

# United States Court of Appeals for the Federal Circuit

---

IN RE: JOHN L. COUVARAS,  
*Appellant*

---

2022-1489

---

Appeal from the United States Patent and Trademark  
Office, Patent Trial and Appeal Board in No. 15/131,442.

---

Decided: June 14, 2023

---

LAURENCE M. SANDELL, Mei & Mark LLP, Washington,  
DC, argued for appellant John L. Couvaras. Also repre-  
sented by GUANG-YU ZHU.

MAUREEN DONOVAN QUELER, Office of the Solicitor,  
United States Patent and Trademark Office, Alexandria,  
VA, argued for appellee Katherine K. Vidal. Also repre-  
sented by KAKOLI CAPRIHAN, THOMAS W. KRAUSE, AMY J.  
NELSON, FARHEENA YASMEEN RASHEED.

---

Before LOURIE, DYK, and STOLL, *Circuit Judges*.

LOURIE, *Circuit Judge*.

John L. Couvaras appeals from a decision of the U.S.  
Patent and Trademark Office Patent Trial and Appeal  
Board (“the Board”) affirming an Examiner’s rejection of  
the pending claims of U.S. Patent Application 15/131,442

as unpatentable as obvious in view of the asserted prior art. *In re: John L. Couvaras*, No. 2022-001037, 2021 WL 6124743 (P.T.A.B. Dec. 24, 2021) (“*Decision*”). For the following reasons, we affirm.

#### BACKGROUND

The pending claims of the ’422 application literally recite methods of increasing prostacyclin release in the systemic blood vessels of a human with essential hypertension to improve vasodilation. That increased prostacyclin release is achieved by co-administering two well-known types of antihypertensive agents: a GABA-a agonist and an Angiotensin II Receptor Blocker (“ARB”). In reality, the claims relate to combatting hypertension with known antihypertensive agents and claiming their previously unappreciated mechanism of action.

Representative claim 11 is presented below:

11. A method of increasing prostacyclin release in systemic blood vessels of a human individual with essential hypertension to improve vasodilation, the method comprising the steps of:

providing a human individual expressing GABA-a receptors in systemic blood vessels due to essential hypertension;

providing a composition of a dosage of a GABA-a agonist and a dosage of an ARB combined into a deliverable form, the ARB being an Angiotensin II, type 1 receptor antagonist;

delivering the composition to the human individual’s circulatory system by co-administering the dosage of a GABA-a agonist and the dosage of the ARB to the human individual orally or via IV;

synergistically promoting increased release of

IN RE: COUVARAS

3

prostacyclin by blockading angiotensin II in the human individual through the action of the dosage of the ARB to reduce GABA-a receptor inhibition due to angiotensin II presence during a period of time, and

activating the uninhibited GABA-a receptors through the action of the GABA-a agonist during the period of time; and

relaxing smooth muscle of the systemic blood vessels as a result of increased prostacyclin release.

J.A. at 981–82 (emphases added). Other independent claims recite similar methods but state that the GABA-a receptors are expressed in smooth muscle and the endothelium. *Id.* at 984–85. Dependent claims include limitations drawn to dosing amounts and time-release formulations, and those drawn to relaxing smooth muscle through increased prostacyclin release as well as reducing blood pressure due to said relaxation. *Id.* at 982–87. All of the claims stand or fall based on the arguments presented and evaluated here.

During prosecution, Couvaras conceded that GABA-a agonists and ARBs “have been known as essential hypertension treatments for many, many decades.” J.A. at 998. The Examiner agreed, citing ten references establishing that GABA-a agonists and ARBs lower blood pressure, and thereby treat hypertension. The Examiner also found that the claimed results of the compounds’ administration (*i.e.*, increased prostacyclin release, activation of uninhibited GABA-a receptors, and smooth muscle relaxation) were not patentable because they naturally flowed from the claimed administration of the known antihypertensive agents. *Id.* at 1011–18.

Couvaras appealed to the Board, asserting that the prostacyclin increase was unexpected, and therefore

should be patentable. Couvaras also asserted that *objective indicia* overcame any existing prima facie case of obviousness. Unpersuaded, the Board affirmed the rejection. *Decision* at \*9. In particular, the Board held that the claimed result of an increased prostacyclin release was inherent in the obvious administration of the two known antihypertension agents. *Id.* at \*3–4, \*7. The Board also found that Couvaras’s *objective indicia* arguments did not overcome the prima facie case of obviousness, namely, because no evidence existed to support a finding of any *objective indicium*. *Id.* at \*4–9.

