United States Court of Appeals for the Federal Circuit

MERCK & CIE,
Appellant

v.

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

2014-1779

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00117.

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

JOSEPH CWIK, Amin Talati & Upadhye, LLC, Chicago, IL, argued for appellee. 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*.

Merck & Cie appeals from the Patent Trial and Appeal Board's decision that the contested claims of its patent are invalid for obviousness. Merck argues that the prior art taught away from the claimed method, and that objective indicia of non-obviousness further support the patentability of the claims. Because the Board's factual findings to the contrary were supported by substantial evidence and because we agree with the Board's ultimate conclusion of obviousness, we affirm.

I

A

Merck owns U.S. Patent No. 6,011,040. At the request of Gnosis S.p.A., Gnosis Bioresearch S.A., and Gnosis U.S.A. (collectively, Gnosis) the Board instituted inter partes review of claims 1–3, 5, 6, 8, 9, 11–15, and 19–22 of the '040 patent. Merck filed a response and a motion to cancel claims 1–3, 5, 6, and 13, which the Board granted. Accordingly, the Board only reviewed the patentability of dependent claims 8, 9, 11, 12, 14, 15, and 19–22.

The '040 patent relates to methods of using folates to lower levels of homocysteine in the human body. '040 patent, col. 1 ll. 10–14. Homocysteine is an amino acid that, when present in excessive quantities, can cause severe cardiovascular, ocular, neurological, and skeletal disorders. *Id.* at col. 1 ll. 60–62. One way the body regulates homocysteine levels is through a metabolic process called the methionine cycle, in which homocysteine is converted to methionine. A common cause of elevated homocysteine levels, or hyperhomocysteinemia, is a deficiency of the enzymes and other compounds used in

the methionine cycle to dispose of homocysteine. *Id.* at col. 1 l. 45.

One such compound is 5-methyl-tetrahydrofolic acid (5-MTHF). 5-MTHF is a reduced folate, meaning it is less oxidized than folic acid. 5-MTHF occurs naturally in foods, and is also produced when folic acid is metabolized in the body. The methionine cycle uses 5-MTHF and vitamin B_{12} to convert homocysteine to methionine.

There are two stereoisomers of 5-MTHF relevant here. Stereoisomers are compounds with the same chemical formula, but with different three-dimensional orientations. The "natural" stereoisomer of 5-MTHF is 5-methyl-(6S)-tetrahydrofolic acid or L-5-MTHF. The "unnatural" stereoisomer is 5-methyl-(6R)-tetrahydrofolic acid or D-5-MTHF, and is a mirror image of L-5-MTHF.

Claims 8 and 9 of the '040 patent recite a method of "preventing or treating disease associated with increased levels of homocysteine . . . comprising administering at least one tetrahydrofolate in natural stereoisomeric form," wherein the tetrahydrofolate is L-5-MTHF or a salt thereof. '040 patent, col. 5 ll. 26–31, 56–57, col. 6 ll. 1–3.

Claims 11 and 12 further require that the increased levels of homocysteine are associated with a deficiency of methylene tetrahydrofolate reductase, an enzyme that helps generate L-5-MTHF for the methionine cycle. *Id.* at col. 6 ll. 7–17. In claims 14 and 15, the deficiency specifically involves thermolabile (i.e. easily affected by heat) methylene tetrahydrofolate reductase. *Id.* at col. 6 ll. 23–33.

Claim 21 limits the method in claim 11 to require administration of L-5-MTHF "in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance," and claim 22 specifies that the pharmaceutically compatible active substance "comprises at least one B-

vitamin." *Id.* at col. 6 ll. 49–56. Claims 19 and 20 apply the same "pharmaceutically compatible active substance" limitations to the method in claim 5, in which the administered tetrahydrofolate is one of a list of compounds that includes L-5-MTHF. *Id.* at col. 5 ll. 36–41.

B

The Board found that all of the contested claims were obvious in light of three prior art references: European Patent App. No. 0 595 005 (Serfontein); U.S. Patent No. 5,194,611 (Marazza); and Johan Ubbink et al., *Vitamin B-12, Vitamin B-6, and Folate Nutritional Status in Men with Hyperhomocysteinemia*, 57 Am. J. Clinical Nutrition, 47, 47–53 (1993) (Ubbink).

Serfontein discloses "a pharmaceutical preparation for lowering levels of homocysteine . . . in a patient." Serfontein, at 4 ll. 37–39. Serfontein teaches that elevated levels of homocysteine are linked to numerous clinical defects, including cardiovascular problems such as precocious occlusive vascular disease; and abnormalities in the eyes, skeletal system, and central nervous system. Serfontein also explains that high levels of homocysteine are often associated with folate deficiencies, and are sometimes caused by hereditary enzyme deficiencies. Thus, to treat high levels of homocysteine, Serfontein discloses a preparation that includes "folate or a suitable active metabolite of folate," along with vitamins B_6 and B_{12}. *Id.* at ll. 37–42.

