United States Court of Appeals for the Federal Circuit

TEVA PHARMACEUTICALS INTERNATIONAL GMBH,
Appellant

v.

ELI LILLY AND COMPANY,
Appellee

ANDREW HIRSHFELD, PERFORMING THE FUNCTIONS AND DUTIES OF THE UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Intervenor

2020-1747, 2020-1748, 2020-1750

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2018-01422, IPR2018-01423, IPR2018-01425.

Decided: August 16, 2021

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for appellant. Also represented by ELAINE BLAIS, EDWINA CLARKE, ALEXANDRA LU, Boston, MA;

NATASHA ELISE DAUGHTREY, Los Angeles, CA; WILLIAM MILLIKEN, DEBORAH STERLING, Sterne Kessler Goldstein & Fox, PLLC, Washington, DC.

WILLIAM BARRETT RAICH, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for appellee. Also represented by CHARLES COLLINS-CHASE, PIER DEROO, ERIN SOMMERS, YIEYIE YANG; SANJAY M. JIVRAJ, MARK STEWART, Eli Lilly and Company, Indianapolis, IN.

MONICA BARNES LATEEF, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, for intervenor. Also represented by THOMAS W. KRAUSE, BRIAN RACILLA, FARHEENA YASMEEN RASHEED.

Before LOURIE, BRYSON, and O'MALLEY, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Teva Pharmaceuticals International GmbH ("Teva") appeals from a combined final written decision of the U.S. Patent and Trademark Office ("PTO") Patent Trial and Appeal Board ("Board") holding that the claims of U.S. Patents 9,340,614 ("'614 patent"), 9,266,951 ("'951 patent"), and 9,890,210 ("'210 patent") are unpatentable because they would have been obvious over the cited prior art. *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, Nos. IPR2018-01422, IPR2018-01423, IPR2018-01425, 2020 WL 806932 (P.T.A.B. Feb. 18, 2020) ("*Board Decision*"). For the reasons provided below, we affirm.

BACKGROUND

I. Patents

Teva owns the '614, '951, and '210 patents (collectively, the "challenged patents") directed to humanized antagonist antibodies that target calcitonin gene-related peptide

("CGRP"). CGRP is a 37-amino acid peptide that is "a neurotransmitter in the central nervous system, and has been shown to be a potent vasodilator in the periphery, where CGRP-containing neurons are closely associated with blood vessels." '614 patent, col. 1 ll. 49–53.

The challenged patents explain that "CGRP has been noted for its possible connection to vasomotor symptoms," *id.* at col. 1 ll. 57–58, such as "all forms of vascular headache, including migraines." *Id.* at col 2 ll. 22–23. Although at the time of the challenged patents the pathophysiology of migraine was not well understood, dilation of blood vessels was associated with and thought to exacerbate the pain symptoms of migraine. *Id.* at col. 3 ll. 33–44. Thus, even before the challenged patents, the possible connection between CGRP as a vasodilator and the pathology of migraine informed the development of treatments for migraine that sought to restrict the activity of CGRP in the body. For example:

> Possible CGRP involvement in migraine has been the basis for the development and testing of a number of compounds that inhibit release of CGRP (e.g., sumatriptan), antagonize at the CGRP receptor (e.g., dipeptide derivative BIBN4096BS (Boe[]hringer Ingelheim); CGRP(8-37)), or interact with one or more of receptor-associated proteins, such as, receptor activity membrane protein (RAMP) or receptor component protein (RCP), both of which affect binding of CGRP to its receptors.

Id. at col. 2 ll. 32–40.

The challenged patents are directed to humanized antibodies that antagonize CGRP and thus inhibit its activity in the body by targeting and binding to the CGRP ligand (as opposed to CGRP receptors). The written description describes "anti-CGRP antagonist antibodies and methods of using anti-CGRP antagonist antibodies for treating or preventing vasomotor symptoms, such as headaches, such

as migraine." *Id.* at col. 3 ll. 55–63. For purposes of this appeal, however, the claims at issue are directed to the antibodies themselves.[1] Claim 1 in each patent is the only independent claim:

> 1. A human or humanized monoclonal anti-CGRP antagonist antibody that preferentially binds to human α-CGRP as compared to amylin.

'614 patent, col. 101 ll. 32–34.

> 1. A human or humanized monoclonal anti-CGRP antagonist antibody that (1) binds human α-CGRP and (2) inhibits cyclic adenosine monophosphate (cAMP) activation in cells.

'951 patent, col. 99 ll. 21–23.

