United States Court of Appeals for the Federal Circuit

IN RE BRIMONIDINE PATENT LITIGATION

ALLERGAN, INC.,
Plaintiff-Appellee,

v.

EXELA PHARMSCI INC. AND EXELA PHARMSCI PVT., LTD.,
Defendants-Appellants,

and

APOTEX INC. AND APOTEX CORP.,
Defendants-Appellants.

2010-1102,-1103

Appeal from the United States District Court for the District of Delaware in Case No. 07-MD-1866, Chief Judge Gregory M. Sleet.

Decided: May 19, 2011

JONATHAN E. SINGER, Fish & Richardson, P.C. of Minneapolis, Minnesota, argued for plaintiff-appellee. With him on the brief were DEANNA J. REICHEL and JUANITA R.

BROOKS, of San Diego, California, and W. CHAD SHEAR, of Dallas, Texas.

HAROLD C. WEGNER, Foley & Lardner, LLP, of Washington, DC, argued for defendants-appellants Exela Pharmsci Inc., et al. With him on the brief were C. EDWARD POLK, JR. and STEPHEN B. MAEBIUS. Of counsel was DOUGLAS H. CARSTEN, of San Diego, California.

ROBERT B. BREISBLATT, Katten Muchin & Rosenman, LLP, of Chicago, Illinois, argued for plaintiffs-appellants Apotex Inc. et al. With him on the brief were RACHEL M. VORBECK, BRIAN J. SODIKOFF and STEPHEN P. BENSON. Of counsel was CHARLES PARADIS.

Before BRYSON, DYK, and PROST, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* BRYSON.
Opinion concurring-in-part and dissenting-in-part filed by *Circuit Judge* DYK.

BRYSON, *Circuit Judge*.

This patent case involves a dispute over an eyedrop formulation used to treat glaucoma. The appellee, Allergan, Inc., has various patents that protect its glaucoma drug Alphagan® P. The appellants, Apotex, Inc., and Exela Pharmsci, Inc., each filed an Abbreviated New Drug Application ("ANDA") seeking permission from the Food and Drug Administration ("FDA") to market a generic version of Alphagan® P. Allergan sued both Apotex and Exela for infringement. After an eight-day bench trial, the district court found that Allergan's asserted patents were not invalid and that Apotex and Exela infringed those patents. The court enjoined both Apotex and Exela from making or selling the products described in each defendant's ANDA.

Apotex appeals only the validity portion of the judgment against it; Exela appeals only the finding of infringement. On Apotex's appeal, we affirm-in-part, reverse-in-part, and affirm the entry of the injunction, as explained below. On Exela's appeal, we reverse.

I

Brimonidine tartrate is an α-2-adrenergic agonist that reduces the elevated intraocular pressure (IOP) of the eye that is associated with glaucoma. In 1996, Allergan introduced Alphagan®, an aqueous eyedrop solution containing 0.2% brimonidine. Alphagan® is adjusted to a pH between 6.3 and 6.5. It includes a detergent preservative, benzalkonium chloride. Alphagan® was commercially successful. However, a sizeable percentage of Alphagan® users developed an allergic reaction to brimonidine known as allergic conjunctivitis.

Allergan's efforts to address this allergic response led to the introduction of Alphagan® P in 2001. Allergan sells Alphagan® P at two brimonidine concentrations, 0.15% and 0.1%, each of which is lower than the 0.2% brimonidine concentration in Alphagan®. Alphagan® P has a pH between 7.15 and 7.8, a range that is higher than that of Alphagan®. The lower concentration Alphagan® P formulation is sold at a pH of 7.6 to 7.8; the higher concentration is sold at a pH of 7.15 to 7.3.

Two therapeutic benefits accompany the elevated pH. First, the pH of Alphagan® P is closer to that of the human eye than is the pH of Alphagan®. Therefore, Alphagan® P does not produce a stinging sensation when administered. Second, because brimonidine is an ionizable drug, a lower concentration of brimonidine at the elevated pH of Alphagan® P will provide therapeutic benefits similar to the

benefits provided by a higher concentration at a lower pH. At an elevated pH, a higher fraction of brimonidine is un-ionized as compared to the fraction that is un-ionized at the slightly acidic pH of Alphagan®. The un-ionized species is more lipid soluble and thus more readily crosses the corneal membrane than does the ionized species. Because the brimonidine-induced allergic reaction is dose-dependent, Alphagan® P—with its lower concentration of brimonidine—does not pose the same risk of allergic response as the original Alphagan®. Yet because a higher percentage of the brimonidine passes into the eye at the higher pH, Alphagan® P remains as therapeutically effective as Alphagan®.

The Allergan researchers who developed Alphagan® P were concerned that brimonidine would not be soluble at a pH as high as 7.15 or above; accordingly, they included a solubility-enhancing component, carboxymethylcellulose ("CMC"). The original Alphagan® included a detergent preservative, benzalkonium chloride, which was known to be somewhat irritating to the eye. The preservative in Alphagan® P is stabilized chlorine dioxide ("SCD"), an oxidative preservative that was known to be compatible with the eye. Although the formulators expressed concern that SCD would oxidize brimonidine, they found that the two were compatible. Both the preservative, SCD, and the solubility-enhancing component, CMC, are components of Refresh Tears®, an Allergan artificial tears solution with a pH between 7.2 and 7.9.