Although Serfontein does not specify what constitutes a "suitable active metabolite of folate," Marazza identifies L-5-MTHF as a "natural metabolite" that may be used "as at least one active compound" in a treatment for folate deficiency. Marazza, col. 1 ll. 25–28. Marazza explains that commercially available forms of 5-MTHF at the time were mixtures of L-5-MTHF and its enantiomer D-5-MTHF. *Id.* at col. 2 ll. 3–6. It then discusses previous studies suggesting that the unnatural enantiomer

D-5-MTHF may interfere with the transport of folate through the cell membranes in humans. *Id.* at col. 2 ll. 16–20. To address this issue, Marazza teaches a process by which a mixture of these 5-MTHF stereoisomers may be separated into pure L-5-MTHF and D-5-MTHF forms. *Id.* at col. 3 ll. 32–36.

Ubbink is a study of folate levels in men with elevated levels of homocysteine. Ubbink affirms that "[n]umerous studies have indicated that elevated plasma homocysteine concentrations are associated with increased risk for premature vascular disease." J.A. 836. It also states that the reasons for hyperhomocysteinemia include enzyme defects such as "cystathionine-ß-synthase deficiency, or possession of a thermolabile variant of methylenetetrahydrofolate reductase, an enzyme required in the remethylation of homocysteine to methionine." J.A. 836 (citations omitted). Ubbink describes the positive results of treating these conditions with a vitamin supplement containing folic acid.

The Board found that, because of the close similarity of purpose and disclosure between Serfontein and Marazza, a person of ordinary skill in the art would have been motivated to combine the two references to arrive at a method of treating elevated levels of homocysteine with L-5-MTHF, as recited in claims 8, 9, 19, and 20 of the '040 patent. Further, the Board found a person of skill would have been motivated to use this method in the situation disclosed in Ubbink, in which the elevated homocysteine levels are associated with certain enzyme deficiencies. The Board found that this combination of Serfontein, Marazza, and Ubbink discloses the additional limitations of claims 11, 12, 14, 15, 21, and 22.

The Board also considered objective indicia of non-obviousness. The Board concluded that Merck failed to demonstrate an adequate nexus between the novel features of the '040 patent and the evidence of commercial

success, licensing, copying, and industry praise. It also found that the evidence of long-felt but unmet need, unexpected results, and industry skepticism was unpersuasive.

Accordingly, the Board concluded that the asserted claims of the '040 patent would have been obvious to a person of ordinary skill at the time of the invention. The Board also found that Serfontein anticipates claims 8, 9, 19, and 20. And the Board construed the claims not to exclude the administration of a mixture that includes both L-5-MTHF and D-5-MTHF.

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

II

Merck appeals the Board's obviousness determination, anticipation finding, and claim construction. Because we affirm the Board's determinations that the asserted claims are invalid as obvious, we need not reach Merck's arguments with respect to anticipation and claim construction.[1]

Obviousness is a question of law based on underlying findings of fact. *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009). The factual findings include: "(1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if

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[1] During oral argument, Merck agreed that even if the Board's claim construction is incorrect, it did not affect the obviousness determination. *See* Oral Argument at 1:47, *Merck & Cie v. Gnosis S.P.A.*, No. 14-1779 (Apr. 7, 2015), *available at* http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2014-1779.mp3.

any." *Id.*; *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). If all elements of the claims are found in a combination of prior art references, as is the case here, the factfinder should further consider whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have a reasonable expectation of success. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006). In appeals of Board decisions, these factual findings are reviewed for substantial evidence. *In re Gartside*, 203 F.3d 1305, 1313 (Fed. Cir. 2000); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1280 (Fed. Cir. 2015). Based on the underlying factual findings, we review the Board's ultimate conclusion of obviousness de novo. *In re Mouttet*, 686 F.3d 1322, 1330–31 (Fed. Cir. 2012).

The Board's finding of a motivation to combine Serfontein, Marazza, and Ubbink to arrive at the claimed method was supported by substantial evidence. So was the Board's finding that the proffered evidence of objective indicia of non-obviousness lacked an adequate nexus with the merits of the claimed invention. In light of these factual findings, we agree with the Board's ultimate conclusion that the asserted claims were obvious under 35 U.S.C. § 103.

A

The record amply supports the Board's finding of a motivation to combine Serfontein and Marazza. Serfontein explains that elevated levels of homocysteine are often associated with folate deficiencies. Accordingly, Serfontein discloses a method of treating elevated levels of homocysteine using a "suitable active metabolite of folate" and B-vitamins. While Serfontein does not specifically identify which metabolites of folate are "suitable" for addressing folate deficiencies, Marazza does. It highlights 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. Thus, as the Board found, a person of ordinary skill viewing Serfontein and Marazza would have been motivated to use L-5-MTHF as the "suitable active metabolite of folate" called for by the method disclosed in Serfontein.

Merck argues that the prior art teaches away from this combination by suggesting: (1) administering 5-MTHF would actually increase levels of homocysteine, (2) 5-MTHF would be too unstable for therapeutic use, and (3) L-5-MTHF is a poor substrate for polyglutamation, a process that facilitates retention and use of L-5-MTHF in the cell. Merck cites isolated prior art disclosures for support. Viewing the prior art as a whole, however, the Board's finding that the prior art does not teach away from combining Serfontein and Marazza is supported by substantial evidence.