> 1. A humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:
>
> two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and
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> two light chains, each light chain comprising three CDRs and four framework regions;

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[1] In contrast to the claims at issue in this case, which are directed to the antibodies themselves, Teva also owns related patents with claims directed to methods of treatment comprising a step of administering such antibodies. Those claims are at issue in Appeal Nos. 2020-1876, 2020-1877, and 2020-1878.

> wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO:43.

'210 patent, col. 103 ll. 35–45. The differences between these claims have not been argued as significant to these appeals.

II. IPR Petitions and Prior Art

Eli Lilly and Company ("Lilly") filed petitions for *inter partes* review ("IPR") of claims 1–7 and 15–20 of the '614 patent, claims 1–6 and 14–19 of the '951 patent, and claims 1–5 of the '210 patent. Lilly asserted that each of the challenged claims would have been obvious over a combination of prior art references that includes Tan,[2] Wimalawansa,[3] and Queen.[4]

Tan is a publication describing an *in vivo* study in rats using an anti-CGRP monoclonal antibody for immunoblockade.[5] The study investigated the anti-CGRP activity of a full-length monoclonal antibody called "MAb C4.19" as

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[2] K.K.C. Tan et al., *Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies in vivo with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab' fragment*, 89 CLINICAL SCI. 6, 565–73 (1995).

[3] S.J. Wimalawansa, *Calcitonin Gene-Related Peptide and its Receptors: Molecular Genetics, Physiology, Pathophysiology, and Therapeutic Potentials*, 17 ENDOCRINE REVIEWS 5, 533–85 (1996).

[4] U.S. Patent 6,180,370.

[5] Tan defines "immunoblockade" as "the blockade of the effects of a biological mediator by inhibition of its binding to specific receptors with antibodies directed against the mediator." J.A. 4996.

well as its Fab' fragment.[6] *See* J.A. 4995–5003. Tan describes the results of one experiment demonstrating that both the full-length antibody and the Fab' fragment successfully achieved immunoblockade by inhibiting the effects of exogenously administered CGRP. *See* J.A. 4996–97. Tan also describes the results of a second experiment analyzing whether the antibody and its Fab' fragment inhibit endogenous CGRP-induced blood flow after a prescribed incubation period. J.A. 4999. The results demonstrated that the Fab' fragment effectively blocked skin blood flow after a 30-minute incubation period. The full-length antibody did not block skin blood flow after a 60-minute incubation, but a 2-hour incubation period and higher dose resulted in a 16% block in skin blood flow. *Id.* Tan posited that "much larger doses and longer distribution times are required for successful immunoblockade" with the full-length antibody. J.A. 5001.

Wimalawansa is a review article that describes CGRP, including the history of its discovery, its molecular genetics and structure, its biological actions, and its therapeutic potentials. *See* J.A. 6552–604. Most of Wimalawansa's discussion focuses on the therapeutic potential of activating CGRP in the body with CGRP agonists. *See* J.A. 6578–86. Wimalawansa also includes a brief discussion, however, of the therapeutic potential of CGRP antagonists, noting that "[e]vidence is accumulating that inappropriate release of CGRP is a potential causative factor in several diseases, including migraine." J.A. 6586–87. To treat such diseases, Wimalawansa states that the "role of CGRP antagonists and humanized monoclonal antibodies should be explored." *See* J.A. 6589.

Queen "relates generally to the combination of recombinant DNA and monoclonal antibody technologies for

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[6] A "Fab' fragment" is the portion of an antibody that binds to the target antigen.

developing novel therapeutic agents." J.A. 5063 at col. 1 ll. 19–21. Specifically, Queen discloses a method of humanizing antibodies to address traditional problems associated with injecting monoclonal antibodies from donors (*e.g.*, mice) into humans.

III. Board Decision

After a combined oral hearing in the three IPR proceedings, the Board issued a combined final written decision holding that the challenged claims in all three patents are unpatentable as they would have been obvious over various cited references. The Board first found that the prior art disclosed or suggested each and every limitation of the challenged claims. *See Board Decision*, 2020 WL 806932, at *12–15. The Board then found that a skilled artisan would have been motivated to combine the teachings of the prior art, *id.* at *40–41, and would have had a reasonable expectation of successfully achieving the claimed invention, *id.* at *43. Lastly, the Board addressed secondary considerations of nonobviousness. *Id.* at *43–61.

