NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

GENZYME CORPORATION, SANOFI-AVENTIS U.S., LLC,
Plaintiffs-Appellees

v.

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., TEVA PHARMACEUTICALS USA INC,
Defendants-Appellants

2016-2206, 2016-2207

Appeals from the United States District Court for the District of Delaware in Nos. 1:13-cv-01506-GMS, 1:13-cv-01508-GMS, Judge Gregory M. Sleet.

Decided: December 18, 2017

PAUL HENRY BERGHOFF, McDonnell, Boehnen, Hulbert & Berghoff, LLP, Chicago, IL, argued for plaintiffs-appellees. Also represented by ALISON JAMEEN BALDWIN, PAULA FRITSCH, JAMES LEE LOVSIN, JEREMY E. NOE, KURT WILLIAM RHODE; JEFFREY B. BOVE, Ratner Prestia, Wilmington, DE.

MARTIN B. PAVANE, Cozen O'Connor, New York, NY, argued for all defendants-appellants. Defendants-appellants Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc. also represented by MARILYN NEIMAN.

ELAINE BLAIS, Goodwin Procter LLP, Boston, MA, for defendant-appellant Teva Pharmaceuticals USA Inc. Also represented by EMILY L. RAPALINO; MICHAEL B. COTTLER, NATASHA ELISE DAUGHTREY, ALEXANDRA D. VALENTI, New York, NY; WILLIAM M. JAY, Washington, DC.

Before MOORE, PLAGER, and CHEN, *Circuit Judges*.

CHEN, *Circuit Judge*.

This consolidated set of appeals arises from a Hatch-Waxman action brought by Genzyme Corporation and Sanofi-Aventis U.S. LLC (collectively, Genzyme) against Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc., and Teva Pharmaceuticals USA, Inc. (collectively, DRL). After a bench trial, the district court held, *inter alia*, that DRL failed to prove that claim 19 of U.S. Patent No. 7,897,590 (the '590 Patent) is invalid for obviousness.

We *affirm*.

BACKGROUND

Stem cells are immature blood cells that reside in the bone marrow, where they can develop into mature blood cells, including white blood cells. Although stem cells are normally present in the blood in very small numbers, they can be "mobilized" from the bone marrow into the peripheral blood under certain conditions.

I. The '590 Patent

Genzyme developed a method for mobilizing and harvesting stem cells by sequentially administering two drug products. Specifically, the '590 Patent makes use of a

regimen comprising a combination of granulocyte-colony stimulating factor (G-CSF) and plerixafor[1] to increase the number of stem cells in the blood for collection. *See* '590 Patent, col. 3 l. 34–col. 4 l. 27.

Under normal conditions, stem cells are anchored to the bone marrow at least in part through a bond between a particular receptor (CXCR-4) located on the stem cell and a protein (SDF-1) produced in the bone marrow. *See id.* at col. 2 ll. 31–63. Plerixafor releases the stem cells into the bloodstream by disrupting that bond.

Claim 19 of the '590 Patent is the only claim at issue in this set of appeals. It recites a "method to obtain progenitor and/or stem cells" by (1) administering G-CSF to a subject; (2) administering plerixafor or a pharmaceutically acceptable salt thereof to the subject, in an amount effective to mobilize the progenitor and/or stem cells; and (3) harvesting the progenitor and/or stem cells. *See* '590 Patent, claim 19.

II. Procedural History

Following a four-day bench trial before the district court, the parties submitted proposed findings of facts and conclusions of law. J.A. 63. DRL filed a motion under Fed. R. Civ. P. 52(c) for a judgment on partial findings on its affirmative defense and counterclaim asserting invalidity of claim 19 of the '590 Patent. J.A. 64.

The district court concluded that claim 19 was not invalid for obviousness and entered a final judgment enjoining DRL from commercially manufacturing, using, offering for sale, selling, or importing its generic products before expiration of the '590 Patent. J.A. 1–30.

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[1] Plerixafor (also known as JM-3100 and AMD-3100) is the active chemical ingredient in Mozobil® and Genzyme's ANDA products. *See* J.A. 6-9.

DRL timely appealed. J.A. 2334–37. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

The determination of obviousness is a legal conclusion based on underlying facts. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1290–91 (Fed. Cir. 2013). After a bench trial, we review the district court's factual findings for clear error and its conclusions of law *de novo*. *Honeywell Int'l, Inc. v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010).

A patent claim is invalid for obviousness if "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103.

The "underlying factual considerations in an obviousness analysis include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations[,]" which include "commercial success, long-felt but unsolved needs, failure of others, and unexpected results." *Allergan*, 726 F.3d at 1290–91 (citations omitted). Patent invalidity must be established by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95, 131 S.Ct., 180 L.Ed.2d 131 (2011).

