United States Court of Appeals for the Federal Circuit

FOREST LABORATORIES, LLC, FKA FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS LTD.,
Plaintiffs-Cross-Appellants

v.

SIGMAPHARM LABORATORIES, LLC,
Defendant-Appellee

HIKMA PHARMACEUTICALS LLC, HIKMA PHARMACEUTICALS PLC, HIKMA PHARMACEUTICALS USA INC., FKA WEST-WARD PHARMACEUTICALS CORP., BRECKENRIDGE PHARMACEUTICAL INC., ALEMBIC PHARMACEUTICALS LTD., ALEMBIC GLOBAL HOLDING S.A., ALEMBIC PHARMACEUTICALS INC., AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK LLC, AMNEAL PHARMACEUTICALS CO. INDIA PVT. LTD.,
Defendants-Appellants

2017-2369, 2017-2370, 2017-2372, 2017-2373, 2017-2374, 2017-2375, 2017-2376, 2017-2389, 2017-2412, 2017-2436, 2017-2438, 2017-2440, 2017-2441

Appeals from the United States District Court for the District of Delaware in Nos. 1:14-cv-01119-MSG, 1:14-cv-

01266-SLR-SRF, 1:14-cv-01504-SLR-SRF, 1:15-cv-00158-SLR, 1:15-cv-00430-SLR, Judge Sue L. Robinson.

Decided: March 14, 2019

HOWARD WARREN LEVINE, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for plaintiffs-cross-appellants. Also represented by JONATHAN ROBERT DAVIES, SANYA SUKDUANG; CHARLES E. LIPSEY, Reston, VA.

ANTHONY R. FRIEDMAN, The Simon Law Firm, P.C., St. Louis, MO, argued for defendant-appellee. Also represented by ANTHONY G. SIMON.

CLIFFORD KATZ, Kelley Drye & Warren, LLP, New York, NY, argued for all defendants-appellants. Defendant-appellant Breckenridge Pharmaceutical Inc. also represented by MALAVIKA RAO.

IMRON T. ALY, Schiff Hardin LLP, Chicago, IL, for defendants-appellants Hikma Pharmaceuticals LLC, Hikma Pharmaceuticals PLC, Hikma Pharmaceuticals USA Inc. Also represented by JOEL M. WALLACE.

KSENIA TAKHISTOVA, Hunton Andrews Kurth LLP, New York, NY, for defendants-appellants Alembic Pharmaceuticals Ltd., Alembic Global Holding S.A., Alembic Pharmaceuticals Inc.

MICHAEL R. DZWONCZYK, Sughrue Mion PLLC, Washington, DC, for defendants-appellants Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals of New York LLC, Amneal Pharmaceuticals Co. India Pvt. Ltd.

Before PROST, *Chief Judge,* DYK and MOORE, *Circuit Judges.*

MOORE, *Circuit Judge*.

Sigmapharm Laboratories, LLC, ("Sigmapharm"), Hikma Pharmaceuticals LLC, Hikma Pharmaceuticals PLC, Hikma Pharmaceuticals USA Inc., (collectively, "Hikma"), Breckenridge Pharmaceuticals Inc. ("Breckenridge"), Alembic Pharmaceuticals Ltd., Alembic Global Holdings S.A., Alembic Pharmaceuticals Inc., (collectively, "Alembic"), Amneal Pharmaceuticals LLC, and Amneal Pharmaceuticals Co. India Pvt. Ltd. (collectively "Amneal") are drug manufacturers who filed Abbreviated New Drug Applications with the Food and Drug Administration seeking to market generic versions of Saphris, a drug product sold by Forest Laboratories, LLC. Saphris is a sublingually administered, atypical antipsychotic containing asenapine maleate.

Forest sued for patent infringement, asserting that Appellants' proposed generic products would infringe claims 1–2, 4–6, and 9–10 of U.S. Patent No. 5,763,476. The parties have stipulated that the validity of claims 2, 5, and 6 rises and falls with that of claim 1, and the validity of claims 9 and 10 rises and falls with that of claim 4. Forest, Breckenridge, and Alembic have further stipulated that infringement of claims 9 and 10 rises and falls with that of claim 4. Claims 1 and 4 recite:

> 1. A pharmaceutical composition comprising as a medicinally active compound: trans-5-chloro-2-methyl-2,3,3a, 12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof; wherein the composition is a solid composition and disintegrates within 30 seconds in water at 37° C.
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> 4. A method for treating tension, excitation, anxiety, and psychotic and schizophrenic disorders,

> comprising administering sublingually or buccally an effective amount of a pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a, 12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof.

Trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz [2,3:6,7]oxepino[4,5-c]pyrrole is also known as asenapine. Forest sells an atypical antipsychotic containing asenapine maleate under the name Saphris, which was developed by non-party Organon, another pharmaceutical company. Asenapine was originally developed as a conventional oral tablet. Conventional oral tablets are swallowed and enter into the digestive system before being metabolized. In contrast, Saphris is administered sublingually, meaning the formulation is placed under the tongue, where it dissolves. Buccal administration is similar, but in the cheek cavity.

Following a bench trial, the district court held Appellants had not established claims 1–2, 4–6, and 9–10 to be invalid and held Forest had not established infringement of claims 4, 9, and 10 as to Alembic and Breckenridge. Appellants appeal the district court's construction of claim 1 and its determination that the claims have not been established to be invalid. Forest cross-appeals, arguing the district court's finding that Breckenridge and Alembic do not infringe claim 4 was clearly erroneous. We have jurisdiction under 28 U.S.C. § 1295(a)(1). We vacate and remand the district court's validity determination, and we vacate and remand for it to reconsider infringement under a corrected claim construction.

DISCUSSION

I. Construction of Claim 1

While claim 4 is expressly limited to sublingual or buccal formulations of asenapine, claim 1 is not and instead

states that "the composition is a solid composition and disintegrates within 30 seconds in water at 37° C." The district court nevertheless construed claim 1 to be limited to buccal and sublingual formulations. Appellants argue the district court erred in construing claim 1 this way. We review a district court's ultimate claim construction and its interpretations of intrinsic evidence de novo and any subsidiary fact findings about extrinsic evidence for clear error. *CardSoft, (Assignment for the Benefit of Creditors), LLC v. VeriFone, Inc.*, 807 F.3d 1346, 1348 (Fed. Cir. 2015).

We see no error in the district court's construction. Although claim 1 does not expressly refer to buccal or sublingual administration, the claims "must be read in view of the specification, of which they are a part." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc) (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995)). "When a patent . . . describes the features of the 'present invention' as a whole, this description limits the scope of the invention." *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007). Here, the '476 patent states "[t]he invention relates to a sublingual or buccal pharmaceutical composition," '476 patent at 1:6–7, strongly supporting the district court's construction. *See also id.* at 1:33–36. That construction is further supported by additional language in the specification, which explains the benefits of sublingual and buccal treatment over the prior art. *Id.* at 1:33–34 ("The invention therefore relates to a sublingual or buccal pharmaceutical composition . . . ."). The patent is also expressly titled "Sublingual or Buccal Pharmaceutical Composition." *See, e.g.*, *UltimatePointer, L.L.C. v. Nintendo Co.*, 816 F.3d 816, 823 (Fed. Cir. 2016) (using patent title to inform claim construction). Additionally, the claim language "disintegrates within 30 seconds in water at 37° C" appears in the '476 patent as the definition of "[r]apid disintegration." '476 patent at 1:59–61. The specification states that "[p]referred pharmaceutical compositions are

solid pharmaceutical compositions which rapidly disintegrate in the mouth of a subject, upon insertion into the buccal pouch or upon placement under the tongue." *Id.* at 1:56–59. This strongly suggests that the language "the composition is a solid composition and disintegrates within 30 seconds in water at 37° C" was meant to limit the claim to buccal and sublingual formulations.

Appellants suggest that this improperly reads a method step into the claim by requiring a particular method of administration, namely sublingual or buccal. The specification, however, repeatedly uses "sublingual or buccal" to modify "composition," indicating that these are properties of the composition itself. *See, e.g.*, *Id.* at 1:6–7.

We have considered Appellants' remaining arguments as to claim construction and find them unpersuasive.[1] Given the claim language and the language in the specification, we hold the district court properly construed claim 1 to be limited to buccal and sublingual formulations. We do not, therefore, reach Appellants' validity challenges based on its proposed alternative construction.

