United States Court of Appeals for the Federal Circuit

SOUTH ALABAMA MEDICAL SCIENCE FOUNDATION,
Appellant

v.

GNOSIS S.P.A., GNOSIS BIORESEARCH S.A., GNOSIS U.S.A., INC.,
Appellees

2014-1778, 2014-1780, 2014-1781

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00116.

Decided: December 17, 2015

THOMAS J. PARKER, Alston & Bird LLP, New York, NY argued for appellant. Also represented by JITENDRA MALIK, Durham, NC; KIRK T. BRADLEY, Charlotte, NC; PETER ROGALSKYJ, Law Office of Peter Rogalskyj, Livonia, NY.

JOSEPH CWIK, Amin Talati & Upadhye, LLC, Chicago, IL argued for appellees. Also represented by JONATHAN JACOB KRIT, Amin Talati, LLC, Chicago, IL.

Before NEWMAN, PLAGER, and HUGHES, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* HUGHES.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

HUGHES, *Circuit Judge.*

This is a companion case to *Merck & Cie v. Gnosis S.p.A.*, No. 14-1777 (Fed. Cir. Dec. 17, 2015) (*Gnosis I*), also decided today. As Merck argued in that case, South Alabama Medical Science Foundation argues here that the prior art taught away from its claimed use of a reduced folate to treat folate deficiency, and that objective indicia of non-obviousness further demonstrate the validity of its patents. Although the Patent Trial and Appeal Board erred in its assessment of the evidence of licensing, the Board's other factual findings are supported by substantial evidence. Because we agree with the Board's ultimate conclusion of obviousness in light of those findings, we affirm.

I

South Alabama Medical Science Foundation (SAMSF) owns U.S. Patent Nos. 5,997,915 ('915 patent), 6,673,381 ('381 patent), and 7,172,778 ('778 patent). At the request of Gnosis S.p.A., Gnosis Bioresearch S.A., and Gnosis U.S.A. (collectively, Gnosis) and after granting SAMSF's motion to cancel certain claims, the Board instituted review of claims 37, 94–97, 99–100, and 110–111 of the '915 patent; claim 32 of the '381 patent; and claim 15 of the '778 patent.

All three patents relate to administering the "natural" stereoisomer of 5-methyl-tetrahydrofolic acid (L-5-MTHF) and other vitamins to treat symptoms associated with folate deficiency. We explained the background for this technology in *Gnosis I*, slip op. at 2–3. In brief, 5-MTHF is a reduced folate that is a critical component of certain metabolic cycles. A deficiency of folate causes a variety of

health issues, including cardiovascular disease, neurological disorders, birth defects, and skeletal disorders.

Claim 37 of the '915 patent recites "a method of increasing a human subject's dietary intake of folate comprising administering . . . one or more natural isomers of reduced folate selected from [a group including L-5-MTHF]" and "an essential nutrient preparation . . . comprising a vitamin other than ascorbic acid . . . in an amount equal to or greater than 25% of the daily requirement for the vitamin." '915 patent, col. 23 ll. 16–31. Claims 94–97, 99–100, and 110–111 ultimately depend from claim 37, and specifically require that "the one or more natural isomers of reduced folate is substantially chirally pure [5-MTHF] or a polyglutamyl derivative thereof." '915 patent, reexamination certificate, col. 4 ll. 34–50, 55–62; col. 6 ll. 26–31.

Claim 32 of the '381 patent similarly recites a method of treating vascular disease using a composition including one or more substantially chirally pure natural isomers of reduced folate (e.g. L-5-MTHF) and an essential nutrient preparation comprising a vitamin other than ascorbic acid. '381 patent, col. 18 ll. 33–35.

Claim 15 of the '778 patent covers a composition containing substantially chirally pure natural isomers of reduced folate (e.g. L-5-MTHF), in an amount effective for the treatment of vascular disease and certain pregnancy-related conditions, and an essential nutrient preparation containing a vitamin other than ascorbic acid. '778 patent, col. 18 ll. 18–20.

The Board found that all of the contested claims were obvious in light of two prior art references: European Patent App. No. 0 595 005 (Serfontein) and U.S. Patent No. 5,194,611 (Marazza). Serfontein discloses a pharmaceutical preparation for treating elevated levels of homocysteine, which is often associated with folate deficiency. The preparation includes "folate or a suitable active

metabolite of folate," along with vitamins B_6 and B_{12}. Serfontein, at 4 ll. 37–42. Marazza identifies L-5-MTHF as a "natural metabolite" of folate in which there is an "increasing interest" for the treatment of folate deficiencies. Marazza, col. 1 ll. 26–29.[1] As in *Gnosis I*, the Board found that based on the close similarity of purpose and disclosure of these references a person of ordinary skill would have been motivated to combine them to arrive at the claimed use of L-5-MTHF and a vitamin supplement to treat symptoms of folate deficiency.