Allergan submitted five patents associated with Alphagan® P to the FDA for publication in the FDA's list of patents on branded drugs, known as the Orange Book. The first patent, U.S. Patent No. 5,424,078 ("the '078 patent"), is directed to a sterilized ophthalmic solution at physiologic pH and osmolality. The other four patents, which the

parties refer to as the "related patents," are directed to medicated ophthalmic solutions.

In 2007, Apotex submitted two ANDAs to the FDA seeking approval to manufacture and sell a generic version of Alphagan® P in the 0.1% and 0.15% brimonidine concentrations. Exela filed a single ANDA targeting the 0.15% brimonidine product. Allergan sued Exela in the United States District Court for the Central District of California for patent infringement under 35 U.S.C. § 271(e)(2). Allergan filed a similar suit against Apotex in the United States District Court for the District of Delaware.

The multidistrict litigation panel consolidated both cases in the District of Delaware. Following a bench trial, the district court upheld the validity of all the asserted claims of the '078 and related patents against an obviousness challenge. Apotex stipulated to infringement. The district court held a bench trial on the infringement action against Exela and found that the product proposed in Exela's ANDA would infringe the asserted claims. Accordingly, the court enjoined both Apotex and Exela from making or selling the products described in their respective ANDAs.

II

Apotex challenges the district court's determination that the asserted patents are not invalid. With respect to the '078 patent, we hold that the asserted claims would have been obvious. With respect to the four "related patents," however, we uphold the district court's determination that the claims would not have been obvious. The injunction against Apotex stands unless Apotex overcomes the presumption of validity for every claim of the '078 patent and the "related patents." Because Apotex failed to meet this

burden with respect to the "related patents," we affirm the court's award of injunctive relief in favor of Allergan.

A

The '078 patent describes and claims a buffered, aqueous ophthalmic solution at a pH of about 6.8 to 8, which roughly corresponds to the pH of the human eye. Claim 1 recites a method for preserving an aqueous ophthalmic formulation. The claimed method employs a solution having three active components: an amount of stabilized chlorine dioxide sufficient to serve as the sole preservative, an ophthalmically acceptable buffer component effective to maintain a pH range of about 6.8 to 8, and an ophthalmically acceptable tonicity component effective to maintain an osmolality of at least 200 mOsmol/kg. Stabilized chlorine dioxide is a salt-balanced, aqueous solution of chlorite, ClO_2^-. The addition of an acid (or an oxidant) to an SCD solution "activates" the SCD by oxidizing chlorite to chlorine dioxide, ClO_2. Both SCD and chlorine dioxide are oxidants, although chlorine dioxide is the stronger of the two.

Apotex's invalidity argument focuses on two references, U.S. Patent No. 4,499,077 ("Stockel") and U.S. Patent No. 4,689,215 ("Ratcliff"). The district court determined that those references were insufficient to rebut the presumption of validity. According to the district court, Ratcliff discloses "stabilized chlorine dioxide as a starting material, and the use of chlorine dioxide as the active antimicrobial species for ophthalmic applications." The court found that Stockel teaches away from the claimed invention. The court explained that the claims of the Stockel patent require enough SCD to serve as the sole preservative, whereas Stockel's written description states that an antimicrobial solution that relies only on SCD would require so much SCD that the solution would irritate the eye. For that reason, Stockel

suggests the use of a second preservative along with SCD if the disclosed solution is used in an ophthalmic formulation. Stockel, col. 10, ll. 1-6.

Apotex argues that the only difference between Ratcliff and the asserted claims is that the claims specify a pH range and include a buffer component and a tonicity component. Apotex contends that those modifications would have been obvious. Allergan acknowledges that Ratcliff discloses an SCD solution, but responds that Ratcliff "only teaches the use of stabilized chlorine dioxide as a starting material." According to Allergan, Ratcliff teaches the use of *chlorine dioxide* as a preservative, not the use of *stabilized* chlorine dioxide, i.e., the chlorite ion. Allergan maintains that the solution disclosed in Ratcliff is distinct from the claims because Ratcliff requires "activation" of the disclosed SCD solution, such as by adding an acid to convert the SCD to chlorine dioxide.

Contrary to Allergan's contention, nothing in the Ratcliff patent provides that its SCD must be "activated." Instead, it simply discloses and claims the use of an SCD solution as an antimicrobial agent. For instance, with respect to the first example, a deodorizing mouthwash, the specification states: "The chlorine dioxide mouthwash or rinse solution serves to attack production and origin of malodor from the mouth [by breaking sulfide bonds]. Therefore, delivery of stabilized chlorine dioxide will reduce the number of [oral] microorganisms." Ratcliff, col. 3, ll. 25-34. Nowhere in the first example—or in any other example—does the protocol disclosed by Ratcliff require "activation" of the SCD solution. Moreover, even if Ratcliff did disclose an "activation" step, the distinction would not be relevant to Allergan's patentability arguments, as the claims of the '078 patent are directed to an SCD solution irrespective of its "activation."

Example 8 of Ratcliff is a contact lens soak with a preferred concentration of 0.005% to 2.0% SCD in water. *Id.*, col. 11, ll. 20-27. That example clearly discloses an ophthalmic SCD solution. The only distinction between that solution and the claimed invention is the presence of tonicity and buffering components and an explicit pH limitation.