Couvaras appealed the Board’s decision. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. § 141(a).

#### DISCUSSION

We review the Board’s legal determinations *de novo*, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), and the Board’s factual findings for substantial evidence, *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). A finding is supported by substantial evidence if a reasonable mind might accept the evidence as adequate to support the finding. *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938).

Couvaras raises several issues on appeal. First, Couvaras contends that the Board erred in affirming that a skilled artisan would have had a motivation to combine the art asserted by the Examiner. Second, Couvaras contends that the claimed mechanism of action was unexpected, and that the Board erred in discounting its patentable weight by deeming it simply inherent in the claimed method. Third, Couvaras contends that the Board erred in weighing *objective indicia* of nonobviousness. We address these

arguments in turn.<sup>1</sup>

## I

Couvaras contends that the Board erred in affirming that a skilled artisan would have had a motivation to combine the prior art as asserted by the Examiner. Couvaras also asserts that the Board failed to address whether or not a skilled artisan would have had a reasonable expectation of success.

As explained by the Examiner and affirmed by the Board, “[i]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose.” *Decision* at \*3 (quoting *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980)). Couvaras does not challenge that the two types of active agents recited in the claims, GABA-a agonists and ARBs, were known. *See, e.g.*, Appellant’s Br. at 9 (“The use of ARBs has been known for more than 30 years.”); *id.* at 4 (“GABA has been known for more than 65 years”); *see also* Oral Arg. at 13:27–13:40, [https://oralarguments.cafc.uscourts.gov/default.aspx?fl=22-1489\\_05032023.mp3](https://oralarguments.cafc.uscourts.gov/default.aspx?fl=22-1489_05032023.mp3) (referring to GABA-a agonists and ARBs as “super well-known compounds”). Nor does Couvaras challenge that GABA-a agonists and ARBs were known to be useful for the same purpose—alleviating hypertension. *See, e.g.*, Appellant’s Br. at 8 (conceding the “undisputed, basic proposition that GABA agonists are effective in treating hypertension in both animals and humans” and that “[t]here is no dispute that such uses of GABA have been known for 65

---

<sup>1</sup> Couvaras also asserted that the Board violated the Administrative Procedure Act by relying on an obviousness rationale that was disavowed by the Examiner. Couvaras has since withdrawn this issue on appeal; thus, we need not address it here. *See* Appellant’s Reply Br. at 4 n.2.

years”); *id.* at 8–9 (conceding the “undisputed, basic proposition that oral administration of ARBs are known to treat hypertension” and that “[t]here is no dispute that ARBs have been known and used for such purposes for more than 30 years”). The Board was correct that this fact alone can serve as a motivation to combine because “the idea of combining [these compounds] flows logically from their having been individually taught in the prior art.” *Kerkhoven*, 626 F.2d at 850.

Couvaras suggests that this reasoning is too generic to support finding a motivation to combine in the clinical context under *Cardiac Pacemakers v. St. Jude Medical*, 381 F.3d 1371 (Fed. Cir. 2004). We do not agree. In *Cardiac Pacemakers*, it was undisputed that, before the work of the inventor, there was no device capable of treating the conditions of interest. Here, however, the opposite is true. It is undisputed that, before the work of Couvaras, the antihypertensive agents recited in the claims existed and were known to treat hypertension.

Couvaras further concedes that the prior art teaches the combination of ARBs with other antihypertensive agents to improve treatment. Appellant’s Br. at 16. In particular, the Board took note of the Examiner’s reliance on the prior art Kjeldsen<sup>2</sup> reference, which teaches not only the use of ARBs “in combination with other classes of antihypertensive agents to lower blood pressure,” but also that various guidelines “acknowledge the need for multiple-drug therapy in many patients to adequately lower blood pressure.” *Decision* at \*3; J.A. at 1473. The motivation to combine was thus not a general motivation to cure

---

<sup>2</sup> S.E. Kjeldsen et al., *Targeting the renin-angiotensin system for the reduction of cardiovascular outcomes in hypertension: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers*, 10 EXPERT OP. EMERGING DRUGS, 729 (2005); J.A. at 1472–89.