As part of its obviousness challenge, DRL presented, *inter alia*, the following prior art: (1) Hendrix et al., *Pharmacokinetics and Safety of AMD-3100, a Novel Antagonist of the CXCR-4 Chemokine Receptor, in Human Volunteers*, 44:6 ANTIMICRO. AGTS. AND CHEMO. 1667–73 (Jun. 2000) (Hendrix); (2) International Patent Application Publication No. WO 00/45814 (WO '814); and (3) U.S. Patent No. 5,824,304 (the '304 Patent).

I. Hendrix in combination with the '304 Patent

DRL's first § 103 challenge to the '590 Patent is based on a combination of Hendrix and the '304 Patent. Hendrix focused on evaluating the safety and pharmacology of plerixafor for treating HIV. J.A. 18. The authors of Hendrix reported an increase in white blood cells (WBCs) in the peripheral blood of all subjects after an administration of plerixafor. J.A. 12286. To explain this phenomenon, Hendrix observed the following: (1) Chemokines such as stromal cell-derived factor 1 (SDF-1) are produced locally in tissue, and their primary purpose is the trafficking and chemoattraction of lymphocytes; (2) the CXCR-4 cell receptor is widely expressed;[2] and (3) in experiments, plerixafor has been shown to "completely inhibit" binding of SDF-1 to CXCR-4. J.A. 12288. From these observations, Hendrix hypothesized that "binding of [plerixafor] to CXCR4 may inhibit the chemotactic effects of SDF-1α, causing release of WBCs from the endothelium and/or stem cells from bone marrow." *Id.*

The '304 Patent teaches a method for increasing the number of stem cells in the peripheral blood by administering a blocking agent of VLA-4 antigens. The VLA-4 block agent releases stem cells from the marrow to the peripheral blood by inhibiting the VLA-4 receptor on stem cells, thereby disrupting the tether between the receptor and its natural ligand, VCAM-1, found in the marrow. J.A. 2617–20; J.A. 12819; J.A. 12834. The '304 Patent also teaches that G-CSF mobilized stem cells from the marrow to the peripheral blood by stimulating production of such cells in the marrow. J.A. 12834; J.A. 12836. Thus, by administering G-CSF and a VLA-4 blocking agent, mobilization is achieved. *Id.*

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[2] The CXCR-4 receptor is not unique to stem cells and can be on found on blood cells that are more mature. J.A. 2591.

DRL argues that the only difference between the claimed invention and the '304 Patent is that the '304 Patent does not teach that the blocking agent can be plerixafor. But that would have been obvious, DRL argues, because Hendrix expressly suggested that plerixafor could function as a blocking agent for releasing stem cells from the marrow.

The district court, however, found that Hendrix was not analogous art. J.A. 19–20. Whereas Hendrix focused on HIV treatment, the '590 Patent focused on mobilizing stem cells for subsequent harvest and transplantation. Although the parties agreed that a person of ordinary skill in the art would have been aware of the need for a better stem cell mobilizing regimen, they disputed the likelihood that CXCR-4 (and using plerixafor as a CXCR-4 antagonist) would become the object of research as a stem cell mobilizing agent. J.A. 18. The Court found that Defendants failed to show that a POSA would have pursued CXCR-4 over the field of cytokines and other possible stem cell mobilizers. J.A. 19. Without a specific focus on CXCR-4, the district court concluded that Hendrix would not have been reasonably pertinent to an ordinarily-skilled artisan focused on harvesting stem cells. *Id*.

But even if Hendrix were deemed analogous art, the district court found that Hendrix would not have rendered claim 19 obvious. J.A. 20. The district court expressly rejected DRL's position that it was "reasonably predictable in October 2000 that plerixafor would mobilize stem cells in sufficient numbers for harvesting and tranplantation." J.A. 23. It also found that the evidence established a "history of failure in the field[.]" *Id.*

While we have carefully considered the findings below and all of the parties' arguments, we discuss principally the parties' dispute over whether a person of skill in the art would have had a "reasonable expectation of success" in achieving the claimed invention by combining the prior

art. *See Insite Vision Inc. v. Sandoz Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). "Whether a person of ordinary skill in the art would narrow the research focus to lead to the invention depends on the facts." *Id.* at 860. Here, the district court found that a skilled artisan would not have had a reasonable expectation of success that plerixafor would mobilize stem cells. DRL has not shown that this determination was clearly erroneous.

As noted, the '304 Patent discloses that blocking the receptor VLA-4 with an antibody can result in mobilization of stem cells. J.A. 12834. To render the '590 Patent obvious, DRL combines this teaching with the use of plerixafor in Hendrix to argue that plerixafor can mobilize stem cells in the same way – i.e., by blocking CXCR-4, a different receptor, and disrupting the connection between CXCR-4 and SDF-1.

