NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

IN RE: MERCK & CIE,
Appellant

2017-1960

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. 12/688,034.

Decided: April 11, 2018

CSABA HENTER, Millen, White, Zelano & Branigan PC, Arlington, VA, argued for appellant. Also represented by RYAN POOL.

KAKOLI CAPRIHAN, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, argued for appellee Andrei Iancu. Also represented by NATHAN K. KELLEY, THOMAS W. KRAUSE, LORE A. UNT.

Before O'MALLEY, MAYER, and TARANTO, *Circuit Judges*.

TARANTO, *Circuit Judge*.

The Patent Trial and Appeal Board, affirming the examiner, rejected, as unpatentable for obviousness, certain

claims of U.S. Patent Application No. 12/688,034, titled "Use of Folates for the Prevention and Treatment of Vascular Diseases." Merck & Cie is the real party in interest in the prosecution of this patent. The application describes and claims the use of folates to improve dilation of blood vessels—specifically, nitric oxide (NO) mediated endothelial dependent vasomotor responses. As the matter was presented to the Board and is presented to us, claim 35 is representative. It reads:

> 35. A method for improving NO-mediated endothelial-dependent vasomotor responses consisting of:
>
> administering to a subject with a cardiovascular disease an effective amount of a pharmaceutical composition consisting of a pharmaceutically active agent suitable for improving NO-mediated endothelial-dependent vasomotor responses and one or more pharmaceutically acceptable carriers,
>
> wherein the pharmaceutically active agent consists of one or more folates or a pharmaceutically acceptable salt or ester thereof,
>
> and wherein said effective amount of the pharmaceutical composition achieves improvement of the NO-mediated endothelial-dependent vasomotor responses.

The Board concluded, and it is undisputed before us, that the restrictive "consists of" language limits the claim to administering one or more folates (or salt or ester) alone—"folate alone," as a shorthand—not in combination with any other substance related to NO-mediated endothelial-dependent vasomotor responses, though a combination with drugs unrelated to such responses is not excluded. *Ex parte Antoniades*, Appeal 2016-003411, at 7–8 (P.T.A.B. Feb. 28, 2017) (*Decision*).

The Board's decision in this matter rested entirely on the van Etten prior art: R.W. van Etten et al., "Impaired

NO-dependent vasodilation in patients with Type II (non-insulin-dependent) diabetes mellitus is restored by acute administration of folate," 45 Diabetologia 1004–1010 (2002). The article first notes that the authors "recently showed that folate reverses eNOS [endothelial nitric oxide synthase] uncoupling in vitro" and on that basis the authors hypothesized "that folate improves endothelial function in Type II (non-insulin dependent) diabetes mellitus in vivo." *Id.* at 1004. The article then reports the results of a study the authors conducted to test the hypothesis.

The study involved testing the effect of "5-methyltetrahydrofolate (5-MTHF, the active form of folic acid)" on forearm blood flow in twenty-three patients with Type II diabetes (some given 5-MTHF, some not) and twenty-one control (no diabetes, no 5-MTHF) subjects. *Id.* at 1004, 1007. The ratio of blood flow in the infused (measurement) arm to blood flow in the other (control) arm—the M:C ratio—was recorded in two tests. *Id.* at 1006–07. In one, all subjects were infused with serotonin (a stimulator of vasodilation dependent on nitric oxide); in the other, all subjects were infused with sodium nitroprusside (a stimulator of "endothelium-independent vasodilation"). *Id.*

Figures 1 and 2 of the article show the test results for the three subgroups ("control"; "diabetes"; "diabetes+MTHF"—as the article labels them):