The prior art does not unambiguously teach that administration of 5-MTHF would increase homocysteine levels. Merck relies on two prior art references: Harpey 1, a journal article discussing the treatment of an infant with chronically high levels of homocysteine; and Harpey 2, a letter to the editor of the journal with updates on that treatment. *See* J.A. 1253–57. Merck argues that, based on its expert testimony, these references show that administration of 5-MTHF increases homocysteine levels, because the infant's homocysteine levels rose during administration of 5-MTHF from 0 μmol/L to 13 μmol/L. But this conclusion relies on the wrong starting point. Prior to treatment, the infant's homocysteine levels were 233 μmol/L, whereas 0 μmol/L was normal. Only after a variety of other treatments were the infant's levels of homocysteine reduced to 0 μmol/L. Thus, although switching to 5-MTHF may have correlated with a slight increase in homocysteine, the net effect is still a reduction of homocysteine levels. Moreover, the researchers themselves seemed to think that 5-MTHF controlled the in-

fant's homocysteine levels. If they thought otherwise, they would have terminated treatment for that reason, given that the infant's symptoms from elevated homocysteine levels were severe. But they did not. Instead, the stated reason for eventually withdrawing 5-MTHF was "because of its instability." J.A. 1257. Given this context, substantial evidence supports the Board's finding that a person of ordinary skill would not understand the Harpey references to teach that 5-MTHF would increase previously untreated homocysteine levels.

Nor does the prior art compel a finding that a person of ordinary skill would have thought 5-MTHF was too unstable for therapeutic use. The Harpey references, published in 1981 and 1983 respectively, certainly suggest 5-MTHF was unstable. Harpey 1 states that "[a]lthough [5-MTHF] would be desirable for use in therapy, it is probably too unstable." J.A. 1255. Harpey 2 explains that treatment with 5-MTHF "had to be withdrawn because of its instability." J.A. 1257. But subsequent references disclose that 5-MTHF is suitable for pharmaceutical use. A study published in 1986 explains that although prior "[s]tudies of MTHF . . . were hampered by its chemical instability[,] [a] new and stable preparation of MTHF has become available for clinical trials." J.A. 1243 (Reggev reference); *see also* J.A. 3188 (Pattini reference discussing 1988 study in which 5-MTHF was administered to cross-country skiers daily); J.A. 840 (Godfrey reference reporting 1990 study in which 5-MTHF was administered to treat psychiatric disorders). And in 1990, the Marazza reference clearly identified L-5-MTHF as a suitable compound for treating folate deficiency. Marazza, col. 1 ll. 25–28. Because the prior art must be considered as a whole, *Medichem*, 437 F.3d at 1166, the Board's finding that a person of ordinary skill would not have thought that 5-MTHF was too unstable for pharmaceutical use is supported by substantial evidence.

Finally, although some prior art references suggest that L-5-MTHF is a poor substrate for polyglutamation, others disclose that L-5-MTHF is nonetheless effective for treatment of elevated homocysteine levels. Merck argues that because L-5-MTHF was understood to have a poor capacity for polyglutamation, a process that helps retain folates in the cell, a person of ordinary skill at the time would have thought that L-5-MTHF does not accumulate within the cell, where the conversion of homocysteine to methionine occurs. According to Merck, a person of skill would therefore would have been discouraged from using L-5-MTHF to lower homocysteine levels.

This argument, however, ignores other prior art disclosing that 5-MTHF does, in fact, accumulate in the cell. The Wagner reference states that at least 20% of 5-MTHF was retained within the cell in that study, as Merck conceded before the Board. J.A. 512, 2068. And another reference, Regland, teaches that 5-MTHF was the "drug of choice" because "MTHF is the form of folate that is taken up by the cells." J.A. 851. Accordingly, the prior art as a whole supports the Board's conclusion that a person of ordinary skill would not have avoided L-5-MTHF because it does not accumulate within the cells.

Merck further argues that L-5-MTHF's poor capacity for polyglutamation makes it a less effective substrate for the enzymes involved in converting homocysteine to methionine. Merck seizes on a prior art statement that "[m]etabolism of folates to polyglutamates [i.e. polyglutamation] is required for their biological activity because polyglutamate forms are much more effective substrates for folate-dependent enzymes than are the monoglutamate derivatives." J.A. 1313 (declaration of Dr. Gregory (quoting article by Dr. Shane)). Merck also points to an isolated statement in the Wagner reference that "under the conditions of the present study, isolated [liver cells] did not significantly metabolize [5-MTHF]." J.A. 2070.

Again, other prior art references show that 5-MTHF would nonetheless be effective for lowering homocysteine levels. The Ueland reference discloses, and Merck agrees, that folic acid is an effective means of decreasing homocysteine levels. And according to Ueland, folic acid accomplishes this reduction by "increas[ing] the intracellular pool of [5-MTHF] which in turn may serve as a methyl-donor in the [methionine cycle]." J.A. 801. Merck failed to present credible evidence that 5-MTHF derived from folic acid is any more capable of polyglutamation in the cell or any more effective as a substrate for folate-dependent enzymes than natural L-5-MTHF administered directly. Indeed, a 1989 reference concludes that directly administered 5-MTHF is actually more efficient than folic acid: "In some cells, the concentration of folic acid required to generate adequate concentrations of intracellular folates is 100-200 times that of reduced folates such as [5-MTHF] . . . ." J.A. 1275. And other references disclose that 5-MTHF is effective for treating symptoms associated with folate deficiency. *See* Marazza, col. 1 ll. 25–28; J.A. 840 (Godfrey reference); J.A. 844 (Regland reference). In view of these references, a person of skill in the art would have had reason to use L-5-MTHF instead of folic acid, notwithstanding prior suggestions that L-5-MTHF has a poor capacity for polyglutamation. Accordingly, the record amply supports the Board's finding that a person of ordinary skill would not understand the prior art to teach away from using 5-MTHF based on its capacity for polyglutamation.

