ALCON RESEARCH, LTD. (FORMERLY KNOWN AS ALCON MANUFACTURING, LTD.), ALCON LABORATORIES, INC., AND KYOWA HAKKO KIRIN CO. LTD., Plaintiffs-Appellees, v. APOTEX INC. AND APOTEX CORP., Defendants-Appellants.

2011-1455

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

687 F.3d 1362*; *2012 U.S. App. LEXIS 16503*; *103 U.S.P.Q.2D (BNA) 1737

August 8, 2012, Decided

SUBSEQUENT HISTORY: US Supreme Court certiorari denied by *Alcon Research, Ltd. v. Apotex, Inc., 133 S. Ct. 1736, 185 L. Ed. 2d 787, 2013 U.S. LEXIS 2613 (U.S., 2013)*
Related proceeding at *Alcon Research, Ltd. v. Apotex, Inc., 2013 U.S. Dist. LEXIS 71432 (S.D. Ind., May 21, 2013)*

PRIOR HISTORY: [1]**
Appeal from the United States District Court for the Southern District of Indiana in case no.06-CV-1642, Judge Richard L. Young.
Alcon Research, Ltd. v. Apotex Inc., 2012 U.S. App. LEXIS 1521 (Fed. Cir., Jan. 25, 2012)

DISPOSITION: REVERSED-IN-PART, AFFIRMED-IN-PART.

COUNSEL: KANNON KUMAR SHAMUGAM, Williams & Connolly, LLP, of Washington, DC, argued for plaintiffs-appellees. With him on the brief were ADAM L. PERLMAN, THOMAS H. L. SELBY and SHELLEY J. WEBB.

ROBERT B. BREISBLATT, Katten Muchin Rosenman, LLP, of Chicago, Illinois, argued for defendants-appellants. With him on the brief were CRAIG M. KUCHII, BRIAN J. SODIKOFF and THOMAS J. MAAS. Of counsel on the brief was SHASHANK UPADHYE, Apotex, Inc., of Toronto, Ontario, Canada.

JUDGES: Before PROST, MOORE, and O'MALLEY, Circuit Judges.

OPINION BY: MOORE

OPINION

[*1738] [*1363]** MOORE, *Circuit Judge*.

Apotex Inc. and Apotex Corp. (collectively, Apotex) submitted an Abbreviated New Drug **[***1739]** Application (ANDA) to the Food and Drug Administration seeking approval to market a generic version of the anti-allergy eye drop Patanol®. Alcon Research, Ltd. et al. (collectively, Alcon), who market Patanol®, sued Apotex for patent infringement under *35 U.S.C. § 271(e)(2)(A)*. Alcon asserted claims 1-8 of *U.S. Patent No. 5,641,805 ('805 patent)*, which is listed in the Approved Drug Products with **[**2]** Therapeutic Equivalence Evaluations (Orange Book) entry for Patanol®. For the reasons set forth below, we *reverse* the district court's holding that claims 1-3 and 5-7 would not have been obvious over the prior art but *affirm* the court's holding that claims 4 and 8 are not invalid.

BACKGROUND

An allergic reaction is the body's mechanism for expelling antigens, such as pollen or pet dander. Exposure to an antigen causes the body to produce antibodies. These antibodies bind to the surface of mast cells, which are specialized cells that exist in many places in the body and are the primary cells involved in allergic reactions. This binding sensitizes the mast cells to that antigen. If the mast cells are subsequently exposed to the same antigen again, the antigen binds to the antibodies on the surface of the mast cell. This causes the mast cells to release chemicals called mediators, such as histamine and heparin. These mediators bind to receptors in surrounding tissues, triggering the reactions commonly identified as allergic symptoms, such as itching and redness. In the human eye, mast cells are located in the conjunctiva, which is the membrane that covers the inner surface of the eyelid **[**3]** and the white part of the eyeball.

Anti-allergy drugs can treat allergic symptoms by interfering at one of several points in this process. Antihistamines, for example, prevent the histamine that is released from mast cells from binding to receptors in surrounding tissues and also displace the histamine that is already bound to receptors. By contrast, drugs known as mast cell stabilizers prevent mast cells from releasing mediators, and thus counteract the effects of histamine and other mediators that cause allergic symptoms.