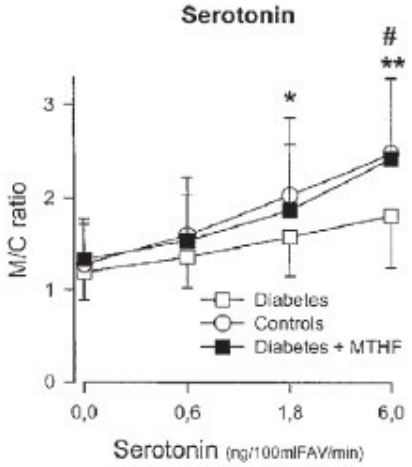

Fig. 1. Change in M:C ratio after stimulation of NO-mediated, endothelium-dependent vasodilation with serotonin. NO-dependent vasodilation is impaired in patients with Type II diabetes (□) compared with matched control subjects (○) (*p<0.01, **p<0.005). 5-MTHF normalised NO-mediated vasodilation in patients with Type II diabetes (■) (#p<0.05)

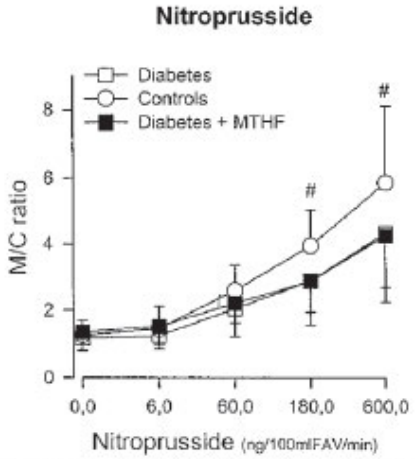

Fig. 2. Change in M:C ratio after stimulation of endothelium-independent vasodilation by sodium nitroprusside. Endothelium-independent vasodilation is modestly reduced in patients with Type II diabetes (□) compared with matched control subjects (●). (#p<0.05). 5-MTHF has no effect on endothelium-independent vasodilation in patients with Type II diabetes (■)

The figures reveal the following. *First*: in both tests, as the non-folate external stimulator (serotonin, nitroprusside) increased from zero to various higher levels, so did the M:C ratio, for all three subgroups. *Second*: in both tests, the M:C ratio for all three subgroups was essentially the same when there was no external stimulator. *Third*: in the serotonin test, the diabetes+MTHF subgroup showed M:C ratios, as the level of serotonin administered rose, very close to the M:C ratios of the control group, noticeably higher than those of the diabetes (no MTHF) subgroup. *Fourth*: in the nitroprusside test, the diabetes+MTHF subgroup showed M:C ratios, as the level of nitroprusside administered rose, very close to the M:C ratios of the diabetes (no MTHF) subgroup, noticeably lower than those of the control group. *Id.*

The article contains a number of observations of significance to the present case. (All emphases in the following quotes have been added.) *"[A]melioration of eNOS function also can be achieved by using folic acid*. The active form of folic acid, 5-methyltetrahydrofolate (5-MTHF), restores the function of uncoupled eNOS." *Id.* at 1005. "*If folate is capable of restoring the endothelial dysfunction*, commonly encountered in diabetic patients, this could have important clinical implications because endothelial dysfunction is associated with increased cardiovascular risk." *Id.* "[I]n patients with Type II diabetes, administration of 5-MTHF, the active form of folic acid, restores endothelial dysfunction as measured by serotonin-induced vasodilation. In addition to serotonin-induced vasodilation, also nitroprusside-induced vasodilation was impaired in patients with Type II diabetes. Nitroprusside-induced vasodilation, however, was not affected by 5-MTHF infusion. *These data indicate an important role of 5-MTHF on endogenous NO-availability and could support previous studies suggesting a direct beneficial effect of 5-MTHF on NO-synthase function*." *Id.* at 1007. "[The study] showed that *5-MTHF administra-*

tion restores impaired NO-mediated vasodilation in patients with Type II diabetes despite the presence of several diabetes-related risk factors such as hyperglycaemia, dyslipidaemia and hypertension." *Id.* at 1008. "*The ameliorative effect of 5-MTHF seems to be specific for endothelium-derived NO*, because an improvement could not be observed for endothelium-independent NO-mediated vasodilation." *Id.* The "conclusion/interpretation" of van Etten states:

> These data imply that *folate can be used to improve nitric oxide status and to restore endothelial dysfunction in patients with Type II diabetes*. Our results provide *a strong rationale for the initiation of studies that investigate whether supplementation with folic acid prevents future cardiovascular events in this patient group*.