The record, however, shows that CXCR-4 is in a completely different family of receptors than VLA-4. The '304 Patent never mentions CXCR-4, SDF-1, or plerixafor. It explains that the stem cell mobilization seen with VLA-4 antagonists is "due to the specific blocking of VLA-4." J.A. 12839. Further, DRL's expert testified that a typical stem cell has around one hundred different types of receptors on its surface. J.A. 2679; 3261–62. The district court, noting the parties' arguments and evidence, agreed with Genzyme that "the '304 Patent's discussion of VLA-4 antibody blocking agents would not have rendered obvious claim 19, which covers CXCR-1 and not VLA-4." J.A. 21–22. There is no evidence that VLA-4 localizes stem cells in the marrow like the CXCR-4/SDF-1 bond, and no expectation that CXCR-4 and VLA-4 would behave similarly concerning mobilization.

Although Hendrix hypothesized in an isolated sentence, without explanation, that plerixafor may cause stem cell mobilization, the rest of the seven-page article focused on the elevation of WBC counts. Hendrix men-

tioned SDF-1 and its function of attracting lymphocytes, not stem cells. J.A. 12288. The discussion of CXCR-4 being widely expressed was also directed to different types of WBCs rather than stem cells. *Id.* A skilled artisan would have recognized that Hendrix never tested for the presence of stem cells. J.A. 2877–78. The primary speculation in Hendrix for the phenomenon associated with elevated WBC counts was "demargination," which refers to the release of WBCs from the endothelium. J.A. 2882. This emphasis on demargination is consistent with how an independent group of contemporary researchers perceived Hendrix. J.A. 13245.

The district court's finding that stem cell mobilization was highly unpredictable at the time of the invention also runs counter to an expectation of success. J.A. 23. In particular, there was great uncertainty about the role of SDF-1 or CXCR-4, if any, in the process of stem cell mobilization. J.A. 27. CXCR-4 antagonists were only studied in the HIV field, and there was a history of failure resulting from the investigation of more than a dozen candidates in the search for a better stem cell mobilization agent. J.A. 23. No one had ever mobilized stem cells with any CXCR-4 antagonist, let alone plerixafor.[3] And there were many different cytokines and growth factors that were the subject of research for a skilled artisan looking for a better stem cell mobilizer. The district court

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[3] DRL's reliance on various secondary references (Aiuti, Mohle, Peled, and Ma) to establish the CXCR-4/SDF-1 connection does not call for a different result in this case. Some of the references focused on the migration of stem cells to the marrow, the opposite of mobilization of stem cells from the bone marrow into the peripheral blood. None of the papers report any *in vivo* experiments demonstrating that manipulation of either CXCR-4 or SDF-1 mobilizes stem cells.

weighed all evidence and assessed the credibility of witnesses. Its view that there was no reasonable expectation of success, based on the evidence presented at trial on a combination of Hendrix and the '304 Patent, was not clearly erroneous.

II. WO '814 in combination with the '304 Patent

DRL's alternative basis for invalidating the '590 Patent is the combination of the WO '814 Patent and the '304 Patent. Like Hendrix, "WO '814 does not disclose information about using plerixafor to mobilize stem cells, but instead reveals the relationship between plerixafor and white blood cell elevation." J.A. 22. As the district court explained, DRL's argument that WO '814 would have led a skilled artisan to use plerixafor to mobilize stem cells "depends upon the assumption that a [person of ordinary skill in the art] would have known that white blood cells are a proxy for stem cells." J.A. 22. But the record included ample evidence showing that an increased WBC count did not necessarily correlate to stem cell mobilization. J.A. 2906–9; J.A. 2870.

Ultimately, the deficiency regarding the combination of Hendrix and the '304 Patent also undercuts the combination of WO '814 and the '304 Patent. As noted, sufficient evidence supports the district court's finding of a lack of a reasonable expectation of success. It is also significant that a gap exists between using plerixafor to enhance WBC counts and for stem cell mobilization. DRL attempted to bridge that gap with the '304 Patent by analogizing plerixafor's antagonism of CXCR-4 to the stem cell-mobilizing effect of the '304 Patent's anti-VLA-4 antibody. But the district court considered and reasonably rejected this analogy. J.A. 22 ("[T]he court is not persuaded . . . that the '304 Patent would teach a POSA to use plerixafor as a CXCR-4 blocking agent, simply because plerixafor is an agent like an anti-VLA-4 blocking agent.").

CONCLUSION

After reviewing the record surrounding the prior art and analyzing the arguments of the parties, we conclude that the district court's factual conclusions regarding an insufficient reasonable expectation of success were not clearly erroneous. That evidence is sufficient to uphold the district court's determination against the arguments DRL has presented for reversal, and we need not review the district court's analysis of secondary considerations that, if sound, could only further undermine DRL's argument for obviousness.

We have considered DRL's remaining arguments but find them unpersuasive. For the foregoing reasons, we affirm the district court's holding that the '590 Patent is not invalid.

AFFIRMED