IN RE: COUVARAS

7

hypertension, but, rather, the motivation to create a particular cure by co-administering ARBs with another class of known antihypertensive agents as instructed by Kjeldsen.

Couvaras further asserts that, even if there had been a motivation to co-administer two hypertension treatments, such a motivation would fail to identify a “finite number of identified, predictable solutions” as required by *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007). See Appellant’s Br. at 29 n.12. We do not agree. First, Couvaras makes this argument in a footnote, and “[a]rguments raised only in footnotes [] are waived.” *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1294 (Fed. Cir. 2012). Second, while Couvaras argues that there was a “substantial number of hypertension treatment agent classes” that could be considered for such a combination, he does not cite any evidence supporting this assertion. The Board’s conclusion that there was a motivation to combine, on the other hand, was supported by substantial evidence and properly aligns with the tenets of *KSR*.

Finally, Couvaras asserts that the Board erred in failing to address reasonable expectation of success. Appellant’s Br. at 25–29. But Couvaras did not present any arguments against the Examiner’s findings of a reasonable expectation of success when he appealed the Examiner’s Final Rejection to the Board. See J.A. at 1139–76. Absent exceptional circumstances, see *In re DBC*, 545 F.3d 1373, 1379–80 (Fed. Cir. 2008), we generally do not consider arguments that the applicant failed to present to the Board, *In re Watts*, 354 F.3d 1362, 1367–68 (Fed. Cir. 2004). Here, no such exceptional circumstances exist. It was not an error for the Board to fail to make express findings regarding that prong of the obviousness analysis.

## II

Couvaras next asserts that the Board downgraded the patentable weight of limitations drawn to the

antihypertensive agents' mechanism of action by deeming them to be merely inherent. According to Couvaras, even if the recited mechanism of action is, effectively, inherent in the claimed administration of a GABA-a agonist and an ARB, that mechanism, specifically the increased release of prostacyclin, was unexpected. Couvaras contends that because the increased prostacyclin release was unexpected, under *Honeywell International Inc. v. Mexichem Amanco Holdings S.A.*, it cannot be dismissed as having no patentable weight due to inherency. 865 F.3d 1348, 1355 (Fed. Cir. 2017). But *Honeywell* held that “unexpected properties may cause what may appear to be an obvious composition to be nonobvious,” not that unexpected mechanisms of action must be found to make the known use of known compounds nonobvious. *Id.* (emphasis added).

Here, Couvaras attempts to claim a mechanism of action that naturally flows from the co-administration of two known antihypertensive agents. See Oral Arg. at 03:18–03:39 (acknowledging that Appellant has not argued “specifically against that,” *i.e.*, that the claimed co-administration will result in the claimed mechanism of action); *id.* at 03:56–04:06 (answering a question as to whether or not Appellant agrees that the claimed steps are “necessarily” the mechanism by stating “Yeah, this is the mechanism by which it works”). In the prostacyclin mechanism, the two antihypertension agents exert the same ultimate result as the two separate compounds were known to effect: a decrease in blood pressure. We have previously held that “[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.” *In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012) (citation omitted); see also *In re Huai-Hung Kao*, 639 F.3d 1057, 1070–71 (Fed. Cir. 2011) (holding that a “food effect” was obvious because the effect was an inherent property of the composition). While mechanisms of action may not always meet the most rigid standards for inherency, they are still simply results that naturally flow from



IN RE: COUVARAS

9

the administration of a given compound or mixture of compounds. Reciting the mechanism for known compounds to yield a known result cannot overcome a prima facie case of obviousness, even if the nature of that mechanism is unexpected.

We therefore agree with the Board that the recitation of various mechanistic steps in the pending claims are insufficient to overcome the prima facie obviousness of the claimed methods.

### III

Lastly, Couvaras contends that the Board erred in weighing *objective indicia* of nonobviousness. The Board's findings regarding *objective indicia* involve questions of fact that we review for substantial evidence. *Gartside*, 203 F.3d at 1316.