The Board also considered SAMSF's evidence of objective indicia of non-obviousness. The Board found that SAMSF failed to demonstrate an adequate nexus between that evidence and the novel features of the contested claims. Accordingly, the Board concluded that the contested claims of the '915, '381, and '778 patents are invalid for obviousness under 35 U.S.C. § 103.

SAMSF appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

II

Obviousness is a question of law based on underlying findings of fact, which include the motivation to combine multiple prior art references and any objective indicia of non-obviousness. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006); *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). We review the Board's factual findings for substantial evidence and the ultimate conclusion of obviousness de novo. *In re Mouttet*, 686 F.3d 1322, 1330–31 (Fed. Cir. 2012).

SAMSF makes essentially the same arguments for reversing the Board's obviousness analysis that Merck

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[1] For more detail on these references, see *Gnosis I*, slip op. at 4–5.

made in *Gnosis I*. SAMSF argues that the Board's obviousness analysis was insufficiently thorough, and that the prior art teaches away from combining Serfontein and Marazza, because it suggests that L-5-MTHF may increase homocysteine levels, is too unstable for therapeutic use, and is a poor substrate for polyglutamation. SAMSF also argues that the Board imposed an overly strict nexus requirement to find that its evidence of objective indicia of non-obviousness is not sufficiently tied to the novel features of the contested claims.

For the same reasons discussed in *Gnosis I*, slip op. 7–13, the Board's finding of a motivation to combine Serfontein and Marazza was adequately explained and supported by substantial evidence. Serfontein calls for a "suitable active metabolite of folate," and Marazza discloses that an increasingly popular option for treating folate deficiency is L-5-MTHF. Although SAMSF points to isolated disclosures suggesting L-5-MTHF may not be "suitable," substantial evidence supports the Board's finding that the prior art as a whole teaches otherwise. We find no error in the Board's conclusion that the prior art and expert testimony here provide strong evidence that the contested claims were obvious.

The Board also properly determined that SAMSF's evidence of objective indicia of non-obviousness was insufficient to overcome the other evidence of obviousness. Like Merck in *Gnosis I*, SAMSF argued here that the commercial success of the Metanx®, Cerefolin®, CerefolinNAC®, Néevo®, and NéevoDHA® products manufactured by Pamlab demonstrate non-obviousness. But these products contain a specific combination of L-5-MTHF and several vitamins and other active ingredients that are not recited in the claims. *See Gnosis I*, slip op. at 14–15. Substantial evidence thus supports the Board's finding that the commercial success of these products was inadequately linked to the claimed methods and composition—which call for L-5-MTHF or another reduced folate and

any number of vitamins other than ascorbic acid—as opposed to the specific formulations in these products.

Contrary to SAMSF's argument, the Board's analysis does not effectively require SAMSF to produce evidence of commercial success for every potential embodiment of the claims. *See Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (holding such a strict requirement is improper). Rather, the Board applied the appropriate standard and found that the commercially successful products were not "reasonably commensurate in scope with the claims" and that SAMSF had not provided an "adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner." J.A. 39–40, 84–86, 131–32 (citing *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). We therefore reject SAMSF's contention that the Board applied an overly strict nexus requirement.

The Board's nexus analysis for the evidence of industry praise was also sound. This evidence consisted of praise for the Pamlab products, which the Board found were not reasonably commensurate with the scope of the claims. Moreover, substantial evidence supports the Board's finding that the praise was particularly directed to the use of L-5-MTHF, an element already known in the prior art. The industry award touted by SAMSF was for Metafolin®, the L-5-MTHF ingredient in the Pamlab products. Likewise, although the industry praised the positive patient outcomes associated with the Pamlab products, SAMSF's experts testified that those outcomes are attributable to the patient's increased dietary intake of folate, referring to the L-5-MTHF ingredient. The Board's finding that SAMSF failed to connect the evidence of industry praise to the novel elements of the claims was thus supported by substantial evidence.