Serfontein specifically calls for a "suitable active metabolite of folate" to help lower homocysteine levels, and Marazza provides that L-5-MTHF is one such metabolite. The Board properly concluded that any doubt about the suitability of L-5-MTHF was overcome by the weight of the prior art. We therefore conclude that substantial evidence supports the Board's finding that a person of ordinary skill would have been motivated to use

L-5-MTHF to treat elevated levels of homocysteine in the manner recited in claims 8, 9, 19, and 20 of the '040 patent.

The Board's additional finding of a motivation to use the method disclosed in Serfontein and Marazza to treat elevated homocysteine levels associated with certain enzyme deficiencies, as disclosed in Ubbink, is also supported by substantial evidence. Merck's sole argument against this finding is that Ubbink used folic acid, not reduced folates such as L-5-MTHF, to treat elevated levels of homocysteine associated with certain enzyme deficiencies. As the Board found, however, this distinction would not have undermined a person of ordinary skill's motivation to combine. Ubbink involved a deficiency in the enzyme methylenetetrahydrofolate reductase. According to the prior art, this enzyme is important because it helps produce 5-MTHF for the methionine cycle. J.A. 786 (Ueland reference). A deficiency in this enzyme, therefore, reduces the amount of 5-MTHF available for converting homocysteine to methionine. *Id.* In Ubbink, patients with this deficiency were treated using folic acid, which reduces homocysteine levels by increasing the intracellular pool of 5-MTHF. J.A. 801 (Ueland reference). As mentioned above, a person of skill would have known that administering 5-MTHF directly would accomplish a similar result. *See* J.A. 1275 (study suggesting 100-200 times more folic acid would be needed to match the results of directly administered 5-MTHF); Marazza, col. 1 ll. 25–28 (describing 5-MTHF as a popular supplement for the treatment of folate deficiency). Thus, the record supports the Board's finding that the method of using L-5-MTHF disclosed in Serfontein and Marazza was a natural alternative to using folic acid when elevated homocysteine levels are associated with enzyme deficiencies, as disclosed in Ubbink. The resulting combination discloses each limitation of claims 11, 12, 14, 15, 21, and 22.

In a final challenge to the Board's decision, Merck complains that the Board never made an express finding that a person of ordinary skill would have a reasonable expectation of success in combining Serfontein and Marazza, or in further combining Serfontein, Marazza, and Ubbink. Under *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 418, (2007), a factfinder's analysis of a reason to combine known elements in the art "should be made explicit." But *KSR* does not require an explicit statement of a reasonable expectation of success in every case. *Cf. id.* at 419 (cautioning against confining the obviousness analysis using formalistic rules). Here, the Board addressed Merck's arguments against a reasonable expectation of success in the context of its teaching away arguments. By rejecting Merck's argument that the prior art taught away from combining Serfontein, Marazza, and Ubbink, the Board impliedly found a reasonable expectation of success. We decline to overturn the Board's decision for failure to state expressly that a person of ordinary skill would have had a reasonable expectation of success.

Merck fails to establish that the Board's factual determinations are not supported by substantial evidence. In light of those findings, we agree with the Board that the prior art and expert testimony present strong evidence of obviousness.

B

Objective indicia of nonobviousness can serve as an important check against hindsight bias and "must always when present be considered." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075–76 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983)). Even when present, however, objective indicia "do not necessarily control the obviousness determination." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

"For objective evidence of secondary considerations to be accorded substantial weight, its proponents must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Where objective indicia "result[ ] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Id.* "To the extent that the patentee demonstrates the required nexus, his objective evidence of nonobviousness will be accorded more or less weight." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

Here, the Board properly considered Merck's evidence regarding objective indicia of nonobviousness, but found that the nexus between the merits of the invention and the evidence of commercial success, licensing, copying, and industry praise was weak. The Board also found the evidence of long-felt but unmet need was unpersuasive. The Board therefore afforded the evidence of objective considerations little weight. We conclude that these factual findings are supported by substantial evidence.

Merck's evidence of commercial success relates to several products manufactured and sold by Merck's licensee, Pamlab (the Pamlab products). The Metanx®, Cerefolin®, CerefolinNAC®, Néevo®, and NéevoDHA® products contain L-5-MTHF in addition to other active ingredients. In the Deplin® product, the only active ingredient is L-5-MTHF. Deplin® is intended for use as a supplemental treatment of major depressive disorder (MDD) or schizophrenia.