Based on the evidence presented at trial, we are convinced that it would have been obvious to one skilled in the art to adjust the SCD solution disclosed in Ratcliff to approximate physiologic pH, to include a buffer component to maintain that pH, and to include a tonicity component to approximate physiologic osmolality. Stockel explicitly discloses the modifications that Allergan argues impart patentability. That reference discloses the use of SCD as a preservative in an ophthalmic solution and teaches that "[i]t is desirable to make the solution isotonic and for this purpose any of the well-known agents may be used." Stockel, col. 10, ll. 57-58. The Stockel patent continues: "Other materials commonly used in contact lens solutions may also be employed such as buffering, chelating and thickening agents." *Id.*, col. 10, ll. 62-64. Allergan points out that Stockel also discloses that the amount of SCD necessary to serve as the sole preservative would irritate the eye, and accordingly recommends a combination of two preservative agents. But Stockel's teachings with respect to the required quantity of SCD do not undercut the force of its disclosure that maintenance of a physiologic pH and osmolality by use of buffer and tonicity components would have been simple and well-known modifications. *See, e.g.*, *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("Even if a reference discloses an inoperative device, it is prior art for all that it teaches."). And Ratcliff, which postdates Stockel by nearly two years, discloses that SCD can be used as an effective sole preservative for an ophthalmic solution. Although the burden to negate pat-

entability remains firmly with Apotex, we note that there is no evidence in the record that the tonicity or buffer components are incompatible with SCD. We therefore hold that the district court committed legal error in concluding that it would not have been obvious to one skilled in the art to create an ophthalmic solution that was adjusted to ocular pH and tonicity and that relied on SCD as the sole preservative agent.

B

With respect to the four "related patents," we reach a different conclusion. Neither party argued its validity case to the district court on a claim-by-claim basis and neither presents a claim-by-claim argument to this court. Apotex stipulated to infringement of all asserted claims of the related patents, so the injunction stands unless Apotex can demonstrate that all of the 69 asserted claims are invalid. For purposes of Apotex's appeal, we therefore focus on the narrowest claims, as they are the least vulnerable to Apotex's validity challenge. Based on our careful review of the proceedings at trial, we reject Apotex's argument that as to each of the asserted claims of those patents, the district court erred in concluding that Apotex failed to overcome the presumption of validity by clear and convincing evidence.

The first of those patents is U.S. Patent No. 6,562,873 ("the '873 patent"). Claim 33, the narrowest of the asserted claims, recites an aqueous solution including brimonidine in an amount effective to provide a therapeutic benefit, along with CMC as a solubility-enhancing component and chlorite (i.e., SCD) as a preservative. That claim does not specify a pH level for the solution. The second patent, U.S. Patent No. 6,627,210 ("the '210 patent"), claims brimonidine, as well as the general class of α-2-adrenergic agonists, along with various anionic solubility enhancers. Many of the

asserted claims are silent as to the preservative to be used, but claims 26, 30, and 34 require chlorite. Claims 13 and 14 do not require any particular preservative, but they require that the pH of the solution be above 7.0. The third patent, U.S. Patent No. 6,641,834 ("the '834 patent"), is a continuation of the '210 patent. Claims 7 and 16 of the '834 patent recite a 0.15% brimonidine solution with a pH of 7.0 or greater with chlorite as a preservative. Although the '834 patent specification discusses the use of CMC and other solubilizers, none of the asserted claims requires the use of CMC. The fourth patent, U.S. Patent No. 6,673,337 ("the '337 patent") is also a continuation of the '210 patent. Each of the two asserted claims of that patent is directed to the general class of α-2 adrenergic agonists along with an anionic solubility-enhancing component other than a cyclodextrin. Neither claim requires the presence of chlorite, and neither is specific as to pH.

Apotex points out that every asserted claim reads on a combination of two Allergan products: Alphagan® (brimonidine) and Refresh Tears®. Refresh Tears® is a non-medicated eyedrop adjusted to a pH of 7.2 to 7.9. It includes SCD as a preservative and CMC as a viscosity agent. Apotex argued to the district court that combining the two solutions would have been obvious, but the district court disagreed. The court found that one skilled in the art would have expected brimonidine to present solubility problems at the elevated pH of Refresh Tears®. The court did not agree with Apotex that one skilled in the art would have expected CMC to increase the solubility of brimonidine. And it found that one of ordinary skill in the art would have expected SCD to oxidize brimonidine. Apotex challenges those factual findings. Apotex further argues that, at a minimum, the combination would have been obvious to try and that the claims reciting that combination are therefore invalid for obviousness.

1. Solubility

The district court credited the testimony of Allergan's expert witness, Dr. Valentino Stella, and found that one skilled in the art would not have expected therapeutically effective concentrations of brimonidine to be soluble at the slightly alkaline pH range of Refresh Tears®, 7.2 to 7.9. Apotex challenges the court's finding by focusing on a solubility table that it did not rely on at trial. The table is excerpted from a New Drug Application ("NDA") filed by Allergan with the FDA. The table recites that at the neutral pH of 7.0, the water solubility of brimonidine is 1.94 mg/mL, or 0.194%. Every asserted claim reads on a solution with a pH of at least 7.0. Claims 11-13 of the '834 patent are directed to a 0.15% brimonidine solution at a pH of 7.0 or above, and all of the other asserted claims are directed to a therapeutically effective quantity.[1] Apotex and Allergan