The *'805 patent* is directed to a method for treating allergic eye disease in humans comprising stabilizing conjunctival mast cells by topically administering an olopatadine **[*1364]** [1] composition. *'805 patent* col.1 ll.7-15, col.2 l.64 - col.3 l.3. The specification explains that the discovery that olopatadine can treat human eye allergies through this mechanism of action -- stabilizing mast cells in the human eye -- is the novel aspect of the *'805 patent*. *See, e.g., id.* col.2 ll.56-61 ("What is needed are topically administrable drug compounds which have demonstrated stabilizing activity on mast cells obtained from human conjunctiva, the target cells for treating allergic eye **[**4]** diseases."); *see also id.* col.3 ll.18-23 ("[Olopatadine] has human conjunctival mast cell stabilizing activity, and may be applied as infrequently as once or twice a day in some cases.").

> 1 The method claimed in the *'805 patent* uses the compound 11-(3-dimethylaminopropylidene)-6,11-dih ydrodibenz(b,e) oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof. Although this compound has two geometric isomers (a cis and a trans form), we refer to these compounds throughout this opinion simply as olopatadine (the cis form).

The specification states that at the time of invention, it was already known in the art that olopatadine was an effective antihistamine and that some chemicals in olopatadine's genus may have mast cell stabilizing activity. *Id.* col.1 l.16 - col.2 l.61. Indeed, both the olopatadine compound itself and a method of treating allergies using the class of chemicals that encompasses olopatadine were both already patented. *See U.S. Patent No. 5,116,863*; *U.S. Patent No. 4,923,892*. The *'805 patent* specification states, however, that it was not known whether olopatadine would stabilize mast cells in human eyes. *Id.* col.1 ll.43-58. The specification explains that this was **[**5]** because mast cells in different species, and in different tissues within the same species, exhibit different biological responses -- a concept called mast cell heterogeneity. *Id.* col.1 ll.43-58. As a result, a compound's activity in a rodent's conjunctival mast cells or in mast cells located elsewhere in the human body cannot predict its ability to stabilize mast cells in the human eye. *Id.* col.1 l.43 - col.2 l.19. The *'805 patent*'s inventors conducted in vitro testing showing that olopatadine stabilizes conjunctival mast cells in humans. *'805 patent* col.3 ll.18-23, col.3 l.43 - col.5 l.55.

The *'805 patent* claims are limited to a method of treating human eye allergies that **[***1740]** comprises stabilizing conjunctival mast cells. Claim 1 reads:

> A method for treating allergic eye diseases in humans *comprising stabilizing conjunctival mast cells* by topically administering to the eye a composition comprising a *therapeutically effective amount* of 11-(3-dimethylaminopropylidene)-6,11-dih ydrodibenz(b,e) oxepin-2-acetic acid or a pharmaceutically acceptable salt thereof.

'805 patent cl.1 (emphases added). The parties do not dispute the district court's construction of "stabilizing conjunctival mast cells" **[**6]** as "preventing or reducing release of mediators including histamine from mast cells in the conjunctiva to an extent clinically relevant in the treatment of allergic eye disease." J.A. 176. Although

independent claim 1 does not specify the "therapeutically effective amount" of olopatadine required to stabilize conjunctival mast cells, dependent claims limit the method of claim 1 to specific concentration ranges. Claims 2 and 6, for example, are limited to using a composition that contains from about 0.0001% w/v to about 5% w/v of olopatadine. Claims 4 and 8 are limited to a concentration of 0.1% w/v of olopatadine.

Alcon's Patanol® product, an anti-allergy eye drop with a 0.1% w/v concentration of olopatadine, is a commercial embodiment of the *'805 patent*. Apotex filed an **[*1365]** ANDA seeking permission to sell a generic version of Patanol® and included a Paragraph IV certification that the *'805 patent* was invalid, unenforceable, and/or would not be infringed by Apotex's generic product. Alcon sued Apotex for patent infringement, asserting claims 1-8. In a bench trial, the district court held that the *'805 patent* was enforceable and not invalid, and that Apotex's generic product infringed the **[**7]** asserted claims. *Alcon Research, Ltd. v. Apotex Inc., 790 F. Supp. 2d 868, 944-45 (S.D. Ind. 2011)*.