As the Board found, the "mixed" products—Metanx®, Cerefolin®, CerefolinNAC®, Néevo®, and NéevoDHA®—have material features beyond those disclosed and claimed in the '040 patent. While the asserted claims most closely related to these products recites a method of

treating elevated homocysteine levels using a mixture of L-5-MTHF and "at least one B-vitamin," *see* '040 patent, col. 6 ll. 46–48 (claim 19); *id.* at ll. 54–55 (claim 21), these products go further and contain a specific combination of specific forms of B-vitamins and other active ingredients. For example, the Cerefolin® product combines L-5-MTHF with specific quantities of riboflavin (vitamin B_2), cyanocobalamin (a form of vitamin B_{12}), and pyridoxine hydrochloride (a form of vitamin B_6). Merck failed to establish that the commercial success of these products was due to the claimed method—using L-5-MTHF and "at least one B-vitamin"—as opposed to the specific formulations in the mixed products. Indeed, a Pamlab executive stated that the success of two of these products was due to the "unique combination" of their ingredients. J.A. 1855–56; *see also* J.A. 1542 (expert stating that effectiveness of Metanx® "was likely due to the synergistic interactions of its components"). Thus, the Board's finding that this evidence of commercial success should be afforded little weight was supported by substantial evidence.

The alleged nexus between the asserted claims and the Deplin® product was also tenuous. "If commercial success is due to an element in the prior art, no nexus exists." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011). The Board identified two prior art references disclosing compounds containing 5-MTHF that were used to treat depression associated with folate deficiencies, just like the Deplin® product. The Godfrey reference describes a study in which administering 5-MTHF improved the recovery of patients with major depression or schizophrenia and a folate deficiency. Similarly, the LeGrazie reference discloses the use of 5-MTHF to treat a subject with "organic mental disturbances with depression of mood." J.A. 750. Thus, substantial evidence supports the Board's finding that the use of 5-MTHF for treating major depressive disorder and schizophrenia was known in the prior art, and therefore

Merck could not show a sufficient nexus between the commercial success of the Deplin® products and the novel features in the asserted claims.

Merck's evidence of copying and industry praise was based on the same Pamlab products. Like the evidence of commercial success, Merck failed to show an adequate nexus between these objective indicia and the novel features of the asserted claims. Thus, substantial evidence supports the Board's finding that evidence copying and industry praise is entitled to little weight.

Merck's evidence of licensing is similarly unavailing. Although Merck successfully licensed the '040 patent to Pamlab, the licensing agreement also covered several other patents. One of those patents claims the stable form of L-5-MTHF used in Pamlab's products more precisely than the '040 patent. *See* U.S. Patent No. 6,441,168. A Pamlab executive explained that Pamlab desired this stable form "[b]ecause of its uniqueness and its novel properties," J.A. 3879, and touted the ingredient as "[o]ne particular differentiator that makes our product unique," J.A. 1848. It is therefore difficult to determine the extent to which the licensing agreement was a result of the novel features in the '040 patent, as opposed to the other patents involved. In light of this ambiguity, the Board's finding that the evidence of licensing should not be afforded much weight was reasonable.

Finally, Merck alleges that the '040 patent resolved a long-felt but unmet need for a supplemental therapy for treating MDD. As mentioned, however, substantial evidence supports the Board's finding that the prior art disclosed the use of 5-MTHF to treat depression associated with folate deficiencies, such as MDD. Merck's argument that the '040 patent met a long-felt need for MDD treatment, therefore, is not sufficiently connected with the novel elements of the asserted claims.

Although another factfinder may have reasonably evaluated Merck's evidence of objective indicia of non-obviousness differently in the first instance, the Board's conclusion that this evidence was not persuasively tied to the novel features of the asserted claims is supported by substantial evidence. In light of this finding, we agree with the Board that these objective indicia carry little weight.

III

The Board found persuasive evidence that the claimed method of treating elevated levels of homocysteine would have been obvious to a person of skill in light of the prior art, particularly Serfontein, Marazza, and Ubbink. And the Board found that Merck's evidence of objective indicia of non-obviousness was not closely tied to the allegedly novel features of the claimed invention. These findings were supported by substantial evidence and, on balance, provide strong evidence of obviousness. We therefore agree with the Board's ultimate legal conclusion that claims 8, 9, 11, 12, 14, 15, and 19–22 of the '040 patent are invalid under 35 U.S.C. § 103.

AFFIRMED

United States Court of Appeals for the Federal Circuit

MERCK & CIE,
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GNOSIS S.P.A., GNOSIS BIORESEARCH S.A., GNOSIS U.S.A., INC.,
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2014-1779

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00117.

NEWMAN, *Circuit Judge,* dissenting.

This appeal is from a decision of the Patent Trial and Appeal Board ("PTAB"), on Inter Partes Review in accordance with the America Invents Act. The PTAB held the claims of the patent in suit invalid. My concern is with the court's implementation of this new statute, lest its legislative purpose be unfulfilled.

The America Invents Act ("AIA") is the fruit of eight years of study, as legislators and other concerned persons considered how to revive industrial innovation in the United States. Loss of an effective patent incentive was believed to have contributed to diminished technologic advance and consequent losses in economic growth. *See*

157 Cong. Rec. S948-49 (daily ed. Feb. 28, 2011) (statement of Sen. Leahy) ("High quality patents are the key to our economic growth."); 157 Cong. Rec. H4423 (daily ed. June 22, 2011) (statement of Rep. Smith) ("The current patent system is outdated and dragged down by frivolous lawsuits and uncertainty regarding patent ownership. Unwarranted lawsuits that typically cost $5 million to defend prevent legitimate inventors and industrious companies from creating products and generating jobs."); 153 Cong. Rec. HE773 (daily ed. Apr. 18, 2007) (statement of Rep. Berman) (introducing a predecessor bill) ("These studies offer a number of recommendations for increasing patent quality and ensuring that patent protection promotes—rather than inhibits—economic growth and scientific progress.").