[1] The district court gave the phrase "therapeutically effective ophthalmic composition" its ordinary meaning. According to the dissent, those of ordinary skill in the art knew brimonidine was therapeutically effective at concentrations below .2%, and would have been motivated to combine a .15% brimonidine solution with Refresh Tears®. As support for that position, the dissent points to a 1997 journal article entitled "Brimonidine Tartrate: A One-Month Dose Response Study" ("Derick"), which was not mentioned in either party's brief. The dissent characterizes that article as establishing that a 0.08% brimonidine solution was known to be clinically effective and soluble at the elevated pH range of Refresh Tears®. Derick, however, did not indicate the pH of the carrier; because the therapeutic efficacy of brimonidine varies with pH, the article is of little value for that reason. In any event, Dr. Robert Noecker, an Allergan expert witness, testified that the results of the Derick study did not lead him to conclude that brimonidine could be therapeutically effective at concentrations as low as 0.08%. He explained that clinicians evaluating such a drug's therapeutic efficacy look for at least a 20% reduction

agree that brimonidine's solubility decreases as the pH of a solution increases. Apotex argues that the solubility table establishes that the district court was wrong in finding that brimonidine would have presented solubility problems at the elevated pH of Refresh Tears®. But Apotex did not focus on the table at trial. It did not provide any supporting testimony calling the district court's attention to the table nor did it explain how one skilled in the relevant art would have assessed the information from the table. Under these circumstances, we do not see clear error in the district court's finding as to the expected solubility of brimonidine at the 7.2 to 7.9 pH range. *See H.H. Robertson, Co. v. United Steel Deck, Inc.*, 820 F.2d 384, 389 (Fed. Cir. 1987) ("[Defendants] argue that because this reference had first been offered to the district court it is not in fact presented for the first time on appeal. But this reference, although placed in the record by the district court, was not the subject of testimony or any other form of evaluation by that court. Initial consideration of evidence is not the appellate role.").

2. CMC as a Solubility-Enhancing Component

The district court found that one of ordinary skill in the art would not have turned to CMC as a solubility enhancer. In response, Apotex presents two arguments. First, it points out that Alphagan® and Refresh Tears®, which contains CMC, were routinely prescribed together. This fact alone does not establish that it would have been obvious to

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in baseline IOP and that he did not regard Derick's results demonstrating that threshold level of effectiveness at the 0.08% concentration level. While there was conflicting expert testimony on that issue, on this record the Derick article cannot be said to be a sufficiently clear teaching that a brimonidine solution at the 0.08% level would be therapeutically effective as to require upsetting the trial court's ruling on obviousness.

combine the two in a single formulation. Two ingredients might be therapeutically effective when used separately as part of an overall treatment regimen, yet be incompatible or ineffective when combined in a single solution.

Second, Apotex argues that the claimed invention would have been obvious in light of journal articles by Thorsteinn Loftsson from 1994 and 1997. The district court found that the Loftsson references do not disclose or suggest the use of CMC in connection with any α-2 adrenergic agonist, let alone brimonidine. We agree.

The earlier of the two Loftsson articles is entitled "The Effect of Water-Soluble Polymers on Drug–Cyclodextrin Complexation." Cyclodextrin is a cylindrical molecule with a hydrophobic center and hydrophilic exterior. It acts as a carrier for hydrophobic drugs. Loftsson tested the effect of polymeric solubility enhancers, including CMC, on the water solubility of cyclodextrin–drug complexes. Notably, many of the asserted claims of the "related patents" recite a solution that is "substantially free of cyclodextrins." Even in the case of the claims that lack that proviso, we see no error in the district court's treatment of the Loftsson references. Apotex relies heavily on Loftsson's statement that "the addition of a very small amount of [CMC] resulted in a significant increase in the aqueous solubility of most of the drugs tested." While acknowledging that neither of the two Loftsson articles discusses the use of CMC in connection with brimonidine or even the generic class of α-2-adrenergic agonists, Apotex argues that the articles "certainly would have suggested as much to one of skill given that [they] disclosed CMC enhancing the solubility of the many soluble active ingredients with which it was tested." However, Apotex provided no expert testimony or other evidence to support that proposition, and the generalization made by

counsel on appeal does not undermine the district court's contrary determination following the trial.

Finally, Apotex argues that the district court imported an unclaimed limitation to distinguish the Loftsson references. Loftsson assessed the water solubility of various mixtures, consisting of cyclodextrin, CMC, and a subject drug, after heating the mixture at 120ºC for 20 minutes. The 1997 Loftsson paper makes the need for the heating step explicit: "[s]imply adding the polymers to the solutions without heating does not enhance the complexation or the drug availability." The asserted claims that recite CMC neither require nor exclude a heating step. Apotex contends that the district court erroneously used the absence of a heating step to distinguish the claims from the 1997 Loftsson reference. We disagree. Allergan's expert testified that the high temperature needed to observe the increase in solubility can lead to decomposition of a drug such as brimonidine and to alterations in its crystalline structure. The need for the heating step and its apparent incompatibility with brimonidine further establishes that Loftsson does not teach the combination of brimonidine and CMC. Accordingly, we see no error in the district court's findings based on the Loftsson references.

3. SCD as a Preservative

The district court found that one skilled in the art would not have been motivated to combine Refresh Tears® and Alphagan® because of concerns that SCD would oxidize brimonidine. Apotex challenges that finding by citing an article by Charles P. Thompson entitled "Mechanisms of Adrenergic Agonist Induced Allergy Bioactivation and Antigen Formulation." That article, according to Apotex, proves the oxidative stability of brimonidine. In the article, Thompson describes having incubated brimonidine and

other α-2 agonists with a hydrogen peroxide-producing species for 120 hours and finding that brimonidine "proved stable to the enzymatic oxidation conditions." The district court found the Thompson reference "unpersuasive because, among other things, it teaches nothing about the oxidative stability of brimonidine in a Purite®-containing formulation that needs to be shelf-stable for two years." Purite® is Allergan's trade name for an SCD solution.

