention of Patanol®

A. The Human Eye, the Conjunctiva, and Mast Cells

16. Mast cells are specialized cells that exist in many places throughout the body, including the eye, and are the primary cells involved in allergic reactions. (Kaliner Tr. 466:8-469:2, 476:3-24, 484:15-485:3; Bielory Tr. 1033:1-8, 1051:8-16; 1053:8-16).

17. The mast cells in the eye are located in the conjunctiva, which is the mucous membrane that lines the inner surface **[**8]** of **[*875]** the eyelids and the sclera on the front of the eyeball. (Yanni Tr. 113:24-114:20; AA-026.02; AA-027; Kaliner Tr. 459:25-460:3). The conjunctiva does not cover the tissues responsible for sight, including the cornea, lens, and retina. (Yanni Tr. 114:21-115:3; Kaliner Tr. 460:12-18; AA-027).

18. Like all mucous membranes, the conjunctiva is designed to keep things that are meant to be in the body in, and to prevent foreign matter from entering the body. The secretion of mucous on the surface of the membrane removes and flushes foreign objects from the surface of the membrane and protects the surface. (Kaliner Tr. 461:10-463:16; AA-33; AA-71).

19. The mast cells do not reside on the very surface of the eye. Within the conjunctiva, the epithelial goblet cells are located closest to the surface. (Kaliner Tr. 462:20-463:16, 464:15-466:7; AA-071; AA-033). Below the epithelial layer is a basement membrane. (Kaliner Tr. 464:15-466:7; AA-033; AA-071). Below the basement membrane is an area referred to as either the substantia or lamina propria. (Kaliner Tr. 464:15-466:7; AA-033; AA-071). The mast cells in the eye are located below the basement membrane in the substantia propria. (Kaliner Tr. **[**9]** 465:2-13; AA-071).

20. Mast cells contain granules, each of which contain pre-formed mediators. (Kaliner Tr. 467:10-468:15; AA-30; AA-32). Mediators are chemicals that, if released from the mast cells, have some effect on receptors located in the surrounding tissue. (Kaliner Tr. 467:10-468:15; AA-093). Each granule contains up to 25 different types of chemical mediators. (Kaliner Tr. 467:10-468:15; AA-093).

21. Adjacent to the conjunctiva is the conjunctival sac, which contains an extremely small amount of fluid that keeps the tissues moist. (Kaliner Tr. 460:19-461:6; AA-027).

B. The Allergic Cascade

1. Mediator Release Through Degranulation

22. The allergic response is a mechanism that the human body uses to attempt to expel something it recognizes as a foreign invading substance. (Yanni Tr. 119:16-120:4).

23. In the eye, the most common type of allergic disease is called allergic conjunctivitis. (Kaliner Tr. 507:2-13).

24. In general, an allergic reaction can occur in the sensitized human being upon exposure to an antigen. An antigen is a substance that has the ability to trigger an immunologic reaction, such as the production of antibodies. (Yanni Tr. 116:18-118:14; Kaliner Tr. 470:2-22).

25. **[**10]** Common antigens include substances such as cat dander, pollen, and ragweed. (Yanni Tr. 117:10-118:6; Kaliner Tr. 470:2-22).

26. Exposure occurs when an antigen, like pollen, comes into contact with the outer epithelial layer of the conjunctiva. Small proteins break off from the pollen grain and move through the epithelium, through the basement membrane, and into the substantia or lamina propria where the mast cells are located. (Kaliner Tr. 465:2-13).

27. In the portion of the human population that is genetically predisposed to do so, exposure over a period of time to certain antigens through the mucous membranes causes the body to produce antibodies. The antibodies bind to the surface of the mast cells. (Yanni Tr. 117:10-118:14; Kaliner Tr. 470:2-471:13; AA-19.01-.03).

28. **[**11]** When antibodies bind to the surface of mast cells, they confer sensitivity to these cells. When those cells are subsequently exposed to the antigen, the antigen binds to the antibodies on the surface **[*876]** of the cells, causing them to secrete the chemical mediators within them. This process of releasing the pre-formed mediators is referred to as degranulation. (Yanni Tr. 118:5-119:6; Kaliner Tr. 471:8-472:10; AA-19.04-.07).

29. The pre-formed chemical mediators found in mast cells vary depending on the type of mast cell, and may include histamine, heparin, tryptase, chymase, and other chemicals. (Yanni Tr. 116:17-117:9; Kaliner Tr. 474:3-16; AA-93).

2. Mediator Production in the "Late Phase" of the Allergic Cascade

30. **[**12]** Mast cells also have the ability to synthesize and release other chemical mediators and cytokines that are synthesized and released after the release of pre-formed mediators, which occurs in what is called the late phase of the allergic reaction. (Kaliner Tr. 473:5-18). The late phase reaction is an inflammatory response in which white blood cells, called eosinophils, are attracted to the eye and make the eye quite irritable for an extended period of time. (Kaliner Tr. 473:5-18).

3. Signs and Symptoms of Allergy

31. Within the surrounding tissues of the eye, there are different types of receptors that correspond to the different mediators released from the mast cells. (Yanni Tr. 118:24-119:6; Kaliner Tr. 471:22-473:4; AA-19.01; AA-19.07-.09).

