NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LIMITED,
Appellants

v.

KATHERINE K. VIDAL, UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Intervenor

2019-2171

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-01542.

Decided: April 14, 2022

ARLENE L. CHOW, Latham & Watkins LLP, New York, NY, for appellants. Also represented by JON STEVEN BAUGHMAN, Paul, Weiss, Rifkind, Wharton & Garrison LLP, Washington, DC; JENNIFER GORDON, NICHOLAS P. GROOMBRIDGE, New York, NY.

THOMAS W. KRAUSE, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, for intervenor. Also represented by AMY J. NELSON; MAUREEN DONOVAN QUELER.

Before CHEN, SCHALL, and STOLL, *Circuit Judges*.

CHEN, *Circuit Judge*.

Appellants Amgen Inc. and Amgen Manufacturing Ltd. (collectively, Amgen) appeal a Final Written Decision and reconsideration of the same by the Patent Trial and Appeal Board (Board) in an *inter partes* review proceeding involving U.S. Patent No. 8,952,138 ('138 patent). The Board determined that claims 1–24 of the '138 patent are unpatentable under 35 U.S.C. § 103(a). Amgen appeals the Board's construction of the claim term "final thiol-pair ratio" and determination that claims 1–24 are unpatentable. For the following reasons, we *reverse*.

BACKGROUND

The '138 patent explains that when recombinant proteins are formed in non-mammalian expression systems (e.g., bacterial cells), they can precipitate into limited-solubility aggregates of misfolded proteins called "inclusion bodies." '138 patent at col. 1 ll. 20–24. To obtain properly folded proteins from inclusion bodies, practitioners developed various methods to accomplish refolding. *Id.* at col. 1 ll. 36–38. Such methods generally include steps of (1) extracting the inclusion bodies from the expression system; (2) solubilizing the inclusion bodies in a solubilization buffer, which disassembles the inclusion bodies into individual protein chains and unfolds the proteins; and (3) diluting or washing the unfolded proteins in a refolding buffer, which causes the proteins to refold in the proper manner. *Id.* col. 1 ll. 38–51.

The '138 patent claims methods for refolding proteins at high concentrations using a controlled reduction-oxidation (redox) reaction. *See* '138 patent at claims 1–24; *see also id.* at col. 1 ll. 11–14, col. 2 ll. 52–61. Claim 1 is the only independent claim, and claims 2–24 depend therefrom.

In its Final Written Decision, the Board construed "final thiol-pair ratio," recited in claim 1, to mean "the relationship of the reduced and oxidized redox species used in the redox component of the refold buffer as defined by the [following] equation":

$$\frac{[reductant]^2}{[oxidant]}$$

Apotex Inc. v. Amgen Inc., IPR2016-01542, 2018 WL 935620, at *4 (P.T.A.B. Feb. 15, 2018) (*Final Written Decision*). Based on this construction of "final thiol-pair ratio," the Board determined that Petitioners Apotex Inc. and Apotex Corp. (collectively, Apotex) had demonstrated that claim 1 is unpatentable over Schlegl[1] in view of Hevehan.[2] J.A. 40–47, 62. Since Amgen did not separately argue the patentability of dependent claims 2–17 and 19–24, the Board concluded claims 2–17 and 19–24 are also unpatentable. J.A. 47–55, 58–60. Although the Board was initially unpersuaded that Apotex had demonstrated that claim 18 was unpatentable, the Board later reconsidered and amended its *Final Written Decision* to find claim 18 unpatentable. *Apotex Inc. v. Amgen Inc.*, No. IPR2016-01542, 2019 WL 2180042, at *5–6 (P.T.A.B. May 20, 2019); *see also Final Written Decision*, at *18.

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[1] U.S. Patent Pub. No. 2007/0238860. J.A. 248–60.

[2] Diane L. Hevehan & Eliana De Bernardez Clark, *Oxidative Renaturation of Lysozyme at High Concentrations*, 54 Biotechnology & Bioengineering 221 (1997). J.A. 261–270.