First, Apotex argues that the district court improperly imported a two-year shelf-stability limitation into the claims and used that limitation to avoid the teachings of the prior art. It is true that the claims do not require a particular period of shelf stability, but that was not the only basis for the district court's finding that one skilled in the art would not have expected brimonidine and SCD to be compatible. Dr. Stella, whose testimony was accepted by the court, explained that prior art documents described Purite® as a "strong" oxidant. Even in light of Thompson's findings, Dr. Stella testified that one skilled in the art would have been "extremely hesitant, if not, I would say, directed away from . . . formulating brimonidine with a chlorite compound," i.e., Purite®.

Apotex challenges Dr. Stella's testimony, contending that it is contradicted by Allergan documents. Apotex points to promotional literature associated with Purite® that describes Purite® as having a relatively low oxidation potential compared to hydrogen peroxide. In response to a question about what it means to describe a component or an excipient as a strong oxidant, Dr. Stella replied that "it basically says it's capable of oxidizing drugs, any chemical." When Apotex's attorney asked Dr. Stella about the relative oxidative potentials of hydrogen peroxide and Purite®, Dr. Stella stated that hydrogen peroxide is a strong oxidant and Purite® is a relatively weaker oxidant, but he also stated

that Purite® "is a very good" oxidant. While we recognize that hydrogen peroxide may be a stronger oxidant than the SCD in Purite®, the fact that Allergan touted Purite® as being less reactive than hydrogen peroxide does not establish that one skilled in the art would not have expected SCD to oxidize brimonidine.

C

Apotex faults the district court for considering each asserted reference in isolation. It argues that the modifications that Allergan made to the original Alphagan® formulation consisted essentially of combining of Refresh Tears® and Alphagan®. It contends that the combination would have been obvious to try, rendering the asserted claims invalid for obviousness.

Where "the problem is known, the possible approaches to solving the problem are known and finite, and the solution is predictable through use of a known option," a solution that is obvious to try may indeed be obvious. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008), citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). Apotex points out that both SCD and CMC were components of Refresh Tears®. It argues that in light of the dose-dependent allergenic conjunctivitis associated with the 0.2% brimonidine in the original Alphagan®, there was strong market pressure to reduce the brimonidine concentration of that product. By increasing the pH of the brimonidine solution to that of Refresh Tears®, the formulators could reduce the brimonidine concentration while maintaining therapeutic efficacy. The elevated pH is also more compatible with the human eye than the pH of the original Alphagan®.

Apotex's "obvious to try" arguments, based on *KSR*, are unavailing in light of the district court's factual findings. The district court found that the solutions that Allergan identified and eventually claimed would not have been an "anticipated success." *See Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010). The court found that one of ordinary skill would not have been expected to disregard those roadblocks. Because the court's findings are well supported, we do not agree with Apotex that the trial court's conclusion as to the "obvious to try" issue must be overturned.

D

Apotex's final argument relates to post-trial issues. After trial, both Apotex and Allergan submitted their proposed findings of fact and conclusions of law. In those filings, Apotex made obviousness arguments based on references that were admitted into evidence but that Apotex did not support with expert testimony or otherwise rely on at trial. The court granted Allergan's motion for judgment of a matter of law with respect to Apotex's obviousness arguments made on those references. Apotex contends that it was entitled to make post-verdict arguments that the claims would have been obvious in light of two of these references because (1) the references were admitted into evidence, and (2) the references were incorporated by reference in the patents in suit.

There is no invariable requirement that a prior art reference be accompanied by expert testimony. *E.g.*, *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1242 (Fed. Cir. 2010) ("expert testimony is not required when the references and the invention are easily understandable"). But it is well within a trial judge's discretion to require expert testimony supporting technical references that are relied on to estab-

lish obviousness. That the references at issue in this case were incorporated by reference in Allergan's asserted patents means only that they are treated as if set forth in their entirety in the patents; the incorporation of those references is not relevant to whether the district court erred in disregarding them because of the lack of supporting testimony. We hold that the district court did not abuse its discretion in refusing to consider those references in its obviousness analysis in light of the absence of testimony explaining their relevance to the obviousness issue.

E

To conclude, we reverse the district court's determination that the asserted claims of the '078 patent are not invalid. We affirm the district court's determination that Apotex failed to satisfy its burden to show that each asserted claim of the "related patents" is invalid as a matter of law, and we therefore sustain the court's issuance of an injunction against Apotex, which has stipulated to infringement.

III

Exela is in a different position. Unlike Apotex, Exela appeals the district court's finding that the product proposed in its ANDA infringes Allergan's patent rights.

Allergan asserted only the '834 patent against Exela. Claims 7 and 16 of that patent recite a 0.15% brimonidine solution including SCD as a preservative adjusted to a pH of 7.0 or greater. The only issue in this case is whether the product described in Exela's ANDA infringes that pH limitation. Both Exela and Allergan agree that the highest pH at which Exela requests permission to manufacture and sell its proposed product is 6.7. The district court found that the

lowest pH at which Exela requests permission to manufacture and sell its proposed drug at is 6.5.[2] Both parties agree that to the extent the pH of the formulation changes over time, it will fall, not rise.

The district court found that the pH of Exela's formulation will drop by approximately 0.5 pH units over a period of six months. The court based that finding on the testimony of Allergan's expert witness, Dr. Stella, as well as on a stability study that Exela included in its ANDA. That study showed a drop in pH from an initial pH of 6.7 to a final pH of 6.2 over a six-month period. The district court reasoned that Exela would take this 0.5 unit drop in pH into account when manufacturing its brimonidine formulation. To produce a product that will maintain a pH greater than 6.5, the district court concluded that Exela would necessarily manufacture its product at an infringing pH of 7.0 or above.