Regarding the motivation to combine, the Board considered Lilly's asserted reasons why a skilled artisan would have been motivated to combine the teachings of the references to make a humanized anti-CGRP antibody. *Id.* at *16–27. The Board also considered Teva's asserted safety and efficacy concerns as potential reasons not to make a humanized anti-CGRP antibody. *Id.* at *27–40. After weighing the evidence, the Board found "that anti-CGRP antagonist antibodies were well known in the art, and that the art encouraged the development of humanized anti-CGRP antibodies." *Id.* at *40. The Board also found "no evidence that making a humanized anti-CGRP antagonist antibody would raise any safety concerns sufficient to discourage a person of ordinary skill in the art from making a human or humanized anti-CGRP antagonist antibody." *Id.*

In considering whether a skilled artisan would have had a reasonable expectation of success, the Board specifically noted that the challenged claims in this case are directed to humanized antibodies and do not recite any safety or efficacy limitations.[7] *Id.* at *43. Accordingly, the Board rejected Teva's argument that Lilly was required to make a showing that a skilled artisan would have had a reasonable expectation of successfully using the claimed antibodies in the treatment of any disease or condition. *Id.*

Finally, the Board found that Teva failed to establish either a presumption of nexus or a direct showing of nexus between the claims and the asserted secondary considerations based on objective indicia of nonobviousness. *Id.* at *49. For completeness, the Board also considered Teva's evidence relating to the secondary considerations but found that it was entitled to little weight. *Id.* at *49–61.

IV. Teva's Appeal

Teva appealed from the Board's combined final written decision with respect to each of the three challenged patents, and we consolidated the appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

Teva primarily challenged the Board's decision on the merits, including the legal and factual issues underlying the Board's decision regarding unpatentability. Additionally, Teva summarily argued that the panel that issued the Board's final written decision in this case consisted of members who were unconstitutionally appointed in violation of the Appointments Clause. Teva purported to preserve that challenge based on this court's decision in *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019),

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[7] Notably, in contrast to the claims at issue here, the claims at issue in Appeal Nos. 2020-1876, 2020-1877, and 2020-1878 recite methods of treatment using humanized anti-CGRP antagonist antibodies.

vacated, 141 S. Ct. 1970 (2021), as well as the arguments presented to the Supreme Court in the then-pending petition for a writ of certiorari in that case.

While Teva's appeal was pending, the Supreme Court decided *United States v. Arthrex, Inc.*, 141 S. Ct. 1970 (2021). We stayed all deadlines and proceedings in this case and ordered the parties to file supplemental briefs explaining how the case should proceed in light of the Supreme Court's decision in *Arthrex*. On July 7, 2021, Teva filed its supplemental brief, proposing that we should first decide the merits of the appeal, and if we do not otherwise reverse or remand we should then issue a limited remand under *Arthrex*. On July 21, 2021, Lilly and the PTO filed their supplemental briefs. The PTO argued that, because Teva's supplemental brief included a request for a limited remand under *Arthrex*, we should immediately remand the case without deciding the merits. In contrast, Lilly argued that by asking us to decide the merits of the appeal, Teva waived its opportunity for a limited remand under *Arthrex*.

We rejected Teva's proposal and instead ordered Teva to elect one of two options: (i) a request that we issue a remand for the limited purpose of allowing Teva the opportunity to request Director rehearing of the final written decision; or (ii) a waiver of its right to seek Director rehearing of the final written decision. On July 28, 2021, Teva filed its response indicating that it waives its right to a limited remand to seek rehearing by the Director. Accordingly, we lifted the stay, and we now proceed to decide the appeal on the merits.

DISCUSSION

We review the Board's legal determinations de novo, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), but we review the Board's factual findings underlying those determinations 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).

We begin by briefly addressing the Board's finding that each limitation of the challenged claims was individually taught by the prior art. *See Board Decision*, 2020 WL 806932, at *12–15. The challenged patents' written description concedes that "[a]nti-CGRP antagonist antibodies [we]re known in the art" and commercially available. *See, e.g.*, '614 patent col. 26 ll. 13–17. Additionally, Tan disclosed and described use of an anti-CGRP antagonist antibody, *see* J.A. 4996, Wimalawansa proposed the use of humanized anti-CGRP antibodies, *see* J.A. 6586, and Queen described methods of humanizing monoclonal antibodies, *see* J.A. 5004. The Board also noted that Teva did not contest Lilly's evidence regarding the additional limitations in the independent claims, including that the prior art antibodies preferentially bind to CGRP as compared to amylin ('614 patent, claim 1), that blocking CGRP would inhibit cAMP activation ('951 patent, claim 1), and that the recited heavy and light chains are generic to IgG antibodies and the recited sequence IDs correspond to CGRP ('210 patent, claim 1). Accordingly, the Board's finding that the prior art taught every element of the challenged claims is supported by substantial evidence. Teva does not challenge that finding on appeal.