Amgen appeals the Board's construction of "final thiol-pair ratio" and unpatentability determinations based on the same. Apotex informed this Court that it would not participate in the appeal, ECF No. 2, and the U.S. Patent and Trademark Office (Patent Office) intervened to defend the Board's decision, ECF No. 11. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

A

Because Apotex filed its petition for *inter partes* review before November 13, 2018, we apply the broadest reasonable interpretation claim construction standard. *Valve Corp. v. Ironburg Inventions Ltd.*, 8 F.4th 1364, 1380 n.14 (Fed. Cir. 2021). There being no dispute here about findings or evidence of facts extrinsic to the patent, we conduct a de novo review of the Board's determination of the broadest reasonable interpretation of the claim language. *See In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1279–80 (Fed. Cir. 2015); *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1297 (Fed. Cir. 2015).

Obviousness is a question of law based on underlying factual determinations. *Facebook, Inc. v. Windy City Innovations, LLC*, 973 F.3d 1321, 1339 (Fed. Cir. 2020). We review the Board's legal conclusions de novo and its factual findings for substantial evidence. *ACCO Brands Corp. v. Fellowes, Inc.*, 813 F.3d 1361, 1365 (Fed. Cir. 2016).

B

Amgen argues the Board misconstrued "final thiol-pair ratio" because claim 1's "language makes clear that the redox component is a distinct volume from the refold buffer, and it is that *redox component* [rather than the refold buffer] that comprises the claimed 'final thiol-pair ratio.'" *See* Appellant's Br. 41–42, 43. Since the thiol-pair ratio (TPR) equation is volume-dependent, the TPR value will be different when calculated in the redox component versus

the refold buffer. *Id.* at 40–41, 43–44. The Patent Office responds that redox component is not, and need not be, a separate volume from the refold buffer. Intervenor's Br. 36–37. The Patent Office assumes that the only way to give meaning to the word "final" in "final thiol-pair ratio" and make sense of the '138 patent's claims and specification is to understand "final thiol-pair ratio" in the context of the ultimate solution—i.e., the refold mixture—rather than specific ingredients therein—e.g., the redox component. *Id.* at 38–39. We agree with Amgen.

Claim 1 recites "contacting the protein with a refold buffer comprising a redox component comprising a final thiol-pair ratio. . . . to form a refold mixture." '138 patent at claim 1. A straightforward reading of the claim language indicates that the "final thiol-pair ratio" is an attribute *of the redox component*. *Id.* Additionally, the '138 patent specification distinguishes between "final thiol-pair ratio,"[3] "buffer thiol-pair ratio,"[4] and "system thiol-pair ratio,"[5] which respectively correspond to TPR values calculated in the "redox component," "refold buffer," and "refold

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[3] "In various embodiments the *redox component* has a final thiol-pair ratio." '138 patent at col. 2 ll. 62–64 (emphasis added); *see also id.* at col. 8 ll. 37–43, col. 9 ll. 20–22, col. 10 ll. 22–26, col. 11 ll. 9–13 & 40–42 & 54–63, col. 13 ll. 29–35.

[4] "As used herein, the term 'buffer thiol-pair ratio' is defined by the relationship of the reduced and oxidized redox species used in the *refold buffer* as defined in Equation 1[.]" *Id.* at col. 6 ll. 20–28 (emphasis added); *see also id.* at col. 4 ll. 39–42 & ll. 46–48, col. 10 ll. 45–56.