A

The infringement provision of the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2)(A), states that it is an act of infringement to submit an ANDA that describes "a drug claimed in

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[2] Exela's ANDA presents two pH ranges: the pH range at which Exela proposes to manufacture the drug, and the pH range at which Exela proposes to sell the drug (the "label pH"). The parties agree that the manufacturing pH in Exela's ANDA is 6.5 to 6.7. The parties also agree that the highest label pH set forth in Exela's ANDA is 6.7. The parties do not, however, agree on what the lowest label pH represented in Exela's ANDA is. The district court found that it is 6.5. On appeal, Exela argues that the lower bound of the label pH is 5.5. This factual dispute is ultimately irrelevant to the disposition of this appeal, because we cannot assume that Exela will deviate from the stated upper bound of both the manufacturing and the labeling pH, which is 6.7.

a patent." The infringement action is a hypothetical case that asks the factfinder to determine whether the drug that will be sold upon approval of the ANDA will infringe the asserted patent. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000). In *Abbott Laboratories v. TorPharm, Inc.*, we explained that "[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." 300 F.3d 1367, 1373 (Fed. Cir. 2002).

B

Exela argues that the district court erred by assuming that Exela would manufacture a drug outside of the parameters of the ANDA. In support of the district court's judgment, Allergan argues that in an infringement action provoked by the filing of an ANDA, the court may consider not only the proposed drug as described in the ANDA, but also other relevant information, including the pH drop that the court identified.

We agree with Exela. In *Bayer AG v. Elan Pharmaceutical Research Corp.*, we considered an analogous situation in a different procedural posture. 212 F.3d at 1247-50. Bayer's patent on the reference drug claimed nifedipine crystals with a solid surface area ("SSA") between 1-4 m^2/g. *Id.* at 1247. Elan submitted an ANDA requesting permission to make and sell nifedipine in a crystalline form with an SSA of 5 m^2/g or above. The district court entered summary judgment of noninfringement in favor of Elan, and Bayer appealed. Bayer suggested that there were genuine issues of material fact as to whether Elan would be able to produce a product with the noninfringing SSA as described

in its ANDA. We affirmed. We pointed out that Elan was bound by the representations in its ANDA and noted that substantial penalties, including criminal sanctions, flow from noncompliance. *Id.* at 1249-50. We further explained that "Elan, under its current ANDA specification, will either market a drug with a SSA of 5 m^2/g or greater . . . or Elan will not, legally, market any drug under its ANDA." *Id.* at 1250. The same is true here: the highest pH at which Exela will manufacture and sell its proposed product is 6.7 or Exela will not, legally, market anything at all.

Allergan likens this case to *Abbott Laboratories v. TorPharm, Inc.*, and relies on the following quotation from *Abbott*: "[O]ther evidence may directly contradict the clear representations of the ANDA and create a dispute of material fact regarding the identity of the compound that is likely to be sold following FDA approval." 300 F.3d at 1373. But *Abbott* addressed a different issue, and the quoted sentence is not relevant to Allergan's appeal. In *Abbott*, the claims of the patent on the reference drug recited an oligomeric compound with about 4-6 repeating subunits. *Id.* at 1376-77. TorPharm's ANDA did not specify the number of subunits in the generic formulation. *Id.* at 1376. We vacated the district court's award of summary judgment of noninfringement in favor of TorPharm because there was a disputed issue of fact concerning the number of subunits in the formulation that TorPharm would produce if it operated in compliance with its ANDA. In that instance, we held that it might be appropriate for the court to consider material outside the four corners of the ANDA to determine whether the ANDA describes an infringing product. Here, neither party disputes that if Exela complies with its ANDA, it will never manufacture or sell a product at a pH above 6.7. We cannot assume that Exela will not act in full compliance with its representations to the FDA, and we

accordingly reverse the district court's judgment finding that Exela's filing of the ANDA is an act of infringement.

Each party shall bear its own costs for this appeal.

AFFIRMED IN PART and REVERSED IN PART

United States Court of Appeals for the Federal Circuit

IN RE BRIMONIDINE PATENT LITIGATION

ALLERGAN, INC.,
Plaintiff-Appellee,

v.

EXELA PHARMSCI INC. AND EXELA PHARMSCI PVT., LTD.,
Defendants-Appellants,

and

APOTEX INC. AND APOTEX CORP.,
Defendants-Appellants.

2010-1102, -1103

Appeals from the United States District Court for the District of Delaware in case no. 07-MD-1866, Chief Judge Gregory M. Sleet.

DYK, *Circuit Judge*, concurring-in-part and dissenting-in-part.

I join Parts IIA and III of the majority's opinion. However, I respectfully dissent from Parts IIB, IIC, and IID. In my view, the asserted claims of U.S. Patent Nos.

6,562,873; 6,627,210; 6,641,834; and 6,673,337 (collectively, the "related patents") are invalid as obvious over the combination of Alphagan® and Refresh Tears® in view of the related prior art.