II. Obviousness

Following a bench trial, the district court concluded claims 1 and 4 would not have been obvious. While it is undisputed that both oral formulations of asenapine and sublingual formulations of other drugs were known in the

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[1] Although Appellants now argue this construction renders the claim indefinite, this argument has been waived. The section of their post-trial briefing in which Appellants argue they raised this issue below nowhere mentions indefiniteness. J.A. 3325–35. Instead, it only mentions § 112, the statutory basis for the definiteness challenge, in a parenthetical to the fourth case cited in a string citation. *Id.* This is insufficient to preserve the argument.

prior art, the district court found that there was no motivation in the art to develop sublingual or buccal formulations of asenapine. It found the resolution of the cardiotoxic effects by sublingual administration was an unexpected result. It found sublingual administration met a long-felt need for a safe, effective, and tolerable atypical antipsychotic useful to treat schizophrenia and mania.

Obviousness is a question of law with underlying facts. *Par Pharm. Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014). After a bench trial, we review the district court's conclusion of obviousness de novo and the underlying factual findings for clear error. *Id.* at 1194.

A. Motivation to Combine

The district court found Appellants had not established that there was a motivation to combine asenapine maleate into a sublingual or buccal form, and even if there were a motivation to combine, a skilled artisan would not have had a reasonable expectation that it would work. Whether there was a motivation to combine prior art references is a question of fact. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1359 (Fed. Cir. 2017). We review for clear error.

An invention is not obvious simply because all of the claimed limitations were known in the prior art at the time of the invention. Instead, we ask "whether there is a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success." *Smiths Indus. Med. Sys., Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1356 (Fed. Cir. 1999). The motivation "can be found explicitly or implicitly in the prior art references themselves, in market forces, in design incentives, or in 'any need or problem known in the field of endeavor at the time of invention and addressed by the patent.'" *Arctic Cat*, 876 F.3d at 1359 (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420–21 (2007)).

At trial, Appellants' primary and dominant argument as to motivation to combine was an alleged bioavailability concern with orally administered asenapine. The district court extensively considered this argument and rejected it. On appeal, Appellants have dispensed with their bioavailability argument and instead focus on two other claimed motivations. First, they argue an ordinarily skilled artisan would have been motivated to administer asenapine maleate sublingually or buccally to address known compliance concerns. Second, they argue an ordinarily skilled artisan would have been motivated to administer asenapine maleate sublingually or buccally to obtain more treatment options.

Appellants argue that an ordinarily skilled artisan would have been motivated to administer asenapine maleate sublingually or buccally to address compliance problems and swallowing difficulties in special patient populations. The district court discussed compliance concerns and, citing testimony from Forest's expert witness Dr. McIntyre, explained that "clinicians with experience in treating schizophrenic patients understand that sublingual dosage forms are more burdensome to schizophrenic patients in that they require the patient to hold the dosage form in the mouth under the tongue for a period of time, and also require that the patient refrain from drinking or swallowing for a period of time." J.A. 73 (citing J.A. 592–93). The court further explained that Appellants' "own expert clinician, Dr. Hollander, agreed that sublingual administration would not improve patient compliance." J.A. 73 (citing J.A. 442–43). Summarizing testimony, however, is not a clear finding. Our review would be aided by an express finding regarding whether compliance concerns regarding patients with swallowing difficulties would provide a motivation to combine.

Turning to Appellants' second claimed motivation, we hold that the district court did not clearly err in rejecting Appellants' contention that the benefits of having multiple

treatment options available would provide a motivation to combine. In assessing whether there was a long-felt need, the district court found that "skilled artisans recognized the benefit of having multiple treatment options." J.A. 76. Appellants further argue that their expert Dr. Hollander testified that there was a need for additional treatment options because no single product is appropriate for all patient populations and that in 1994, many antipsychotics were on the market in multiple forms. The district court did not clearly err, however, in concluding that a generic need for more antipsychotic treatment options did not provide a motivation to combine these particular prior art elements.

Appellants argue the district court ignored general suggestions in the prior art indicating a growing interest in sublingual and buccal formulations at the time of filing. The district court was presented with a variety of documentary evidence and testimony as to the state of the prior art. We see no clear error in its weighing of this evidence.

Finally, Appellants suggest that the district court erred in treating the claimed invention as providing a solution to an unrecognized problem in the art. We have recognized that where a problem was not known in the art, the solution to that problem may not be obvious, because "ordinary artisans would not have thought to try at all because they would not have recognized the problem." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013).