It was believed that the PTO was granting patents too easily, and that the courts were not consistently deciding patentability issues. To attempt to remedy these deficiencies, the America Invents Act created a new adjudicative tribunal (the Patent Trial and Appeal Board or PTAB) within the Patent and Trademark Office, and established new procedures including changes in the burdens of proof, limiting the path of judicial review, and providing for finality and strict time limits. The purpose is to restore an effective and balanced system of patents, whereby valid patents may reliably be confirmed and invalid patents efficiently invalidated.

This appeal raises questions of implementation of the statutory plan, for the judicial role includes assuring that the statutory assignment is fulfilled. The Supreme Court has stated:

> Reviewing courts are not obliged to stand aside and rubberstamp their affirmance of administrative decisions that they deem inconsistent with a statutory mandate or that frustrate the congressional policy underlying a statute. Such review is

> always properly within the judicial province, and courts would abdicate their responsibility if they did not fully review such administrative decisions.

N.L.R.B. v. Brown, 380 U.S. 278, 291–92 (1965).

The realignments of burdens and standards of proof established by the America Invents Act are part of the legislative balance, whose target is correctness and efficiency. My concern is that the PTAB and this court have departed from explicit and implicit provisions of the statute. When that departure is rectified, the result is changed. Thus I must, respectfully, dissent.

The Burden of Proof in the PTAB

The America Invents Act requires that the burden of proving invalidity of an issued patent is on the petitioner for post-grant review. 35 U.S.C. § 316(e). The Act established the standard of proof of invalidity to be applied by the PTAB, requiring that invalidity be proved by a preponderance of the evidence, and eliminating any deference to the prior examination and grant of the patent. As an important aspect of the legislation, the Act did not adopt the judicial standard of requiring clear and convincing evidence to establish invalidity.

Although the placement of the burden of proof of invalidity is on the petitioner, the petitioner now may prove invalidity by no more than a preponderance of the evidence. 35 U.S.C. § 316(e).

The AIA established a powerful incentive to challenge patent validity in the PTAB instead of the district court, for the attacker faces a lower standard of proving invalidity in the PTAB. However, the correct law must be applied, and disputed facts found and reviewed on the entirety of the evidence, as the preponderance standard requires.

The Burden of Proof in the Federal Circuit and Finality

Another important aspect of the America Invents Act is the provision for finality and estoppel after the PTAB decision and any appeal to the Federal Circuit. The Act does not permit subsequent review of the PTAB's validity/invalidity decision in any other tribunal, whether by appeal or direct review or as a defense or offense in litigation. The AIA provides that a petitioner (or real party in interest or privy of the petitioner)

> may not assert either in a civil action . . . [or] . . . before the International Trade Commission . . . that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that post-grant review.

35 U.S.C. § 315(e)(2). This change from present law was long-debated, and is directed to the goals of correctness, uniformity, finality, and expedition.

Thus it is incorrect for this court, as the only reviewing tribunal, to review the PTAB decision under the highly deferential "substantial evidence" standard. Our obligation is to assure that the legislative purpose is met, through application of the statute in accordance with its purpose. *See Calvert Cliffs' Coordinating Comm., Inc. v. U. S. Atomic Energy Comm'n*, 449 F.2d 1109, 1111 (D.C. Cir. 1971) ("Our duty, in short, is to see that important legislative purposes, heralded in the halls of Congress, are not lost or misdirected in the vast hallways of the federal bureaucracy."). This court's resort to deferential "substantial evidence" review is at odds with the benefits that Congress intended.

The substantial evidence standard determines whether the decision could reasonably have been made, not whether it was correctly made. *See* 3 Steven Alan Childress & Martha S. Davis, *Federal Standards of Review* §

15.04 (4th ed. 2010). The substantial evidence standard originated with appeals of jury verdicts, in recognition of the role of credibility at trial. *Id.* "Substantial evidence" was incorporated into the Administrative Procedure Act in recognition of the expertise of specialized agencies. *Id.* Here, however, a new system was created to respond to the belief that the agency was making mistakes. *See, e.g.*, 157 Cong. Rec. S1326 (daily ed. March 7, 2011) (statement of Sen. Sessions) ("This will allow invalid patents that were mistakenly issued by the PTO to be fixed early in their life, before they disrupt an entire industry or result in expensive litigation."); 153 Cong. Rec. H10276 (daily ed. Sept. 7, 2007) (statement of Rep. Goodlatte, commenting on a predecessor bill to the AIA) ("The PTO, like any other large government agency, makes mistakes. H.R. 1908 creates a post-grant opposition procedure to allow the private sector to challenge a patent just after it is approved to provide an additional check on the issuance of bogus patents."). This new system is directed at correcting mistakes. Deferential review by the Federal Circuit falls short of the legislative purpose of providing optimum determination of patent validity.

The Federal Circuit is the only review body for these new agency proceedings, for the America Invents Act displaced the alternative path of challenge to PTO decisions in the district court. Thus the PTAB's adjudications must be reviewed for correct application of the standard of proof established by the America Invents Act. In 35 U.S.C. § 316(e):

> In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.