Teva raises three challenges to the Board's decision. First, Teva contends that the Board erred as a matter of law in its motivation to combine analysis by deviating from the motivation asserted by Lilly in its petitions for *inter partes* review. Second, Teva contends that even under the motivation to combine that the Board did analyze, substantial evidence does not support the Board's factual findings. And third, Teva contends that the Board erred in its analysis of secondary considerations of nonobviousness. We address each challenge in turn.

I

Teva first contends that the Board erred by relying on a different motivation to combine from the one that Lilly asserted in its petitions for *inter partes* review. According to Teva, Lilly asserted that a skilled artisan would have been motivated to combine the teachings of the references to make a humanized anti-CGRP monoclonal antibody for therapeutic use in humans, but the Board instead considered whether a skilled artisan would have been motivated to make the antibody merely to study or use it. Teva insists that by not requiring Lilly to support its therapeutic motivation, the Board incorrectly discounted important safety and efficacy concerns that would have been demotivating factors—*i.e.*, reasons why a skilled artisan would have been motivated *not* to make a humanized anti-CGRP monoclonal antibody.

Lilly responds that the Board relied on the same motivation that was asserted in the petitions, and that a motivation to study or use a humanized antibody to assess its therapeutic potential is not meaningfully different from what Teva has termed a "therapeutic motivation." Lilly further contends that the Board extensively relied on prior art disclosures regarding the potential safety and efficacy of anti-CGRP antagonist antibodies for the treatment of migraines and other vasomotor symptoms. For example, Lilly notes that the Board agreed with Lilly's contention that Wimalawansa suggests study of anti-CGRP antibodies in migraine, and that substantial evidence demonstrates that Tan's use of anti-CGRP antibodies in connection with skin vasodilation has relevance to treating disease in humans. As further examples, Lilly points to the Board's reliance on at least four other prior art references demonstrating the therapeutic potential of anti-CGRP antibodies.

As an initial matter, we agree with Lilly that the Board properly analyzed the motivation to combine that Lilly

asserted in its IPR petitions. To be sure, the Board may not "deviate from the grounds in the petition and raise its own obviousness theory." *Sirona Dental Sys. GmbH v. Institut Straumann AG*, 892 F.3d 1349, 1356 (Fed. Cir. 2018). But here, the Board upheld its mandate to "base its decision on arguments that were advanced by a party"—namely, Lilly—"and to which the opposing party"—namely, Teva—"was given a chance to respond." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016).

Lilly argued in its petition that a skilled artisan would have been motivated to make the claimed humanized antibody for therapeutic use in humans. *See, e.g.*, J.A. 829 ("Consequently, a POSA—with her ordinary creativity—would have been motivated to combine [the prior art] *to obtain* a humanized anti-CGRP antagonist antibody that would be suitable for administration to humans . . . ." (emphasis added)). And that was precisely the motivation that the Board found. Common sense and scientific reality dictate that scientists do not "study or use" humanized antibodies with an end goal of treating diseases in test tubes or in rats. At bottom, the prior art supports a motivation to humanize antibodies with the goal of treating human disease.

Teva's argument about the Board's alleged failure to consider safety and efficacy concerns misses the mark. Because the claims are directed to humanized antibodies, the question before the Board was whether a skilled artisan at the time of the invention would have been motivated to make the claimed humanized antibodies, not whether a skilled artisan would have been motivated to use those antibodies to treat human disease. Teva is, of course, correct that the analysis must account for "reasons not to combine," which are facts relevant to the overall consideration of obviousness. *See, e.g.*, *Arctic Cat Inc. v. Bombardier Rec. Prods.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017); *see also id.* at 1363 ("Evidence suggesting reasons to combine cannot be

viewed in a vacuum apart from evidence suggesting reasons not to combine"). But, as it pertains to Teva's argument about safety and efficacy concerns, the relevant inquiry is not (as Teva suggests) whether the asserted concerns would have presented a reason not to use the claimed antibodies in human treatments. Rather, the relevant inquiry—which the Board extensively analyzed—is whether those concerns would have dissuaded a skilled artisan from making the claimed antibodies to study their therapeutic potential in the first place.