The district court characterized the inventors' discovery as a recognition of an unknown problem in the art in conjunction with the discovery of the solution to that problem. J.A. 69–70. It found that the Organon scientists discovered a "previously unknown" problem and developed the claimed sublingual dosage forms as a solution to that problem. Specifically, it found that during early clinical studies Organon discovered intravenous and oral administration of

asenapine resulted in severe cardiotoxic events. As a result, those studies were terminated prior to completion. The district court found, however, that during subsequent testing on beagles, while there was "a clear trend of increased heart effects with an oral tablet," "no such trend was observed with the sublingual forms." J.A. 44–45. The district court found that while Organon became aware of these problems, "[t]here was nothing in the prior art that would have indicated that the oral tablet had problems." J.A. 68.

The district court further held that the solution Organon developed to address the cardiotoxic effect was also non-obvious. It found that Organon's data indicated that the cardiotoxic effect was likely caused by asenapine itself. J.A. 69. During conventional oral administration, asenapine undergoes first-pass metabolism, which processes the parent compound asenapine into metabolites. J.A. 69. In contrast, sublingual administration increases the amount of the parent compound by circumventing first-pass metabolism. J.A. 69. The district court held, therefore, that it would not have been predictable or expected that sublingual administration would provide a solution to the problem of cardiotoxic effects. J.A. 69–70.

Appellants object to this reasoning, arguing that the only reason the cardiotoxicity issue was not publicly known was because Organon concealed and misrepresented the events suffered by patients in clinical studies when it reported the results of those studies. While the actions alleged may raise a variety of concerns, we do not see how they affect the district court's obviousness analysis. Ultimately, we see no clear error in the district court's consideration of the unknown nature of the problem solved by the inventors and the factors that would teach away from their solution.

We have considered Appellants' remaining arguments as to motivation to combine and find them unpersuasive.

However, in light of the district court's failure to make an express finding as to whether compliance concerns for patients with trouble swallowing would provide a motivation to combine, we remand for the district court to address this question.

B. Long-Felt Need

"Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016). Whether or not such a long-felt need existed is a question of fact. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 978 (Fed. Cir. 2014).

The district court found that at the time of the invention, there was a long-felt, but unmet, need for "a safe, effective, and tolerable atypical antipsychotic useful to treat schizophrenia and mania." J.A. 76. In doing so, it found that prior to 1994, "typical antipsychotics were the primary therapeutic options for treating schizophrenia and mania." J.A. 75. It noted, however, that typical antipsychotics "possessed debilitating side effects" and "a significant number of patients did not respond to treatment." J.A. 75. As of 1994, there were also two atypical antipsychotics available. J.A. 75. One "require[d] constant blood monitoring" and had a "life-threatening side effect." J.A. 75. The other had a variety of side effects that resulted in a discontinuation rate of around 74%. J.A. 75–76. Accordingly, the district court found that ordinarily skilled artisans "recognized the need for additional antipsychotic drugs" with improved side effect profiles. J.A. 76. It further found asenapine met this profile. J.A. 76.

Appellants point to evidence that they argue indicates the claimed invention did not satisfy a long-felt but unmet need. Specifically, they argue there were a variety of antipsychotic drugs available at the time of the invention, there

is evidence that physicians did not switch treatment preferences for patients with schizophrenia when Saphris entered the market, and there is evidence that Saphris did not have better efficacy or compliance than other antipsychotics available in 1994. They further argue Saphris itself has many side effects and a high discontinuation rate. They argue the district court's comparison of Saphris with the two other atypical antipsychotics, clozapine and risperidone, ignored evidence that clozapine treated the negative symptoms of schizophrenia, which Saphris does not; that both drugs were superior to Saphris in terms of efficacy and side effects; and that both drugs had much lower all-cause discontinuation rates than Saphris.

In reviewing the district court's fact findings, we do not ask whether evidence could have supported the opposing view, only whether the district court clearly erred. Here it did not. Although there were a variety of existing antipsychotics, they had debilitating negative side effects, which evidence indicates are reduced in Saphris. *See, e.g.*, J.A. 599, 603. While this may not be a particularly strong demonstration of long-felt need, the district court did not clearly err in finding it weighs in favor of non-obviousness.

C. Unexpected Results

A showing of unexpected results can support a conclusion of non-obviousness. *See United States v. Adams*, 383 U.S. 39, 51–52 (1966). In considering unexpected results, courts ask whether "the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). While we have permitted *evidence* from after the patent is granted to be considered in assessing whether there are unexpected results, *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004), the results must be "unexpected by one of ordinary skill in the art at the

time of [the] application," *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997).

