United States Court of Appeals for the Federal Circuit

NEPTUNE GENERICS, LLC, FRESENIUS KABI USA, LLC,
Appellants

v.

ELI LILLY & COMPANY,
Appellee

2018-1257, 2018-1258

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00237, IPR2016-00240, IPR2016-01190, IPR2016-01191, IPR2016-01335, IPR2016-01337, IPR2016-01341, IPR2016-01343.

MYLAN LABORATORIES LIMITED, FRESENIUS KABI USA, LLC,
Appellants

v.

ELI LILLY & COMPANY,
Appellee

2018-1288, 2018-1290

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00318, IPR2016-01340, IPR2016-01393, IPR2016-01429.

Decided: April 26, 2019

SARAH ELIZABETH SPIRES, Skiermont Derby LLP, Dallas, TX, argued for all appellants. Appellant Neptune Generics, LLC also represented by PAUL SKIERMONT; MIEKE K. MALMBERG, Los Angeles, CA; JOSHUA HARLAN HARRIS, Neptune Generics, LLC, Chicago, IL.

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ADAM LAWRENCE PERLMAN, Williams & Connolly LLP, Washington, DC, argued for appellee. Also represented by GALINA I. FOMENKOVA, DOV PHILIP GROSSMAN, DAVID M. KRINSKY, ANDREW P. LEMENS, CHARLES MCCLOUD; JAMES PATRICK LEEDS, Eli Lilly and Company, Indianapolis, IN.

Before MOORE, WALLACH, and HUGHES, *Circuit Judges.*

MOORE, *Circuit Judge*.

Neptune Generics, LLC, Fresenius Kabi USA, LLC, and Mylan Laboratories Ltd. ("Petitioners") appeal the Patent Trial and Appeals Board's inter partes review ("IPR") decisions holding Petitioners did not establish that claims 1–22 of U.S. Patent No. 7,772,209 are unpatentable for

obviousness. Because the Board did not err in its obviousness analysis, substantial evidence supports its underlying fact findings, and subject matter eligibility is not properly before the court in an appeal from an IPR decision, we affirm.

BACKGROUND

The '209 patent is owned by Eli Lilly & Co. and relates to administering folic acid and a methylmalonic acid ("MMA") lowering agent, such as vitamin B12, before administering pemetrexed disodium, a chemotherapy agent, in order to reduce the toxic effects of pemetrexed, an antifolate. '209 patent at 1:19–21, 57–61. Antifolates inhibit enzymes used in making the components of DNA and RNA, slowing the ability of cells to divide. *Id.* at 1:36–38. However, antifolates have toxic effects, which can be life threatening. *E.g.*, *id.* at 1:11–12; 1:62–2:4.

The two independent claims in the patent are method of treatment claims. They recite:

> 1. A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium, wherein
>
> > the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.
>
> 12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

> a) administration of between about 350 µg and about 1000 µg of folic acid prior to the first administration of pemetrexed disodium;
>
> b) administration of about 500 µg to about 1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and
>
> c) administration of pemetrexed disodium.

The Board considered three petitions for IPR, each of which alleged the claims would have been obvious. In IPR2016-00318, Petitioners alleged claims 1–22 would have been obvious over a 1999 article by Hilary Calvert, titled "An Overview of Folate Metabolism: Features Relevant to the Actions and Toxicities of Antifolate Anticancer Agents"; a 1998 abstract by C. Niyikiza, et. al., titled "MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity" ("Niyikiza I"); a 1998 article by John F. Worzalla, et al., titled "Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514"; European Patent Application 0 595 005 A1 ("EP005"); and U.S. Patent No. 5,217,974. In IPR2016-00237, Petitioner alleged the claims would have been obvious over Niyikiza I, the '974 patent, and EP005. In IPR2016-00240, Petitioners alleged the claims would have been obvious over a 1999 article by James J. Rusthoven, et al., titled "Multitargeted Antifolate LY231514 As First-Line Chemotherapy for Patients with Advanced Non-Small-Cell Lung Cancer: A Phase II Study," and EP005.

The Board concluded in each case that the claims were not established to be unpatentable for obviousness. It found that it was known in the prior art that pretreatment with folic acid reduces the toxicity associated with administration of an antifolate, like pemetrexed, but there was not a reason to pretreat with vitamin B12 along with folic

acid before administering pemetrexed to treat cancer. It also found that the skepticism of others, particularly the FDA, supported a conclusion of nonobviousness. Because the Board concluded the independent claims would not have been obvious, it did not consider the additional limitations of the dependent claims.

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

DISCUSSION

We review the Board's legal determinations de novo and its underlying factual findings for substantial evidence. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Obviousness is a question of law based on underlying facts. *Id.* Motivation to combine is a question of fact. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016).