On appeal to the Federal Circuit, our assignment is to determine whether the PTAB ruling is correct in law and supported by a preponderance of the evidence. The panel

majority errs in importing into these proceedings the Administrative Procedure Act standard that applies to initial patent examination decisions, Maj. Op. at 7, citing *In re Gartside*, 203 F.3d 1305, 1313 (Fed. Cir. 2000) (PTO decisions sustained if supported by substantial evidence).

Appellate review of agency rulings on the preponderance standard, accompanied by finality, is not the general APA rule, but has been adopted by statute in other special situations. For example, under the Service Contract Act, "[i]f supported by a preponderance of the evidence, the [agency's] findings are conclusive in any court of the United States." 41 U.S.C. § 6507(e) (formerly 41 U.S.C. § 39). The regional circuits have interpreted the preponderance standard to require review for "clear error" on appeal. *See Dantran, Inc. v. U.S. Dep't of Labor*, 171 F.3d 58, 71 (1st Cir. 1999) (rejecting "substantial evidence" review standard); *see also Amcor, Inc. v. Brock*, 780 F.2d 897, 901 (11th Cir. 1986) ("determination by the administrator . . . must be affirmed unless it is not supported by a preponderance of the evidence.").

Such close appellate scrutiny is critical to the legislative balance of the America Invents Act, whose purpose is to reach an expeditious and reliable determination on which inventors and industry innovators and competitors can rely. The Federal Circuit's adoption of deferential "substantial evidence" review strays from this purpose. If Congress intended that deferential review would apply to PTAB determinations in which "substantial evidence" is "something less than the weight of the evidence," *Consolo v. Fed. Mar. Comm'n*, 383 U.S. 607, 620 (1966), explicit assignment of this standard would reasonably have been expected.

For example, the majority decides that "substantial evidence" supports the PTAB's finding of a motivation to combine the information in the Serfontein and the Marazza references, as I discuss *infra*. The PTAB cited no

source for this finding, other than "[t]he close similarity of purpose and disclosure between these references." PTAB Op. at 23. The panel majority, looking for "substantial evidence" supporting the PTAB, does not discuss the evidence weighing against this finding, such as the known side effects of the L-5-MTHF isomer, its instability, the equivocal clinical observations, and Merck's and the University's commercial success, as well as the long-felt need, failure of others, industry praise, licensing, and copying. Deferential review on a standard that looks at only one side of the evidence is less likely to uncover errors in the balance and burden of proof.

Application of the Correct Appellate Standard

The patent claims the use of a specific tetrahydrofolate stereoisomer, L-5-methyltetrahydrofolate (L-5-MTHF) to treat elevated homocysteine, including a genetic disorder called homocysteinuria, a debilitating affliction that the Serfontein reference (European Patent No. 0595005 (EP'005)) describes as "an inborn error of metabolism which is either caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine." EP'005 at 3, ll. 20–22.

The PTAB found that Serfontein concerns the generic class of "folate or a suitable active metabolite of folate or a substance which releases folate in vivo." PTAB Op. at 23. Serfontein states that "it is known that vitamin B6, vitamin B12 and folate play a role in regulating the methionine-homocysteine pathway and controlling levels of homocysteine," EP'005 at 3, ll. 54–56, and that "[a]t the same time, deficiencies (individually) of each of these vitamins have also been known to be associated with increased homocysteine levels." EP'005 at 3, ll. 31–32. This description does not mention the L-5-MTHF isomer, or that this specific stereoisomer is effective in treating elevated homocysteine.

Serfontein recognized an "association" between folate deficiency and increased homocysteine, but did not suggest that L-5-MTHF is useful to treat elevated homocysteine, with or without B vitamins. The PTAB recognized this gap in Serfontein, and held that Marazza, U.S. Patent No. 5,194,611 ("the '611 Patent"), filled the gap. Marazza states that L-5-MTHF is "the predominant circulating form of reduced folates in mammals," and "[t]here exists an increasing interest for the application of this natural metabolite as at least one active compound in a therapeutical agent, for example as vitamin in folate deficiency states." '611 Patent, col. 3, ll. 23–29.

However, Marazza does not link the L-5-MTHF isomer to treatment of elevated homocysteine, or suggest this use. And Serfontein only states that elevated homocysteine levels are "associated with" folate deficiency. EP '005, col. 3, ll. 31-32. Missing is a teaching or suggestion in either of these references that L-5-MTHF could be effectively used to treat elevated homocysteine with a reasonable expectation of success. Several other references in the record discuss folate biochemistry and report various scientific investigations, yet amid extensive and extremely close prior art, no reference suggests the method described in this patent.[1]

The PTAB erred in concluding that "one reading Serfontein would have considered 5-methyl-(6S)-tetrahydrofolic acid (L-5-MTHF) a viable choice, as expressly taught in Marazza, for a suitable active metabolite of folate in Serfontein's method." PTAB Op. at 25.

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[1] It has been suggested that the claims are unduly broad. This breadth is challenged in the concurrent *inter partes* review of U.S. Patent No. 7,172,778, where an additional reference is discussed.

Marazza does not teach that L-5-MTHF is suitable to treat elevated homocysteine, but only that it is an "active" folate for treating folate deficiency. Amid the uncertain predictability of biological response, this background does not provide a reasonable likelihood of successful treatment with any selected stereoisomer. Only hindsight provides such prophesy.

The evidence of record does not support the PTAB's apparent assumption that any folate would be effective against elevated homocysteine. No reference teaches that L-5-MTHF has this activity. A *prima facie* case cannot be based on the inventor's successful investigations.