On the issue of validity, the district court held that Apotex failed to establish that the claims would have been obvious by clear and convincing evidence. The court recognized that olopatadine was known to be an effective antihistamine, but found that at the time of invention a skilled artisan "understood that there were significant barriers to adapting a known systemic antihistamine for topical use in the eye." *Id. at 877*. The court also found that the prior art as a whole, and specifically an article by Kamei et al., taught away from using olopatadine as a mast cell stabilizer. Kamei tested an ophthalmic formulation of olopatadine in guinea pig eyes at concentrations that overlap with those recited in most of the *'805 patent* claims. Kamei discloses that, although olopatadine is a good antihistamine, it is not an effective mast cell stabilizer. J.A. 10162-63. The court further found that Ka-mei's disclosure of using olopatadine eye drops in guinea pigs would not give a skilled artisan an expectation of success because it does not show whether olopatadine is safe to use in the human **[**8]** eye. The district court rejected Apotex's argument that the prior art need not teach mast cell stabilization because this mechanism of action is an inherent property of olopatadine. In reaching this conclusion, the court relied largely on testimony by Alcon's expert, Dr. Kaliner, that not every concentration of olopatadine will stabilize human conjunctival mast cells to a "clinically relevant" extent, as required by the court's claim construction.

The district court also held that objective evidence supported its holding of nonobviousness. For example, the court found that Patanol® showed unexpected results because a person of ordinary skill would not have expected it to be an effective mast cell stabilizer in the human eye. *Alcon v. Apotex, 790 F. Supp. 2d at 905*. The court concluded that Patanol® satisfied a long-felt but unmet need for a human conjunctival mast cell stabilizer. The court further found that Patanol® has been "an outstanding commercial success," achieving nearly a 70% market share within two years of its launch. *Id. at 904*.

Apotex now appeals from the district court's final judgment that the *'805 patent* would not have been obvious over the prior art and from the grant **[**9]** of a permanent injunction barring Apotex from selling its generic product. We have jurisdiction under *28 U.S.C. § 1295(a)(1)*.

DISCUSSION

A patent is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *35 U.S.C. § 103(a)*. "Obviousness is a question of law, which we review *de novo*, with underlying factual questions, which we review for clear **[***1741]** error following a bench trial." *Honeywell Int'l, Inc. v. United States, 609 F.3d 1292, 1297 (Fed. Cir. 2010)*. These underlying factual inquires are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims **[*1366]** at issue; (3) the level of ordinary skill in the field of the invention; and (4) objective considerations such as commercial success, long felt need, and the failure of others. *KSR Int'l Co., v. Teleflex, Inc., 550 U.S. 398, 406, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007)* (citing *Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)*). Patent invalidity must be established by clear and convincing **[**10]** evidence. *Microsoft Corp. v. i4i Ltd., 131 S. Ct. 2238, 2242, 180 L. Ed. 2d 131 (2011)*.

I. Claims 1-3 and 5-7

Apotex argues that the district court erred by finding that the *'805 patent* claims would not have been obvious over the prior art. Apotex asserts that claims 1-3 and 5-7 would have been obvious over Kamei, which discloses eye drops with olopatadine concentrations that overlap with the claimed concentration ranges. Apotex argues that even though Kamei tested olopatadine formulations only in guinea pig eyes, a person of ordinary skill in the art could use routine methods to adapt these formulations for human use with a reasonable expectation of success. Apotex also argues that the district court erred by focusing on Kamei's lack of disclosure that olopatadine is safe for human use because the '805 claims do not recite a "safety" limitation.