Here, the district court found it was "surprising and unexpected" that the claimed "sublingual route of administration successfully resolved the serious cardiotoxic event reported in the '476 patent." J.A. 74. However, as the district court found, there was nothing in the prior art that indicated cardiotoxic problems existed with other routes of administration. J.A. 68. We explained in *Soni* that the reason why unexpected results support a conclusion of non-obviousness is simple: "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." 54 F.3d at 750. At the time of the claimed invention, a person of ordinary skill could not have been surprised that the sublingual route of administration did not result in cardiotoxic effects because the person of ordinary skill would not have been aware that other routes of administration do result in cardiotoxic effects. The district court, therefore, erred in its analysis of unexpected results.

D. Legal Conclusion

We review the ultimate question of obviousness de novo. *Arctic Cat*, 876 F.3d at 1365. Given the lack of an express finding that compliance concerns with patients who have trouble swallowing would not provide a motivation to combine, we vacate the district court's judgment of non-obviousness and remand.

III. Written Description

Section 112 of the Patent Act requires the specification contain "a written description of the invention." The written description requirement is met when "the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)

(en banc). Written description is a question of fact, which we review for clear error. *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1166 (Fed. Cir. 2012).

Appellants argue the specification fails to describe asenapine free base in a rapidly disintegrating, sublingual, or buccal solid composition. Both claims 1 and 4 require a "pharmaceutical composition" containing "trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino [4,5-c]pyrrole or a pharmaceutically acceptable salt thereof." The parties' experts agree that "trans-5-chloro-2-methyl-2,3,3a, 12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino [4,5-c]pyrrole or a pharmaceutically acceptable" is the free base of asenapine.

The district court's finding that the specification contains sufficient written description support for claims 1 and 4 was not clearly erroneous. Appellants' expert witness Dr. Gould acknowledged asenapine free base was known in the art. The specification repeatedly refers to pharmaceutical compositions containing asenapine free base. *E.g.*, '476 patent at 1:33–36. While Appellants cite evidence that the properties of asenapine free base make it unsuitable for use in pharmaceutical development, the district court did not clearly err in finding that Appellants had not established invalidity for lack of written description by clear and convincing evidence.

IV. Infringement of Claim 4

The district court found Breckenridge and Alembic do not infringe claim 4 directly, indirectly, or under the doctrine of equivalents. **[A82]** Breckenridge and Alembic's proposed generic products are indicated for the treatment of "manic episodes" associated with bipolar I disorder. Claim 4 is directed to "a method for treating tension, excitation, anxiety, and psychotic and schizophrenic disorders." The court construed claim 4 to not cover the treatment of bipolar disorders. J.A. 57. We review the ultimate claim construction de novo and any subsidiary fact

findings about extrinsic evidence for clear error. *CardSoft*, 807 F.3d at 1348. Because we hold that the district court erred in its claim construction, we vacate and remand as to infringement of claim 4.

The claim language and the specification indicate that "excitation" refers to a symptom rather than a "disorder." The use of the conjunction "and" before "psychotic and schizophrenic disorders" indicates that "psychotic and schizophrenic disorders" is a distinct item on the list, and that unlike the terms "psychotic" and "schizophrenic," the words "tension," "excitation," and "anxiety" are not describing "disorders." This is consistent with how "excitation" is used elsewhere in the specification. '476 patent at 5:55–58. Moreover, experts for both parties agree that there is no such thing as an "excitation disorder," J.A. 218, 349, further indicating the claim covers treatment of the symptom "excitation" rather than treatment of an "excitation disorder." Although excitation may be a symptom of bipolar I disorder, the district court nevertheless carved bipolar I disorder out of its construction because it concluded that the "language of the '476 patent is directed to 'diseases' and 'disorders,' not to symptoms of such." J.A. 50. This misreads the plain language of the claims and specification.

Because the district court erred in treating "excitation" as being limited to "excitation disorders," we vacate its finding of non-infringement. We construe "excitation" to refer to a symptom and remand for the district court to assess infringement in light of this construction.

CONCLUSION

We vacate the district court's judgment that Claims 1 and 4 are not invalid and remand for it to consider the limited question of whether compliance concerns with patients who have trouble swallowing would provide a motivation to combine and its impact on the obviousness analysis. We vacate its judgment of non-infringement of claims 4, 9, and 10 as to Breckenridge and Alembic and remand for the

court to consider whether Breckenridge and Alembic infringe under our revised construction.

VACATED AND REMANDED

COSTS

No costs.