On appeal, the parties focus on three references: Niyikiza I, EP005, and another abstract by C. Niyikiza, et al., titled "Relationship of Vitamin Metabolite Profile to Toxicity," ("Niyikiza II"). The lead author on Niyikiza I and II is also the sole named inventor of the '209 patent.

Pretreatment with Vitamin B12

The Board found that that a skilled artisan would not have been motivated to administer an MMA lowering agent, such as vitamin B12, in addition to folic acid. On appeal, Petitioners argue that in making this finding, the Board did not consider EP005 for all that it teaches. Specifically, Petitioners point to EP005's disclosure of the administration of folic acid and vitamin B12 to lower homocysteine levels for all purposes. We disagree and hold that substantial evidence supports the Board's findings.

The Board's findings are based on the prior art's disclosure of the relationships between various biochemicals and toxicity. The Board found that deficiencies in both vitamin

B12 and folate can lead to elevated levels of the biomarker homocysteine. In contrast, it found that elevated levels of MMA are correlated only with vitamin B12 deficiencies and not folate deficiencies. J.A. 61. Therefore, in patients with a vitamin B12 deficiency, but not a folate deficiency, both MMA levels and homocysteine levels would be elevated, while in patients with just a folate deficiency homocysteine levels would be elevated, but MMA levels would not be elevated. The Board further found that while elevated levels of homocysteine were known to be predictive of pemetrexed toxicity, elevated levels of MMA were understood to not be a predictor of pemetrexed toxicity. Because elevated MMA levels are not predictive of toxicity, but do correlate with vitamin B12 deficiency, the Board credited the testimony of Lilly's expert Dr. Bruce Chabner that a skilled artisan would have understood that there was no observed correlation between vitamin B12 deficiency and pemetrexed-induced toxicity. J.A. 62–63.

Each step of the Board's analysis is supported by substantial evidence. In finding that elevated MMA levels correlated with vitamin B12 deficiency but not folate deficiency, the Board considered the disclosures in a prior art article by David G. Savage, et al., which found that in patients with vitamin B12 deficiency 94.8% of MMA levels and 95.9% of homocysteine levels were elevated, but in patients with folate deficiencies, only 12.2% of MMA levels were elevated while 91% of homocysteine levels were. J.A. 61 (citing J.A. 7698). These findings are further supported by additional prior art and are consistent with the testimony of Petitioner's expert Dr. Ron Schiff. J.A. 60–61 (citing J.A. 4404).

The Board's finding that while elevated levels of homocysteine were known to be predictive of pemetrexed toxicity, elevated levels of MMA were understood to not be a predictor of pemetrexed toxicity is also supported by substantial evidence. Niyikiza I discloses that elevated levels of homocysteine are predictive of pemetrexed toxicity,

J.A. 4148, and the Board credited Dr. Chabner's testimony that a skilled artisan would have read Niyikiza II to mean that elevated MMA levels were not a predictor of pemetrexed-induced toxicity, J.A. 62–63 (citing J.A. 9084). The Board further credited Dr. Chabner's testimony that given the link between vitamin B12 deficiency and elevated MMA levels, and the lack of a correlation between elevated MMA levels and pemetrexed-induced toxicity, a skilled artisan would have understood "there was no correlation observed between vitamin B12 deficiency and pemetrexed-induced toxicity." J.A. 62 (quoting J.A. 9084). Because vitamin B12 deficiencies are linked to both elevated levels of MMA and homocysteine, the mere fact that homocysteine is correlated with toxicity does not mean that vitamin B12 levels are linked with toxicity. In short, this evidence indicates that pemetrexed-inducted toxicity correlated with folate deficiencies, but not vitamin B12 deficiencies.

Collectively, this constitutes substantial evidence in support of the Board's finding that the art did not provide a motivation for a skilled artisan to administer an MMA lowering agent, such as vitamin B12, in addition to folic acid. In contrast, the Board found that there would have been a motivation to pretreat with folate, which was a known way to reduce the toxicity associated with administration of an antifolate, like pemetrexed. J.A. 50.

Petitioners argue that EP005 teaches the administration of folic acid and vitamin B12 to lower homocysteine levels for all purposes. Therefore, they argue, a skilled artisan would have been motivated to pretreat with vitamin B12. This is, at heart, a challenge to the Board's factual findings, and the Board's position is supported by substantial evidence. Admittedly, EP005 states that it "is applicable to the lowering of total homocysteine blood levels if elevated by any known cause." J.A. 4409. However, as the Board found, EP005 is concerned with the cardiovascular effects associated with elevated homocysteine levels, does not discuss antifolates generally, and only generally

mentions certain cancers. J.A. 67 (citing J.A. 4407). Moreover, the Board found that the levels of homocysteine associated with elevated pemetrexed toxicity risk were not "elevated" as that term is defined in EP005. J.A. 68–69. This is consistent with the plain language of EP005 and the testimony of Dr. Schiff. J.A. 4417, 7308–09. Likewise, while EP005 also states that methotrexate, an antifolate drug like pemetrexed, "induce[s] elevated homocysteine levels," J.A. 4409, the Board noted that, in contrast, Niyikiza II explained that pemetrexed did not increase homocysteine levels, J.A. 67, 4148. Given the contrast between the specific, directly applicable teachings of Niyikiza II and the tangential, general statements of EP005, substantial evidence supports the Board's finding that EP005 did not provide information as to how pretreatment with folic acid and vitamin B12 would impact toxicity effects. J.A. 69.