As a factual matter, Teva is not correct in asserting that the Board failed to consider whether a skilled artisan would have expected the treatment to be unsafe or unsuccessful. On the contrary, the Board extensively analyzed Teva's asserted safety and efficacy concerns, including those associated with "blocking the CGRP pathway," those raised by "Tan and Wimalawansa," those related to "migraine and stroke," and those based on "differences between blocking a CGRP receptor and an antibody against the CGRP ligand." *See Board Decision*, 2020 WL 806932, at *27–40. After weighing evidence based on expert testimony and numerous publications that the parties presented, the Board reached a factual finding that the safety and efficacy concerns would not be "sufficient to discourage a person of ordinary skill in the art from making a human or humanized anti-CGRP antagonist antibody." *Id.* at *40. The Board specifically noted that Teva relied "heavily on potential safety concerns based on the role of CGRP in the body and general characteristics of antibodies *in vivo*," and that evidence was outweighed by Lilly's reliance on "actual studies of CGRP antagonists, including antibodies." *Id.* at *41. Thus, the Board concluded that "any alleged safety concerns would not have deterred or discouraged the combination of prior art teachings to achieve the invention of the challenged claims." *Id.*

For the foregoing reasons, we are not persuaded by Teva's contention that the Board deviated from Lilly's

asserted motivation to combine, and we disagree with Teva's assertion that the Board improperly discounted potential safety and efficacy concerns associated with the claimed invention. The Board properly considered the evidence relevant to Lilly's asserted motivation to combine.

II

As an alternative to its argument that the Board deviated from Lilly's asserted motivation to combine, Teva argues that the Board relied on unsupported interpretations of isolated statements in the prior art to find a motivation to study or use humanized anti-CGRP antibodies. For example, Teva contends that the Board misinterpreted the phrase "CGRP antagonists and humanized monoclonal antibodies" in Wimalawansa as referring to antibodies that target the CGRP ligand, even though, Teva asserts, a skilled artisan would have understood that term as referring to the extremely specific receptor antagonists that are the focus of Wimalawansa's section on CGRP antagonism. At best, Teva argues, Wimalawansa cautions that further study is needed before CGRP antagonists could be evaluated in humans. Regarding Tan, Teva emphasizes that the full-length antibody was unsuccessful in achieving immunoblockade in rats, and Teva contends that Tan's expression of optimism that its negative results could be overcome does not support a motivation to further explore the full-length antibody.

In response, Lilly argues that substantial evidence supports a motivation to make the claimed antibody. Lilly focuses on the disclosures of the references themselves, as well as the interpretations of the references by expert witnesses and contemporaneous prior art publications. Lilly argues that the disclosures of Tan, Wimalawansa, and numerous other prior art references would have motivated a skilled artisan to make humanized anti-CGRP antibodies with the goal of treating human disease.

We agree with Lilly that substantial evidence supports a motivation to make a humanized anti-CGRP antibody to study its therapeutic potential for use in treatment of human disease. Lilly identifies evidence that supports the Board's reasonable readings of each reference. For example, Lilly points to the testimony of three separate experts supporting the Board's interpretation of Tan's 16% response as a trend toward anti-CGRP activity with the full-length antibody, including the experts' interpretation of Tan's optimism that longer distribution times and higher concentrations would improve the response. *See, e.g.*, J.A. 4716 (testimony of Dr. Alain Vasserot); J.A. 4605–07 (testimony of Dr. Andrew Charles); J.A. 9874–80 (testimony of Dr. Joseph Balthasar). As for Wimalawansa, although the expert witnesses differed regarding the phrase "CGRP antagonists and humanized monoclonal antibodies," Lilly points to evidence of a contemporaneous prior art publication that cited Wimalawansa to support the proposition that the CGRP ligand is a target in migraine treatment. *See, e.g.*, J.A. 6429.

Unsurprisingly, Teva disagrees with the Board's interpretations of Tan and Wimalawansa. But what a piece of prior art teaches presents a question of fact that is reviewed for substantial evidence. *See, e.g.*, *In re Warsaw Orthopedic, Inc.*, 832 F.3d 1327, 1332 (Fed. Cir. 2016) ("An examination of the scope and content of the prior art produces factual findings reviewed for substantial evidence." (citing *Gartside*, 203 F.3d at 1316)). When it comes to competing interpretations of the teachings of prior art references, we must uphold the principle that "[i]f two 'inconsistent conclusions may reasonably be drawn from the evidence in record, the PTAB's decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence.'" *Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1356 (Fed. Cir. 2018) (internal brackets omitted) (quoting *In re Cree, Inc.*, 818 F.3d 694, 701 (Fed. Cir.

2016)). Under this deferential standard of review, we cannot replace the Board's reasonable interpretation of references with Teva's interpretation. For the foregoing reasons, we are not persuaded that the Board committed reversible error with regard to its analysis of the motivation to combine the teachings of the prior art references.