Id. at 1004; *see also id.* at 1008 ("Our results provide a strong rationale for the initiation of studies that investigate whether in this patient group supplementation with folic acid, a safe, readily available, not expensive and well-tolerated drug, prevents future cardiovascular events.").

The Board concluded that the method of claim 35 would have been obvious to a person of ordinary skill in the art in light of van Etten. *Decision* at 5–6. The Board, affirming the examiner, found that van Etten supplied a motivation to use folate alone, as claim 35 requires, with a reasonable expectation of success. *Id.* at 5. It rejected Merck's contentions that van Etten did not supply to a relevant skilled artisan a motivation to use folate alone or a reasonable expectation of success but, to the contrary, taught away from such use. *Id.* at 5–6. These elements of the obviousness analysis, and what van Etten teaches, all present issues of fact, with the Board's findings on those issues reviewed only for substantial evidence. *See*, *e.g.*, *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186,

1196–97 (Fed. Cir. 2014); *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000); *Para-Ordnance Mfg., Inc. v. SGS Importers Int'l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995).

Merck's challenge ultimately rests on its contention that the Board's reading of van Etten, on which the Board's findings of fact rest, is simply unreasonable and therefore unsupported by substantial evidence. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1061 (Fed. Cir. 2016) ("Substantial evidence 'means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.'") (quoting *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938)). This standard does not require the Board's reading of van Etten to be the only reasonable one for us to uphold it. "[T]he possibility of drawing two inconsistent conclusions from the evidence does not prevent an administrative agency's finding from being supported by substantial evidence." *Consolo v. Fed. Maritime Comm'n*, 383 U.S. 607, 620 (1966); *see In re Jolley*, 308 F.3d 1317, 1320 (Fed. Cir. 2002) ("If the evidence in record will support several reasonable but contradictory conclusions, we will not find the Board's decision unsupported by substantial evidence simply because the Board chose one conclusion over another plausible alternative."); *AK Steel Corp. v. United States*, 192 F.3d 1367, 1371 (Fed. Cir. 1999).

At its core, Merck's challenge relies on the *Second* and *Fourth* aspects of the van Etten study, described above: that the only subgroup given MTHF had essentially the same M:C ratio in both tests at the zero level of the non-folate external stimulator; and that, in the nitroprusside test, the M:C ratios were essentially the same for the diabetes+MTHF subgroup and the diabetes (no MTHF) subgroup. Merck contends that those facts would give rise to only one possible understanding to a skilled artisan, namely, that folate alone would have no beneficial effect of the type at issue, but requires a combination with serotonin or another substance that improves dilation

response. As a result, Merck says, the Board was required to find no motivation to use folate alone and no reasonable expectation of success in doing so and, even, to find a teaching away from the claim 35 method.

We need not and do not decide whether Merck's view of what van Etten teaches is the better view. We conclude only that Merck's view is not the only reasonable view. Above we italicized excerpts from van Etten that support the key findings of the Board. Those excerpts are reasonably capable of being read as conveying sufficiently positive implications about the use of folate *alone*—without also administering other substances, like serotonin, related to NO-mediated endothelial-dependent vasomotor responses—that they would provide a relevant skilled artisan a motivation to do what claim 35 requires with a reasonable expectation of success and not leave the artisan discouraged from doing so by the article as a whole within the meaning of the "teaching away" principle. *See*, *e.g.*, *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009).

For that reason, and having considered all of Merck's arguments, we affirm the Board's decision.

No costs.

AFFIRMED