Petitioners attempt to evade the substantial evidence standard of review by manufacturing legal error. Among other things, they argue the Board legally erred in its treatment of EP005 and in requiring the art to directly link vitamin B12 deficiency with pemetrexed toxicity. The Board extensively discussed EP005 both individually and in the context of the prior art, and we see no error in its analysis. Likewise, we see nothing in the Board's opinion that required the art directly link vitamin B12 deficiency with pemetrexed toxicity.

Lilly's Statements to the FDA

During clinical trials of pemetrexed, Lilly engaged in various communications with the FDA. Petitioners argue that the Board erred in not considering these statements and precluding Lilly from taking contrary positions in the IPR. In particular, they argue that in its communications with the FDA, Lilly "inform[ed] the FDA that the prior art suggested that pretreating with folic acid and B12 was a no-risk, predictable way to lower pemetrexed-induced fatalities by lowering pretreatment homocysteine levels."

Appellants' Br. 33. It argues that even if these communications are not in the prior art, they reflect the background knowledge of a skilled artisan and are indicators of the level of ordinary skill in the art.

The level of skill in the art and the scope and content of the prior art are fact questions we review for substantial evidence. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1358 (Fed. Cir. 2017). While, a patent owner's own disclosures to the FDA may be considered in assessing the state of the prior art, *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1030 (Fed. Cir. 2018), a fact finder must not allow its analysis to be distorted by hindsight bias, *KSR Int'l Co. v. Teleflex*, 550 U.S. 398, 421 (2007).

Here, the statements Petitioners argue established the state of the art were made in December 1999, more than five months after the critical date. As the Board found, the views Lilly expressed about the prior art references in its communications are made through the lens of what they had invented. J.A. 81. Therefore, it declined to read the other prior art references in view of these communications. In doing so, the Board did not err.

Skepticism

Evidence of industry skepticism is a question of fact that weighs in favor of non-obviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016). The Board found that evidence of skepticism of others, particularly the FDA, supported a conclusion of nonobviousness. J.A. 87. During Lilly's clinical trials for pemetrexed, a number of fatalities occurred. In response, Lilly recommended supplementation with folic acid and vitamin B12. The FDA responded that the "medical officer does not support adding vitamins to the ongoing . . . trial." J.A. 8748 (capitalization changed). In other communications with Lilly it stated that the information provided to it "does not

appear to support the addition of vitamins," J.A. 8750, and "the addition of vitamins . . . is risky," J.A. 8687.

Petitioners argue that the Board legally erred in holding this evidence sufficient to support a finding of skepticism because, despite the FDA's concerns, it allowed the trial to continue. It argues skepticism must be premised on whether it is "technically infeasible," "unworkable," or "impossible" that the claimed subject matter would work for its intended purpose. Appellants' Br. 51. This position is not consistent with our caselaw, which recognizes a range of third-party opinion that can constitute skepticism. *See, e.g.*, *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1337 (Fed. Cir. 2015) (holding testimony that third parties were "worried" or "surprised" was sufficient to establish skepticism). The FDA's concerns in this case fall well within that range. While evidence that third parties thought the invention was impossible might be entitled to *more* weight, that does not mean the Board erred in giving weight to the skepticism evidence here. Accordingly, the Board did not err in finding that skepticism supported a conclusion of nonobviousness.

Dependent Claims

Petitioners argue the nonobviousness determination should be reversed for the dependent claims as well. Given our affirmance as to the independent claims, we likewise affirm as to the dependent claims.

Patent Eligibility

Finally, Petitioners argue the claims are not directed to patentable subject matter. It argues this issue is properly raised because eligibility is a question of law and in this appeal there are no factual issues that must be decided. We do not agree. Congress expressly limited the scope of inter partes review to a subset of grounds that can be raised under 35 U.S.C. §§ 102 & 103. 35 U.S.C. § 311(b) (stating that in an "inter partes review," a petitioner is

limited to only grounds that "could be raised under section 102 or 103"). The ground of patent eligibility arises under § 101. Accordingly, we may not address it on appeal of an IPR.

CONCLUSION

We have considered Petitioners' remaining arguments and find them unpersuasive. Accordingly, we affirm.

AFFIRMED