Apotex contends that the district court erred by requiring that the prior art provide a motivation to use olopatadine specifically as a mast cell stabilizer. Apotex argues that the prior art's disclosure that olopatadine is an effective antihistamine that can be formulated for ophthalmic use provides sufficient motivation to develop an olopatadine eye drop for **[**11]** humans. Apotex also argues that claiming olopatadine's mechanism of action (stabilizing conjunctival mast cells) cannot impart patentability to the *'805 patent* claims because it is an inherent property of olopatadine. Apotex also asserts that even if this limitation restricts the claims to certain concentrations of olopatadine, the claims nonetheless would have been obvious because the prior art teaches using olopatadine at those concentrations.

Apotex also argues that the district court erred by finding that objective evidence supported its holding of nonobviousness. Specifically, Apotex contends that olopatadine's superior clinical efficacy is due at least in part to its antihistaminic activity, which is not a novel aspect of the *'805 patent*. Apotex thus argues that the district court's findings regarding commercial success, industry praise, and unexpected results lack sufficient nexus to the *'805 patent* claims.

Alcon contends that the court correctly found that a skilled artisan would not be motivated to formulate an olopatadine eye drop solely based on its antihistaminic activity because the prior art does not supply a reason to focus on olopatadine instead of many other promising **[**12]** antihistamines. Alcon also argues that the court correctly found that there would not have been a reasonable expectation of success in formulating an olopatadine eye drop because, at the time of invention, there were barriers to adapting an oral antihistamine for ophthalmic use.

Alcon does not dispute that Kamei teaches using olopatadine eye drops at concentrations that overlap with those in claims 1-3 and 5-7 of the *'805 patent*. Instead, Alcon argues that Kamei does not teach that olopatadine would be a mast cell stabilizer at those concentrations or that it would be safe for use in the human eye. Alcon argues that the district court correctly found that the prior art as a whole teaches away from using olopatadine as a mast cell stabilizer. Alcon also asserts **[*1367]** that the district court correctly found that mast cell stabilization is not an inherent property of olopatadine because only some concentrations stabilize mast cells to a clinically relevant extent, as required by the court's claim construction. Finally, Alcon argues that the district court correctly found that objective evidence supports a finding of nonobviousness.

As an initial matter, we believe the district court erred in **[**13]** its comparison of the *'805 patent* claims and the disclosure of the prior art. Claim 1 recites a method of treating allergic eye disease comprising using a "therapeutically effective amount" of olopatadine to stabilize conjunctival mast cells. The court construed the term "stabilizing conjunctival mast cells" to limit the claims only to concentrations of olopatadine that stabilize conjunctival mast cells "to an extent clinically relevant in the treatment of allergic eye disease." J.A. 176. This construction is not appealed. Because **[***1742]** it is not appealed, we do not decide whether this construction is correct.

On appeal, however, we must determine what olopatadine concentrations constitute a "therapeutically effective amount." The dependent claims are a starting point for ascertaining the concentration of olopatadine covered by claim 1. Claim 2, for example, is directed to the method of claim 1 wherein "the amount of [olopatadine] is from about 0.0001 w/v. % to about 5% (w/v)." Claim 3 further narrows the range to "about 0.001 to about 0.2% (w/v)." Claim 4 further narrows the range to "about 0.1% (w/v)." As far as the concentrations of olopatadine, claims 5-8 mirror the ranges disclosed in **[**14]** 1-4, respectively.

It is axiomatic that a dependent claim cannot be broader than the claim from which it depends. *See 35 U.S.C. § 112* ¶4 ("[A] claim in dependent form shall contain a reference to a claim previously set forth and

then specify a further limitation of the subject matter claimed."); *see also Intamin Ltd. v. Magnetar Techs., Corp., 483 F.3d 1328, 1335 (Fed. Cir. 2007)* ("An independent claim impliedly embraces more subject matter than its narrower dependent claim."); *AK Steel Corp. v. Sollac & Ugine, 344 F.3d 1234, 1242 (Fed. Cir. 2003)* ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."). Therefore if claim 2 covers the range from 0.0001% w/v-5% w/v, claim 1 must cover at least that range. Furthermore, because a dependent claim narrows the claim from which it depends, it must "incorporate . . . all the limitations of the claim to which it refers." *35 U.S.C. § 112* ¶4. As a result, the concentrations recited in the *'805 patent*'s dependent claims must necessarily meet claim 1's limitations of being therapeutically effective for treating allergic eye disease by stabilizing conjunctival **[**15]** mast cells. This is clear from the express claim language. It is also supported by the specification: "The concentration of Compound A is 0.0001 to 5 w/v %, preferably 0.001 to 0.2 w/v %, and most preferably about 0.1 w/v % . . . ." *'805 patent* col.6 ll.43-46.