III

Turning to the issue of secondary considerations of nonobviousness, Teva's primary evidence was based on two commercial products—its own AJOVY® product and Lilly's Emgality® product—both of which are antibodies within the scope of the challenged patent claims. Teva asserted that both products have received industry-wide acclaim, satisfied a long-felt need, achieved unexpected results, faced industry skepticism, and achieved commercial success. Teva also presented evidence of a license it entered into with third parties AlderBio Holdings, LLC and Alder Biopharmaceuticals, Inc. (collectively, "AlderBio") that included the challenged patents. The Board found that the commercial products and the license lacked sufficient nexus to the challenged claims. *See Board Decision*, 2020 WL 806932, at *49–50, 60–61.

Teva argues that the Board made two legal errors. First, Teva argues that, in finding no presumption of nexus between the claims and the secondary considerations based on the commercial products, the Board misapplied this court's holding in *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366 (Fed. Cir. 2019). Second, with regard to the AlderBio license, Teva argues that the Board erred by focusing on AlderBio's products rather than the scope of the license. We address each of Teva's arguments below.

A

In considering the Board's finding that Teva failed to show a nexus between the challenged claims and the commercial AJOVY® and Emgality® products, we begin with a

discussion of the nexus requirement. It is well-established law that in order to accord substantial weight to secondary considerations of nonobviousness, "the evidence of secondary considerations must have a 'nexus' to the claims, *i.e.*, there must be 'a legally and factually sufficient connection' between the evidence and the patented invention." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988)). "The patentee bears the burden of showing that a nexus exists . . . ." *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999) (citing *Cable Elec. Prods., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1027 (Fed. Cir. 1985)). "To determine whether the patentee has met that burden, we consider the correspondence between the objective evidence and the claim scope." *Henny Penny*, 938 F.3d at 1332.

It has long been recognized that "a patentee is entitled to a rebuttable presumption of nexus between the asserted evidence of secondary considerations and a patent claim if the patentee shows that the asserted evidence is tied to a specific product and that the product '*is* the invention disclosed and claimed.'" *Fox Factory*, 944 F.3d at 1373 (quoting *Demaco*, 851 F.2d at 1392). The presumption applies "when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'embodies the claimed features, and is coextensive with them.'" *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) (quoting *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000)). "Conversely, '[w]hen the thing that is commercially successful is not coextensive with the patented invention—for example, if the patented invention is only a component of a commercially successful machine or process,' the patentee is not entitled to a presumption of nexus." *Fox Factory*, 944 F.3d at 1373 (quoting *Demaco*, 851 F.2d at 1392).

Much has been written discussing the "coextensiveness" requirement for the presumption of nexus, and in *Fox Factory* we attempted to summarize the current state of the law. We rejected attempts "to reduce the coextensiveness requirement to an inquiry into whether the patent claims broadly cover the product that is the subject of the evidence of secondary considerations." *Id.* at 1377. Rather, we explained, "the degree of correspondence between a product and a patent claim falls along a spectrum." *Id.* at 1374. At one end of the spectrum lies "perfect or near perfect correspondence," and at the other end lies "no or very little correspondence." *Id.* "Although we do not require the patentee to prove perfect correspondence to meet the coextensiveness requirement, what we do require is that the patentee demonstrate that the product is essentially the claimed invention." *Id.* "Whether a product is coextensive with the patented invention, and therefore whether a presumption of nexus is appropriate in a given case, is a question of fact." *Id.* at 1373.

Bound up with the coextensiveness requirement is the issue of "unclaimed features" in a commercial product, which we also addressed in *Fox Factory*. "[W]e have never held that the existence of one or more unclaimed features, standing alone, means nexus may not be presumed." *Id.* at 1374. Indeed, like the coextensiveness requirement itself, the concept of unclaimed features is best viewed as part of a spectrum. Toward one end of the spectrum, we have said that "if the unclaimed features amount to nothing more than additional insignificant features, presuming nexus may nevertheless be appropriate." *Id.* Toward the other end of the spectrum, we have said that "[a] patent claim is not coextensive with a product that includes a 'critical' unclaimed feature that is claimed by a different patent and that materially impacts the product's functionality." *Id.* at 1375.

In applying our *Fox Factory* holding in this case, the Board stated that it "d[id] not understand *Fox Factory* to

be making a distinction between features that are 'critical' and features that 'materially impact' the functionality of the product." *Board Decision*, 2020 WL 806932, at *48. Accordingly, the Board concluded that in order to defeat a presumption of nexus, a patent challenger need only show that an "unclaimed feature materially affects the functioning of the product that is alleged to be coextensive with the claim." *Id.* Teva argues that this was a misinterpretation of *Fox Factory*, and to the extent the Board announced a bright-line rule that the presumption of nexus does not apply if any unclaimed feature materially affects the functioning of a product that is alleged to be coextensive, we agree with Teva that the Board erred. As Teva argues, under such a rule the presumption of nexus would rarely, if ever, attach because virtually every innovative product inevitably has some unclaimed feature that materially affects its functionality. Such a rule would be unsound. For example, a claim to a new and unobvious pharmaceutical compound would surely have a nexus to the marketed finished product sold to consumers, although that finished product will almost always contain excipients such as solubilizers, antioxidants, stabilizers, etc., that materially affect its functionality. Such excipients should not reasonably be found to destroy the nexus between the claim and the product.