A finding of obviousness under the "obvious to try" standard "does not require absolute predictability of success . . . all that is required is a *reasonable* expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)) (emphasis altered). I think that standard was satisfied here. It is undisputed that all asserted claims of the related patents read on a combination of Alphagan® and Refresh Tears®. The undisputed evidence further establishes that, at the time of the invention, a person having ordinary skill in the art ("PHOSITA") would have known that: (1) Alphagan® had common side effects, two of which included eye irritation and dry eye (known to be exacerbated by its bezalkonium chloride ("BAK") preservative); (2) the higher pH of Refresh Tears®, nearer to that of the human eye, would likely reduce irritation; (3) the "gentle" stabilized chlorine dioxide ("Purite®") preservative in Refresh Tears® would likely be less harmful than Alphagan's® "toxic" BAK preservative; (4) inclusion of Refresh Tears'® carboxymethylcellulose ("CMC") viscosity agent would likely further reduce eye irritation; and (5) physicians were routinely prescribing Refresh Tears® to glaucoma patients on Alphagan® to help alleviate irritation and dry eye, two of Alphagan's® known side effects.

Under these circumstances, I think a PHOSITA would have found a combination of these two commercially successful products "obvious to try." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007).

Despite the extensive evidence of the motivations for a PHOSITA to combine Alphagan® and Refresh Tears®, the district court held that the combination was not obvious to try because a PHOSITA would have had concerns regarding the solubility and oxidation of brimonidine in Refresh Tears®, thereby preventing a PHOSITA from having any anticipated success in combining the products. However, I think the district court made clearly erroneous findings of fact regarding these purported concerns.

The district court first found that "a [PHOSITA] would not have expected effective concentrations of brimonidine to be soluble in [the elevated] pH range" of Refresh Tears®. *In re Brimonidine Patent Litigation*, 666 F. Supp. 2d 429, 442 (D. Del. 2009). The court viewed brimonidine concentrations of 0.2% to 0.5% as necessary for therapeutic effect, and it concluded that a PHOSITA would not have expected these concentrations to be soluble at the 7.2–7.9 pH range of Refresh Tears®. This was based on Dr. Stella's testimony that a PHOSITA would have expected "0.2 percent and 0.5 percent" brimonidine to have solubility problems at higher pHs. J.A. 7922–23. The difficulty with this finding is that the district court improperly assumed that the 0.2% brimonidine in Alphagan® was the lowest dosage concentration that could achieve efficacy. The Derick reference (entitled "Brimonidine Tartrate: A One-Month Dose Response Study") confirms brimonidine's effectiveness at lower dosages. The authors of the Derick reference conducted "a multicentered, double-masked, randomized, placebo-controlled, parallel, 1-month dose response evaluation of brimonidine 0.5%, 0.2%, and 0.08% in patients with open-angle glaucoma or ocular hypertension." J.A. 25670. The study concluded that "[a]ll concentrations of brimonidine significantly reduced IOP, compared to baseline and placebo,

at all follow-up visits." J.A. 25669. A PHOSITA would have understood Derick as disclosing that brimonidine can be therapeutically effective at concentrations as low as 0.08%. There is also no basis for finding that 0.08% brimonidine would be insoluble at the higher pH range of Refresh Tears®.

The majority dismisses the Derick reference by citing Dr. Robert Noecker's testimony that Derick's findings were "not compelling" evidence of 0.08% brimonidine's efficacy and that he would not prescribe 0.08% brimonidine to his patients based on the Derick study. J.A. 7507; *see* Maj. Op. at 11 n.1. But notably, Dr. Noecker said nothing as to whether a PHOSITA would have considered it obvious to try concentrations lower than 0.2% in light of Derick's findings regarding the 0.08% concentration. Dr. Noecker himself acknowledged that the efficacy of a particular drug concentration can never be known for certain "without having . . . the actual concentration tested." J.A. 7508. Derick's plain findings that "23 (51%) of 45 patients in the 0.08% group . . . showed a reduction of 20% or more from baseline at one or more scheduled visits over the course of the study" clearly suggested trying concentrations lower than 0.2%. J.A. 25671.

The majority further dismisses the Derick reference because "the therapeutic efficacy of brimonidine varies with pH," and the study "did not indicate the pH of the carrier." Maj. Op. at 11 n.1. But if the carrier in Derick had a higher pH than Alphagan®, then it demonstrated the likely success of combining Alphagan® and Refresh Tears® using some brimonidine concentration lower than 0.2%. Conversely, if the carrier had a pH lower than Alphagan®, a PHOSITA would have known that the 0.08% concentration would be even more effective at the higher pH range of Refresh Tears® due to the pH Parti-

tion Theory discussed below. Either way, a PHOSITA concerned with the solubility of 0.2% brimonidine at the higher pH of Refresh Tears® would have been prompted by Derick to simply try using a lower dosage.

Quite apart from Derick, there was no reason for a PHOSITA to be deterred from combining Alphagan® and Refresh Tears® because of solubility problems with brimonidine concentrations in the 0.2% to 0.5% range. As the majority recognizes, the pH Partition Theory establishes that an ocular drug's bioavailability (the percentage of the drug that reaches the targeted tissue) increases in correlation with pH, which means that increasing pH lowers the minimum dosage concentration required for efficacy. *See* Maj. Op. at 3–4. The district court failed to recognize that a PHOSITA with knowledge of the pH Partition Theory would have known that some concentration of brimonidine *less than* 0.2% could still achieve efficacy at the higher pH range of Refresh Tears®, and that the lower brimonidine concentration would in turn help offset the expected decrease in the maximum soluble concentration. A PHOSITA thus would have been motivated to lower the dosage concentration below 0.2%.[1]

[1] A PHOSITA also would have found a lower dosage preferable because Alphagan's® high 0.2% brimonidine concentration commonly caused allergic conjunctivitis (inflammation of the inner eyelid tissue), and it was known at the time of the invention that reducing the brimonidine concentration would help alleviate this side effect. *See* J.A. 7486–87, 7493–96, 7512 (Dr. Noecker); J.A. 6737–38 (Dr. Tanna); J.A. 6416 (Dr. Whitcup); J.A. 7580 (Dr. Banker). The pH Partition Theory thus provided an additional affirmative motivation for a PHOSITA to exploit the higher pH range of Refresh Tears® to make a dosage reduction possible.