[5] "The buffer thiol-pair ratio is, however, only one component in determining the total system thiol-pair ratio in the *total reaction*." *Id.* at col. 4 ll. 46–48 (emphasis added); *see also id.* at col. 4 ll. 48–51 & 55–58, col. 9 ll. 3–13.

mixture." In other words, the specification clearly and exclusively describes "final thiol-part ratio" as an attribute of the redox component. If claim 1 covered a TPR calculated in the refold buffer—as the Board construed and analyzed claim 1—claim 1 would have recited a "buffer thiol-pair ratio" rather than "final thiol-pair ratio." Moreover, the specification confirms that the redox component is a chemical or solution that is independent of the refold buffer by expressly defining "'redox component' [to] mean[] any *thiol-reactive chemical or solution comprising such a chemical* that facilitates a reversible thiol exchange with another thiol or the cysteine residues of a protein." *Id.* at col. 6 ll. 63–66 (emphasis added).

Accordingly, claim 1 requires a redox component with concentrations of reductant and oxidant optimized using the TPR equation disclosed in the '138 patent. The Board's construction, which treats the claimed "final thiol-pair ratio" as an attribute of the redox component *in* the refold buffer rather than of the redox component *independent of* the refold buffer, is inconsistent with the plain language of claim 1 and the specification and is therefore unreasonably broad. *See In re Smith Int'l, Inc.*, 871 F.3d 1375, 1382–83 (Fed. Cir. 2017) (stating that "the Board cannot construe the claims so broadly that its constructions are unreasonable under general claim construction principles," and that giving claim terms "a strained breadth in the face of the otherwise different description in the specification [is] unreasonable" (internal quotation marks and emphasis omitted)). As such, the correct construction of "final thiol-pair ratio" in claim 1 under the broadest reasonable interpretation standard is "the relationship of the reduced and oxidized redox species used in the redox component," as defined by the following equation:

$$\frac{[reductant]^2}{[oxidant]}$$

See '138 patent at col. 8 ll. 37–43 ("Thiol-pair ratio [is] defined in Equation[] 1[.]"); *see also id.* at col. 10 ll. 22–26 (stating that "the redox component has a final thiol-pair ratio (*as defined herein*)") (emphasis added), col. 11 ll. 9–13 (same). We therefore hold that the Board misconstrued "final thiol-pair ratio."

C

On the evidence and arguments presented to the Board,[6] there is only one possible evidence-supported finding regarding patentability: Apotex failed to demonstrate that claims 1–24 are unpatentable under § 103(a). Nowhere in the record did Apotex present argument or evidence that Schlegl or Hevehan discloses calculating a final thiol-pair ratio in a redox component independent of the refold buffer. *See*, *e.g.*, J.A. 124–25 (Petition arguing that claim 1's "final thiol-pair ratio" is disclosed in Schlegl and Hevehan's respective refold buffers or mixtures). It is not necessary or appropriate to remand for the Board to determine whether claim 1 is unpatentable over the Schlegl-Hevehan combination under the correct construction of "final thiol-pair ratio" because the only conclusion supported by substantial evidence is that neither Schlegl nor Hevehan disclose a "final thiol-pair ratio." *See Owens Corning v. Fast Felt Corp.*, 873 F.3d 896, 902 (Fed. Cir. 2017) (explaining that in circumstances "where only one answer is supported by substantial evidence and there is neither a request nor an apparent reason to grant a second record-making opportunity, reversal is warranted"). That conclusion requires reversal of the Board's finding that claim 1

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[6] The Patent Office argues for the first time on appeal that Schlegl or Hevehan teaches optimizing thiol concentrations of a redox component within a refold mixture. Intervenor's Br. 26–32. We do not consider this theory as it was not presented to the Board.

and claims 2–24 depending therefrom are unpatentable under § 103(a). [7]

CONCLUSION

For the foregoing reasons, we hold that Apotex failed to demonstrate that claims 1–24 of the '138 patent are unpatentable under § 103(a). The Board's decision is reversed.

REVERSED

COSTS

No costs.

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[7] Amgen also appeals the Board's reconsideration of claim 18. Appellant's Br. 58–71. Since we reverse the Board's patentability determination with respect to claim 1, we need not reach any additional issues raised with respect to claim 18, which depends from claim 1.