Our conclusion that the Board erred in its articulation of the legal standard, however, does not end our inquiry into whether a presumption of nexus applies in this case. The presumption analysis requires the fact finder to consider the unclaimed features of the stated products to determine their level of significance and their impact on the correspondence between the claim and the products. *Fox Factory*, 944 F.3d at 1375. As we discuss further below, despite its incorrect articulation of the law, the Board conducted the necessary factual analysis of the unclaimed features of the AJOVY® and Emgality® products and reached the correct conclusion that no presumption of nexus applies

in this case. Therefore, the Board's error in articulating the legal standard was harmless. *See In re Watts*, 354 F.3d 1362, 1369 (Fed. Cir. 2004) ("[T]he harmless error rule applies to appeals from the Board . . . .").

As we turn to the Board's factual analysis of the unclaimed features, we emphasize that the question whether the presumption of nexus applies in each case turns on the nature of the claims and the specific facts. For example, in *Fox Factory* the relevant comparison was between a structurally claimed mechanical chainring and a product that included an unclaimed "gap filling" feature that was "critical," "claimed by a different patent," "materially impact[ed] the product's functionality," and led "to a chainring that will retain a chain in even the worst conditions." 944 F.3d at 1375. Based on those facts, we determined that "no reasonable fact finder could conclude, under the proper standard, that the X-Sync chainrings are coextensive with the patent claims." *Id.* at 1374–75.

We have also considered the coextensiveness requirement in chemical and biological cases that more closely resemble the technology at issue here. For example, in *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067–68 (Fed. Cir. 2020), the patent claims recited the molecular weight and amino acid sequence of the "protein" to which they were directed. *See* U.S. Patent 8,063,182. There, we held that "[n]exus is appropriately presumed in this case where the court concluded that the claims are directed to the active ingredient in Enbrel® and its method of manufacture." *Immunex*, 964 F.3d at 1067. More generally, it is hard not to imagine a presumption of nexus between a structurally claimed genus of chemical compounds and a commercial product that meets each claim limitation.

In contrast to the claims in *Fox Factory* and *Immunex*, the antibodies in the claims at issue in this case are described, not in terms of their structure, but rather in terms of their function—in particular, their ability to bind to the

CGRP ligand. *See* '614 patent, col. 101 ll. 32–34 ("1. A human or humanized monoclonal anti-CGRP antagonist antibody that preferentially binds to human α-CGRP as compared to amylin."); *see also* '951 patent, col. 99 ll. 21–23 ("1. . . . antibody that (1) binds to human α-CGRP and (2) inhibits [cAMP] activation in cells"); '210 patent, col. 103 ll. 35–45 ("1. . . . wherein the CDRs impart to the antibody specific binding to a CGRP . . . ."). As we have recently noted, functional claim language can lead to broad claims, especially when there are no structural limitations to clearly define the scope. *See, e.g.*, *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1087 (Fed. Cir. 2021) (discussing claims with "broad functional language").[8] A claim to "anything that works" hardly has a nexus to any particular product. Thus, we reject the strained comparisons that the parties and the Board have made between the facts of this case and the facts in other cases dealing with the presumption of nexus.

Because the claims in this case have a broad scope due to their lack of structural limitations, the unclaimed features in the commercial products cited here are of particular importance to the coextensiveness analysis. The Board considered how four such unclaimed features in the AJOVY® and Emgality® antibodies affect the functionality of the products—*i.e.*, their ability to function as anti-CGRP antagonist antibodies. For example, the Board found that, although the claims do not recite amino acid sequences, AJOVY® and Emgality® have specific sequences that critically affect binding affinity and inhibit the ability of the antibodies to kill cells. *See Board Decision*, 2020 WL 806932, at *46–47. The Board also found that, although

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[8] While our *Amgen* decision considered breadth in the context of the enablement requirement of 35 U.S.C. § 112, we see a similar problem here as we must consider the breadth of functional claims to determine whether they are coextensive with specific commercial products.

the claims did not recite limitations regarding picomolar binding affinity, full-length antibodies versus fragments, or IgG antibody classes, all of those features are critical to the ability of the AJOVY® and Emgality® antibodies to function as humanized anti-CGRP antagonist antibodies. *See id.* at *47–49. The Board's factual findings regarding unclaimed features are thus supported by substantial evidence, and Teva has not shown otherwise.