Couvaras contends that the Board found that the “main, beneficial, medical result” of the claimed invention, namely, an increase in prostacyclin, was “unexpected.” See *Decision* at \*7 (holding, at least, that Couvaras had asserted this to be the case). According to Couvaras, the Board erred by nonetheless giving no weight to the unexpected results *indicium* of nonobviousness. But, as discussed above, recitation of a mechanism of action, even an unexpected one, does not necessarily overcome a prima facie case of obviousness. To establish unexpected results, Couvaras would have needed to show that the co-administration of a GABA-a agonist and an ARB provided an unexpected benefit, such as, *e.g.*, better control of hypertension, less toxicity to patients, or the ability to use surprisingly low dosages. We agree with the Board that no such benefits have been shown, and therefore no evidence of unexpected results exist.

Couvaras also asserts various other errors in identifying and weighing additional *indicia* of nonobviousness, including teaching away, failure of others, and the length of

time that elapsed between the initial discovery of GABA-a agonists and ARBs being useful in treating hypertension and Couvaras's claimed method of co-administering these types of compounds. For example, Couvaras asserts that the prior art, in particular, Liu<sup>3</sup>, teaches away from the combined administration recited in the claims. As explained by Couvaras, Liu purportedly includes data that show a lesser reduction in blood pressure following co-administration of an ACE inhibitor with  $\gamma$ -aminobutyric acid (GABA), a GABA-a agonist, compared to administration of an ACE inhibitor alone after 24 hours. Appellant's Br. at 49–50 (citing J.A. at 1198, ¶7.f.ii-iii). But that is insufficient to establish a teaching away. As the Board correctly noted, Liu evaluated ACE inhibitors co-administered with GABA in rats, not ARBs co-administered with GABA-a agonists in humans, as claimed. Even Couvaras admits that ACE inhibitors and ARBs “operate through different biological mechanisms.” Appellant's Br. at 48. The Board was therefore correct to find that Liu did not teach away from the claimed method.

Similarly, Couvaras asserts that there was a failure of others to increase prostacyclin release, but the evidence that Couvaras cites involves merely “experimenting with angiotensin II levels.” Appellant's Br. at 52. As the Board correctly noted, however, an investigation into the impact of angiotensin II is not a failure to find a solution for an inability to increase prostacyclin release or a failure of the claimed method. *Decision* at \*8–9. The Board thus properly found that the purported failure to achieve prostacyclin increase through pursuing an unrelated goal did not establish the nonobviousness of this claimed method.

---

<sup>3</sup> C.F. Liu et al., *Antihypertensive Effects of Lactobacillus-Fermented Milk Orally Administered to Spontaneously Hypertensive Rats*, 59 J. AGRIC. FOOD CHEM. 4537 (2011); J.A. at 1490–96.

IN RE: COUVARAS

11

Couvaras also asserts that the length of time between when the two antihypertensive classes of compounds recited in the claims were first discovered and when Couvaras first thought to combine them also serves as an *objective indicium* of the claims' nonobviousness under *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013). We disagree. In *Leo Pharmaceutical*, we held that the "length of the intervening time between the publication dates of the prior art and the claimed invention can also qualify as an objective indicator of nonobviousness." *Id.* at 1359 (emphasis added). However, that followed from a finding that the record established evidence of a long-felt but unsolved need and failure of others.

Here, such *indicia* of nonobviousness do not exist. Rather, as the Board correctly held, there was no long-felt, unmet need, given the admitted availability of antihypertensive agents and a lack of evidence that the available antihypertensive treatments were somehow insufficient to meet patients' needs. *Decision* at \*5. As discussed above, there is also insufficient evidence to establish a failure of others. The Board was therefore correct to note that the mere length of time that the prior art knew GABA-a agonists and ARBs to be antihypertensive agents "is not persuasive of the unobviousness of the combination of their teachings, absent evidence that, notwithstanding knowledge of the references, the art tried and failed to solve the problem." *Decision* at \*4 (quoting *In re Wright*, 569 F.2d 1124, 1127 (CCPA 1977)). As no such evidence of failure exists here, the Board's conclusion that *objective indicia* did not overcome the prima facie case of obviousness was supported by substantial evidence.

#### CONCLUSION

We have considered Couvaras's remaining arguments and do not find them persuasive. For the foregoing reasons, we affirm the Board's final written decision.

**AFFIRMED**