Despite the clear language of the *'805 patent* claims, Alcon argues that some olopatadine concentrations covered by claims 1-3 and 5-7 do *not* stabilize human conjunctival mast cells to a clinically relevant extent and should therefore be excluded from the claims' scope. The district court found that "[n]ot every concentration of olopatadine applied to the human eye will stabilize the mast cells in the human eye." *Alcon v. Apotex, 790 F. Supp. 2d at 909*. The court cited testimony by Alcon's expert, Dr. Kaliner, that olopatadine at 0.001% w/v (which is covered by claims 1-3 and 5-7) would not stabilize human conjunctival **[*1368]** mast cells to a clinically relevant extent. *Id. at 909, 935*.

Alcon's counsel argued that, "to the extent that the dependent claims cover a broader range than the range that would be operative to stabilize mast cells," the inoperative portion of the range "wouldn't be covered by the claim by virtue of the limitation **[**16]** in claim 1" that mast cell stabilization must occur to a clinically relevant extent. Argument at 14:56-15:22, *Alcon Research v. Apotex*, No. 2011-1455, available at http://oralarguments.cafc.uscourts.gov/default.aspx?fl=20 11-1455.mp3. Alcon's counsel thus contended that the claims "would be operative, just at a narrower concentration" than the claimed range. *Id.* at 15:24-15:27. This is not how patent law works. When you claim a concentration range of 0.0001-5% w/v (as claim 2), you can't simply disavow the invalid portion and keep the valid portion of the claim. If everything up to 0.001% w/v is admittedly not enabled, then the entire claim is invalid. Similarly, if prior art discloses a portion of the claimed range, the entire claim is invalid. Courts do not rewrite the claims to narrow them for the patentee to cover only the valid portion. Alcon cannot have it both ways. Because claim 2 sets forth a concentration range, that range at a minimum must be included in claim 1, whatever its limitations. When analyzing the validity of claim 1 or claim 2, by the express claim language, the clinically relevant therapeutic amount must include 0.0001-5% w/v olopatadine. That is the claimed **[**17]** concentration range which should be compared to the disclosure of the prior art.

The Kamei reference discloses treating eye allergies in guinea pigs using eye drops with olopatadine concentrations ranging from 0.0001% w/v to 0.01% w/v. J.A. 10160-63. This range overlaps with the concentrations covered by claims 1-3 and 5-7. Claims 4 and 8 are directed only to a 0.1% olopatadine formulation, and Kamei does not disclose a concentration **[***1743]** of olopatadine greater than 0.01%. Kamei expressly discloses eye drops with olopatadine concentrations covered by claims 1-3 and 5-7 and thus overlaps with the ranges disclosed in the *'805 patent*.

The only remaining dispute is whether there was a motivation to adapt the formulation disclosed in Kamei, which was tested in guinea pigs, for use in treating allergic eye disease in humans. The district court found, as a factual matter, that animal tests, including guinea pig models, are predictive of a compound's antihistaminic activity and its topical ocular availability in humans. *Alcon v. Apotex, 790 F. Supp. 2d at 881*. Given this fact finding, the district court clearly erred when it concluded that a person of skill in the art would not have been motivated **[**18]** to use the olopatadine concentration disclosed in Kamei in human eyes. The district court's error stemmed from its refusal to look at any motivation beyond that articulated by the patent. We have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same motivation that the patentee had. *See KSR, 550 U.S. at 420* (stating that it is error to look "only to the problem the patentee was trying to solve"); *see also In re Kahn, 441 F.3d 977, 990 (Fed. Cir. 2006)* ("[T]he skilled artisan

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