In short, solubility problems with brimonidine concentrations in the 0.2% to 0.5% range, as found by the district court, would not have deterred a PHOSITA from trying a lower concentration of brimonidine at the higher pH range of Refresh Tears®.

The district court next found that a PHOSITA would have had "concerns that the Purite® preservative in Refresh Tears® would oxidize the brimonidine in Alphagan[ ]®." *In re Brimonidine Patent Litigation*, 666 F. Supp. 2d at 444. However, the court based this holding on two clearly erroneous fact findings.

The court's first error regarding oxidation concerns was its dismissal of the Thompson reference. Thompson discloses a study in which the oxidative effect of hydrogen peroxide on brimonidine and other drugs was tested using electrochemical oxidation. This included placing an electrode in a formulation of hydrogen peroxide and a drug, pouring electrons into the system, and observing how long it took to oxidize the drug. The test lasted for 120 minutes before it was terminated "due to the destruction of the [hydrogen peroxide] under the experimental conditions." J.A. 27315. The least oxidatively stable drug tested was amodiaquine, which oxidized in under one minute; the most oxidatively stable drugs were clonidine and brimonidine, which did not oxidize during the 120 minute test. *Id.* Thompson ultimately concluded that "[c]lonidine and brimonidine proved to be oxidatively stable in sharp contrast to [the other drugs tested]." J.A. 27312. There was no testimony that the Thompson test was in any way inaccurate.

The sole reason the district court gave for dismissing the Thompson reference was that it "teaches nothing about the oxidative stability of brimonidine in a Purite®-

containing formulation that needs to be *shelf-stable for two years*." *In re Brimonidine Patent Litigation*, 666 F. Supp. 2d at 444 (emphasis added). But as the majority appears to acknowledge, it was improper for the district court to distinguish Thompson based on the fact that its oxidation test lasted for only 120 minutes, rather than two years, because "the claims [of the related patents] do not require a particular period of shelf stability." Maj. Op. at 15.

Having accepted the fact that no shelf stability time limit is mandated by the asserted claims of the related patents, the majority must agree that, in view of the teachings of Thompson, a PHOSITA would have known that brimonidine would not oxidize in hydrogen peroxide for a period of at least 120 minutes. The undisputed evidence—including Dr. Stella's testimony and Allergan's own promotional documents—establishes that a PHOSITA would have known that hydrogen peroxide was a stronger oxidant than Purite®. Because hydrogen peroxide was known to be a stronger oxidant than Purite®, and Thompson disclosed that brimonidine is "oxidatively stable" in hydrogen peroxide for at least 120 minutes, a PHOSITA must have known that brimonidine would be oxidatively stable in Purite® for at least 120 minutes. Even if the claims had included a two year stability limitation, the knowledge that brimonidine would be oxidatively stable in Purite® for some time exceeding 120 minutes should have still been enough for a PHOSITA to consider the combination of Alphagan® and Refresh Tears® at least obvious to try.

While the district court's dismissal of the Thompson reference itself provides a sufficient ground for reversal on the oxidation issue, the court made a second clearly erroneous fact finding regarding oxidation. As an af-

firmative basis for finding that a PHOSITA would have had concerns that brimonidine would oxidize in Purite®, the court credited Dr. Stella as having "testified that at the time of these inventions, it was well-known in the art that . . . the structural features of brimonidine made it *particularly susceptible* to oxidation." *In re Brimonidine Patent Litigation*, 666 F. Supp. 2d at 444 (emphasis added). Allergan agreed at oral argument that the testimony the district court attributed to Dr. Stella regarding brimonidine being "particularly susceptible" to oxidation was "important" to the court's finding of non-obviousness. *See* Oral Arg. at 14:47–19:57, *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2010-1102/all. However, Dr. Stella did not testify that brimonidine was "particularly susceptible" to oxidation. The relevant portion of Dr. Stella's testimony reads:

> [I]f you look at the structure of brimonidine, . . . there are elements in the structure, for example, there are nitrogens in a ring structure . . . .
>
> That section of the molecules *lends itself* to, in fact, what we call chlorination as well as N-oxide formation.

J.A. 7918 (emphasis added). While Dr. Stella stated that the structure of brimonidine "lends itself" to N-oxide formation, he said nothing as to whether brimonidine was "particularly susceptible" to oxidation *in comparison to other drugs*. This is significant because the Thompson reference disclosed that "brimonidine proved to be oxidatively stable *in sharp contrast to [the other drugs tested]*," J.A. 27312 (emphasis added), which Dr. Stella's actual testimony does not refute. The district court's finding that oxidation concerns would teach away from the com-

bination of Alphagan® and Refresh Tears® was simply not supported by the record.

Because the undisputed evidence establishes that a PHOSITA would have been motivated to try a combination of Alphagan® and Refresh Tears® to arrive at the claimed formulation, and because the district court made clearly erroneous fact findings in determining that solubility and oxidation concerns would have deterred a PHOSITA from trying this combination, I think that the "obvious to try" standard has been satisfied. I respectfully dissent from the majority's contrary conclusion.