Teva concedes that "at some point"—*i.e.*, somewhere along the coextensiveness spectrum that we described in *Fox Factory*—"the differences between a product and a patent claim become so significant that nexus cannot be presumed." *See* Teva Br. at 52. In view of the extremely broad scope of the functionally claimed antibodies of the challenged claims and the unclaimed features that undisputedly materially affect how AJOVY® and Emgality® function as humanized anti-CGRP antagonist antibodies, no reasonable fact finder could conclude that that point has not been crossed in this case. Thus, Teva has failed to show that a presumption of nexus applies in this case. As Teva does not appear to dispute the Board's statement that the presumption was the sole basis for its assertion of nexus, *see Board Decision*, 2020 WL 806932, at *49, we conclude that there is no nexus between the challenged claims and the secondary considerations based on the AJOVY® and Emgality® products.

B

We finally turn to Teva's arguments based on the AlderBio license. Teva argues that, while the law requires a nexus between the challenged claims and the "licenses themselves," *see In re Antor Media Corp.*, 689 F.3d 1282, 1293–94 (Fed. Cir. 2012) (citing *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)), the Board erred by requiring a direct nexus between the challenged claims and AlderBio's products.

Lilly responds that substantial evidence supports the Board's finding that Teva failed to show a connection between the broad AlderBio license and the challenged claims. Lilly argues that Teva relied exclusively on the fact that the three challenged patents were included among 188 licensed patents, without any meaningful analysis of the economic reasons motivating the licensee. Moreover, Lilly argues, because Teva's witnesses conceded that the license and royalty payments would continue unabated regardless of the validity of the three challenged patents, the license is not probative of the nonobviousness of the challenged patents.

We agree with Lilly that the Board's conclusion that the AlderBio license lacked nexus to the challenged claims was supported by substantial evidence. The significance of licensing a patent as a secondary consideration in enhancing the nonobviousness of an invention is that an independent party with an interest in being free of the patent has chosen to respect it and pay a royalty under it rather than litigate and invalidate it. Such action tends to support its validity. Here, given that 188 patents were licensed, the nexus between the license and the validity of any particular claim is rather tenuous to say the least. Thus, the Board was correct to require that Teva show something more than the mere existence of the license. *See Sibia Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed. Cir. 2000) ("[T]he mere existence of these licenses is insufficient to overcome the conclusion of obviousness . . . ."); *see also Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 838 (Fed. Cir. 2015) ("It is therefore difficult to determine the extent to which the licensing agreement was a result of the novel features in the [challenged] patent, as opposed to the other patents involved.").

Teva failed to show anything more than the existence of the license. Teva did not present direct evidence that AlderBio's motivation for entering into the license was related to the validity or enforceability of the three

challenged patents. In the absence of such evidence, we cannot fault the Board for looking to the license's "whereas" clause to identify the purpose of the license, namely, the development of AlderBio's products. With that purpose in mind, the Board reasonably considered whether Teva had presented evidence of a relationship between the challenged claims and the development of such products. *See S. Ala. Med. Sci. Found. v. Gnosis, S.p.A.*, 808 F.3d 823, 827–28 (Fed. Cir. 2015) (holding that "evidence that the licensee ultimately manufactured a product that embodies the claimed invention may be probative of a nexus between the claimed invention and the licensing activity"). The Board expressly found that Teva did not show "that any of the challenged patents cover the Alder Product by a comparison of the [] product to the challenged claims." *Board Decision*, 2020 WL 806932, at *61.

Teva's argument loses sight of the true purpose of the nexus requirement, which is to consider whether "the fact-finder can infer that the licensing 'arose out of recognition and acceptance of the subject matter claimed' in the patent." *See S. Ala. Med.*, 809 F.3d at 827 (quoting *GPAC*, 57 F.3d at 1580). Teva instead hinges its arguments on subtle differences between terms that have been used in our case law—*e.g.*, the "licensing activity" versus the licensee's "products."

At bottom, the Board found that the relevant facts, which are supported by substantial evidence, "minimize[d] any nexus between the challenged claims and the AlderBio License." *Board Decision*, 2020 WL 806932, at *61. Accordingly, we hold that substantial evidence supports the Board's decision that there is a lack of nexus between the challenged claims and the secondary consideration of licensing.

CONCLUSION

We have considered Teva's remaining arguments but we find them unpersuasive. Accordingly, the Board's decision is affirmed.

AFFIRMED