SAMSF further argues that its inventors were the first to recognize that a subset of the population had

difficulty processing folic acid, and that L-5-MTHF would therefore be an effective alternative. But the claims are not limited to treating this subset of the population. And administering L-5-MTHF generally was known in the prior art. Accordingly, substantial evidence supports the Board's finding that this evidence was not adequately tied to the novel features of the claimed invention.[2]

We agree with SAMSF, however, that the Board erred in assessing SAMSF's licensing evidence. The Board discounted SAMSF's licenses to Merck, and Merck's sublicenses to Pamlab, because SAMSF failed to show a nexus between the claimed inventions and Pamlab's products. But the relevant inquiry is whether there is a nexus between the patent and the licensing activity itself, such that the factfinder can infer that the licensing "arose out of recognition and acceptance of the subject matter claimed" in the patent. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). Although evidence that the licensee ultimately manufactured a product that embodies the claimed invention may be probative of a nexus between the claimed invention and the licensing activity, the patentee is not necessarily required to establish an inde-

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[2] An inventor's discovery of a previously unrecognized problem is generally accounted for in the analysis of the scope of the prior art and a motivation to combine prior art elements. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353–54 (Fed. Cir. 2014) (finding that because the prior art does not disclose the problem discovered, there was no motivation to combine prior art elements to solve that problem). Any error in treating this point as a secondary consideration, however, was harmless. Under either heading, this evidence does not show patentability in this case, because the contested claims are not limited to solving the allegedly unrecognized problem.

pendent nexus between those products and the claimed invention for the licensing activity to be relevant. The Board erred in requiring SAMSF to make this showing here.

Nonetheless, the Board's error was harmless. The Board found persuasive the evidence that a person of ordinary skill would have been motivated to combine Serfontein and Marazza to arrive at the contested claims. And it applied the correct legal standards to the remainder of SAMSF's evidence of secondary considerations, finding that it was not adequately tied to the merits of the claimed inventions. These findings were supported by substantial evidence. Even if the Board had correctly considered SAMSF's evidence of licensing, that evidence is not enough to overcome the strong evidence of obviousness found in the prior art and the expert testimony, relied upon by the Board to reach its conclusion of obviousness. We therefore agree with the Board that the contested claims are invalid for obviousness.

III

Because substantial evidence supports the Board's factual findings, except on the evidence of licensing, and because we agree with the ultimate conclusion of obviousness, we affirm the Board's finding that claims 37, 94–97, 99–100, and 110–111 of the '915 patent; claim 32 of the '381 patent; and claim 15 of the '778 patent are invalid under 35 U.S.C. § 103.

AFFIRMED

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NEWMAN, *Circuit Judge,* dissenting.

This appeal is a companion to *Merck & Cie v. Gnosis S.p.A.*, No. 14-1777 (*Gnosis I*), decided concurrently, and consolidates the appeals of three related Inter Partes Review decisions of the Patent Trial and Appeal Board (PTAB). The claims of the three appeals are directed to compositions containing L-5-methyltetrahydrofolic acid (L-5-MTFA) and various uses thereof. In each IPR proceeding the PTAB held the claims invalid as obvious based on the combination of the Serfontein reference (European Patent No. 0595005 ("EP '005")) and the Marazza reference (United States Patent No. 5,194,611 (the "'611 Patent")). One IPR decision, IPR2013-00119,

included in the combination a third reference, Ueland and Redsum, *Plasma homocysteine, a risk factor for vascular disease: Plasma levels in health, disease, and drug therapy*, J. Lab. Clin. Med., Vol. 114, pp. 473–501 (1989).

For the reasons I discussed in *Gnosis I*, these references do not fill the gap between the folate compounds described by Marazza and the uses described by Serfontein, such that a person of ordinary skill in this field would have been motivated to combine these references to treat elevated homocysteine with a reasonable expectation of success. Ueland provides a description of folate and homocysteine biochemistry, and shows the biochemical relationship between homocysteine and L-5-MTHF. Ueland adds to the scientific investigations that have been conducted, but Ueland does not suggest that L-5-MTHF would successfully treat the specified diseases and overcome the known uncertainties of stability, metabolism, and bioavailability. Ueland does not suggest that there would be a likelihood of success in using L-5-MTHF compositions for the specific purposes discovered and developed by the South Alabama scientists. The scientific acclaim and licensing and copying that followed their work add to the evidence of unobviousness. The PTAB erred in evaluating and weighing this evidence.

For the reasons discussed in my dissenting opinion in *Gnosis I*, obviousness was not established by a preponderance of the evidence. From my colleagues' contrary ruling, I respectfully dissent.