The PTAB states that "Serfontein calls for a 'suitably active metabolite of folate' in preparations used to correct folate deficiency and treat diseases associated with elevated levels of homocysteine." PTAB Op. at 23. This statement appears to enlarge Serfontein, who uses folate for "lowering levels of homocysteine or . . . counteracting the harmful effects associated with homocysteine." EP'005 at 2, ll. 1–3.

The PTAB states that "Marazza specifically identifies chirally-pure L-5-MTHF as an active metabolite of folate suitable for use as a therapeutic agent in folate deficient states." PTAB Op. at 23. The PTAB combines the Serfontein and Marazza references because "the *close similarity of purpose* and disclosure between these references would have provided sufficient rationale for one of ordinary skill in the art to have combined the teachings therein." PTAB Op. at 23. However, there is no suggestion to select and make such combination with a reasonable expectation of success in treating elevated homocysteine. The only source of this concept is hindsight reconstruction using the teachings of these inventors.

The Evidence does not Establish a Reasonable Likelihood of Success

My colleagues find that "the PTAB impliedly found a reasonable expectation of success," observing that the PTAB did not accept Merck's argument that the references "taught away" from Merck's use. It is undisputed that no reference taught Merck's use. There was evidence of instability and failures using the L-5-MTHF isomer in folate treatments. No reference contains a suggestion to use L-5-MTHF or expectation of success. Even Marazza states only that there was "an increasing interest" in L-5-MTHF. '611 Patent, col.1, l.25.

The Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007), in discussing the "obvious to try" standard of obviousness, cautioned that something would be "obvious to try" if "there are a finite number of identified, predictable solutions" with "anticipated success." "The obviousness inquiry entails consideration of whether a person of ordinary skill in the art 'would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so.'" *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (quoting *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)) (elisions in original). Here, the purported "reasonable expectation of success" came from the hindsight knowledge of these inventors' success.

The references are not uniform, as the panel majority acknowledges. Merck provided references showing that experiments administering L-5-MTHF to human subjects were abandoned or not conducted because the compound was too unstable. Merck also provided references describing experiments that show that 5-MTHF is not metabolized by hepatocytes grown in culture. Other references suggest that reduced folates such as L-5-MTHF are less

bioavailable than folic acid. PTAB Op. at 20. These references support the position that adverse effects, or no clear benefit, would reasonably be predicted for L-5-MTHF.

In contrast, Gnosis provided references suggesting that lower concentrations of reduced folates could produce the same intracellular concentrations as folic acid. PTAB Op. at 20-21. Whether or not these inconsistent teachings are viewed as "teaching away" they do not teach toward a reasonable likelihood of success. The panel majority errs in law, in stating that "the PTAB impliedly found a reasonable expectation of success" based on the PTAB's finding of no "teaching away." Such "implication" resides only in the backward-looking eye of the beholder.

Objective Indicia of Non-obviousness

Indicia such as commercial success "may often be the most probative and cogent evidence [of non-obviousness] in the record," *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) (modification in original) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). Such considerations are a foil to judicial hindsight. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075–76 (Fed. Cir. 2012) ("The objective considerations, when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias.").

Here there was a crowded field of science, and the response of the marketplace, in an area of recognized need, is evidence that the assertedly obvious discovery by these inventors was not obvious, for it eluded many scientists in the field.

My colleagues respond to Merck's evidence of commercial success, industry praise, copying, and licensing, by stating that "[e]ven when present, however, objective

indicia 'do not necessarily control the obviousness determination.'" Maj. Op. at 13. However, the law is not that the objective indicia must "control" the result, but that these indicia must be considered, for whatever weight the evidence warrants. The value and need for an invention, and failure of others to solve a known problem, is relevant evidence.

The PTAB discounted Merck's evidence of commercial success, observing that the commercial products contained vitamins in addition to L-5-MTHF. I doubt that this squabble is about the sale of vitamins; there is no suggestion, anywhere in the record before us, that these products were sold and purchased for any purpose other than for the L-5-MTHF to treat homocysteineurea, with or without beneficial B vitamins as in claim 22. *See In re GPAC*, 57 F.3d at 1580 (Fed. Cir. 1995) ("A prima facie case of nexus is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent."). Here there was no argument that consumers purchased the L-5-MTHF product to obtain other ingredients.

The panel majority acknowledges that "although another factfinder may have reasonably evaluated Merck's evidence of objective indicia of non-obviousness differently in the first instance, the Board's conclusion . . . is supported by substantial evidence." Maj. Op. at 17. This is another illustration of the flaw in this court's using the substantial evidence standard, for the question before us is whether the preponderance of the evidence supports the PTAB's decision.

CONCLUSION

The America Invents Act is a remedy for the present regime of uncertainty and unreliability of patents. Our obligation is to assure that the correct law is applied, that

the burdens are correctly placed, and that the statutory standard of proof is met.

The PTAB is not an examining body, but an adjudicatory body, an objective arbiter between opposing parties. On questions that are close, as here illustrated, the standard of review can affect the result. My colleagues err in applying deferential review, instead of assuring that the PTAB's factual findings are supported by the preponderance of the evidence, as the statue requires.

From the court's departure from the criteria of the America Invents Act, and from the incorrect result that ensues in this case, I respectfully dissent.