32. After mediators and cytokines are released from mast cells, they bind to the corresponding receptors and trigger physiological reactions in the body that are commonly identified as allergic symptoms -- redness, itching, swelling, watering eyes, running nose, etc. (Yanni Tr. 119:7-15; Kaliner Tr. 471:22-473:4; AA-19.09; AA-20).

C. Treating Allergic Eye Disease

33. Patients with allergic conditions are treated by interfering with the allergic cascade **[**13]** at one or more points in the process. (Kaliner Tr. 498:15-500:5).

34. In 1995, there were three primary classes of compounds used to treat allergic conjunctivitis: (1) antihistamines; (2) antihistamines combined with vasoconstrictors; and (3) cromolyn sodium, a compound that was reported to be a mast cell stabilizer based on animal testing. (Yanni Tr. 120:5-121:5).

1. Antihistamines (With or Without Vasoconstrictors)

a. Antihistamines Have Limited Effect

35. A standard antihistamine interferes with the allergic cascade toward the end of the process by preventing histamine that has been released from mast cells from binding to particular histamine receptor sites by blocking those receptors. (Kaliner Tr. 496:19-498:8; AA-22.01-.03; AA-22.06; AA-22.08).

36. If an antihistamine is administered after histamine has already been released, the antihistamine can displace histamine from a histamine receptor and replace it, which stops the allergic symptoms caused by that mediator. (Yanni Tr. 122:19-123:25; Kaliner Tr. 496:19-498:8; AA-22.05a; AA-22.05b).

37. Antihistamines are only effective in relieving symptoms caused by histamine binding to those H1 receptors and do not have any effect on signs **[**14]** or symptoms caused by mediators other than histamine that are released from the mast cell. (Yanni Tr. 124:1-8; Kaliner Tr. 498:15-499:4).

38. Antihistamines also do not have any effect on the symptoms caused by the late **[*877]** phase of the allergic reaction. (Kaliner Tr. 498:15-499:20).

b. Many Oral Antihistamines Cannot Be Made Into Topical Ophthalmic Preparations

39. Oral antihistamines have been on the market since around 1950 and were the first treatment used for allergic eye disease. (Kaliner Tr. 493:7-22).

40. Not all antihistamines can be used topically on the eye, (Bielory Tr. 1230:10-12), because of the challenges in turning an orally administered systemic antihistamine into a topically applied antihistamine. (Kaliner Tr. 494:21-495:12). In fact, none of the best-selling systemic antihistamines on the market -- Claritin, Zyrtec, and Allegra -- have been formulated as eye drops despite attempts to do so. (Kaliner Tr. 494:21-495:12; Abelson Tr. 1898:20-1901:3).

41. In 1995, the person of ordinary skill in the art (or "POOS") understood that there were significant barriers to adapting a known systemic antihistamine for topical use in the eye. (Kaliner Tr. 493:15-495:12). Indeed, both sides' **[**15]** experts agree that some antihistamines are simply not bioavailable when applied topically to the eye, others cannot be formulated in an eye drop that is tolerable in the eye or are not sufficiently soluble, and some antihistamines that are systemically effective exhibit unacceptable side effects when applied directly to the eye. (Kaliner Tr. 493:15-495:12; Bielory Tr. 1230:13-21; Abelson Tr. 1901:7-1902:2).

42. In 1995, the POOS would not have been able to have a reasonable expectation regarding whether an antihistamine that was effective when given orally could have been formulated as an effective topical product. (Abelson Tr. 1900:16-1901:3; Kaliner Tr. 495:13-496:14).

43. Furthermore, in 1995, the POOS would not have been able to predict whether an antihistamine that was effective when given orally would be bioavailable and pharmacologically effective if applied topically to the eye. (Kaliner Tr. 496:6-18).

2. Antihistamines with Vasoconstrictors

44. Vasoconstrictors (also called decongestants) have also been used to treat allergic eye disease. (Kaliner Tr. 500:6-501:2). Decongestants act only on the end organ response to the allergic reaction by shrinking the blood vessels. (Kaliner **[**16]** Tr. 500:6-501:2). Decongestants have a limited effect and can lead to a rebound effect where the congestion becomes worse after use is discontinued. (Kaliner Tr. 500:6-501:2).

45. Combinations of antihistamines and vasoconstrictors have been used to try to block the itching caused by histamine and the redness caused by vasodilation. (Kaliner Tr. 501:3-9). These products do not work nearly as well as prescription products. (Kaliner Tr. 501:10-16).

3. Mast Cell Stabilizers

46. A more effective way to provide relief to the patient is to significantly reduce or prevent mast cell mediator release. This is referred to as stabilizing the mast cell or mast cell stabilization. Mast cell stabilization shuts down the start of the allergic cascade and significantly reduces or prevents all allergic symptoms. (Yanni Tr. 124:11-125:19; Kaliner Tr. 499:21-500:5).

47. A mast cell stabilizer will prevent or inhibit all of the mediators -- of which there are many -- from being released from the mast cells. (Kaliner Tr. 499:21-500:5; 474:3-16; AA-93). There are not individual mast cells, or

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