United States Court of Appeals for the Federal Circuit

GENENTECH, INC.,
Appellant

v.

HOSPIRA, INC.,
Appellee

UNITED STATES,
Intervenor

2018-1933

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-01837.

Decided: January 10, 2020

THOMAS S. FLETCHER, Williams & Connolly LLP, Washington, DC, argued for appellant. Also represented by PAUL B. GAFFNEY, EDEN SCHIFFMANN, JONATHAN SIDHU.

THOMAS J. MELORO, Willkie Farr & Gallagher LLP, New York, NY, argued for appellee. Also represented by ALEXANDRA AWAI, MICHAEL JOHNSON.

COURTNEY DIXON, Appellate Staff, Civil Division,

United States Department of Justice, Washington, DC, argued for intervenor. Also represented by KATHERINE TWOMEY ALLEN, SCOTT R. MCINTOSH, JOSEPH H. HUNT; THOMAS W. KRAUSE, JOSEPH MATAL, FARHEENA YASMEEN RASHEED, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA.

Before PROST, *Chief Judge*, NEWMAN and CHEN, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* CHEN.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

CHEN, *Circuit Judge.*

Genentech, Inc. appeals from the final written decision of the United States Patent and Trademark Office (Patent Office) Patent Trial and Appeal Board (the Board) holding claims 1–3 and 5–11 of U.S. Patent 7,807,799 (the '799 patent) unpatentable as anticipated or obvious. *See Genentech, Inc. v. Hospira, Inc.*, No. IPR2016-01837, 2018 WL 1187484 (P.T.A.B. Mar. 6, 2018) (the '837 Decision). The Patent Office intervened in this appeal to defend the constitutionality of *inter partes* review (IPR) proceedings as applied to patents issued before the enactment of the America Invents Act (AIA), Pub. L. No. 112-29, 125 Stat. 284 (2011). For the following reasons, we *affirm*.

BACKGROUND

Genentech owns the '799 patent, which is directed to methods of purifying antibodies and other proteins containing a C_H2/C_H3 region from impurities by protein A affinity chromatography. '799 patent at col. 7 ll. 50–54. Protein A affinity chromatography is a standard purification technique employed in the processing of therapeutic proteins, especially antibodies, which involves "using protein A . . . immobilized on a solid phase." *Id.* at col. 4 ll. 27–30. "The solid phase may comprise a glass, silica,

polystyrene, or agarose surface," such as a chromatography column resin "to which the protein A can . . . be covalently bound." *Id.* at col. 4 ll. 41–47. "Protein A is a useful adsorbent for affinity chromatography of proteins, such as antibodies" because protein A reversibly binds with high affinity to a specific region common to most antibodies, the C_H2/C_H3 region. *Id.* at col. 2 ll. 6–11, col. 4 ll. 20–25, 30–31, col. 5 ll. 17–28.

In protein A affinity chromatography, a composition comprising a mixture of the target antibody and undesired impurities often present in harvested cell culture fluid (HCCF) is placed into the chromatography column. *Id.* at col. 18 ll. 47–51. The target antibody binds to protein A, which is covalently bound to the chromatography column resin, while the impurities and rest of the composition pass through the column. *Id.* at col. 18 ll. 47–51, col. 20 ll. 6–11. Next, the antibody of interest is removed from the chromatography column, typically with a low pH wash. *Id.* at col. 19 ll. 45–51. The antibody is collected as it is washed from the chromatography column, then typically subjected to further purification steps, and used for therapeutic purposes after formulation. *Id.* at col. 19 ll. 51–63.

While protein A affinity chromatography has been "a powerful tool . . . for purifying antibodies," it was known to have a downside. *See id.* at col. 20 ll. 6–12. Small amounts of the protein A that are attached to the chromatography column would "leach" (i.e., detach) from the column and contaminate the otherwise-purified antibody solution. *See id.* at col. 20 ll. 11–15, col. 4 ll. 48–50. Thus, further purification steps are typically employed to remove leached protein A from the antibody solution. *See id.* at col. 20 ll. 12–15.

The invention of the '799 patent "concerns a method for reducing leaching of protein A . . . by reducing [the] temperature" of the "composition that is subjected to protein A affinity chromatography." *Id.* at col. 1 ll. 16–21. The

specification discloses that "[p]referably, . . . the temperature of the composition is reduced below room temperature, for instance in the range from about 3°C to about 20°C, e.g. from about 10°C to about 18°C." *Id.* at col. 18 ll. 4–9. According to the patent, "[t]he temperature of the composition may be reduced prior to and/or during protein A affinity chromatography" and, in a preferred embodiment, involves "lowering the temperature of the harvested cell culture fluid (HCCF) which is subjected to chromatography." *Id.* at col. 18 ll. 9–16.

Claim 1, the sole independent claim at issue, recites:

> 1. A method of purifying a protein which comprises C_H2/C_H3 region, comprising subjecting a composition comprising said protein to protein A affinity chromatography at a temperature in the range *from about 10°C to about 18°C*.

Id. at col. 35 ll. 44–47 (emphasis added).

Hospira, Inc. sought IPR of claims 1–3 and 5–11 of the '799 patent. The Board instituted trial on all eight grounds of unpatentability, which all rely on WO '389[1] or van Sommeren[2] as the primary reference.

The Board determined that all the challenged claims were unpatentable as anticipated by WO '389 or rendered obvious by WO '389 alone or in combination with other prior art references. *'837 Decision*, 2018 WL 1187484, at

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[1] International Patent Application Publication WO 95/22389 A1, J.A. 508–54 (WO '389).

[2] van Sommeren et al., *Effects of Temperature, Flow Rate and Composition of Binding Buffer on Adsorption of Mouse Monoclonal IgG1 Antibodies to Protein A Sepharose 4 Fast Flow*, 22 PREPARATIVE BIOCHEMISTRY 135 (1992), J.A. 555–74 (van Sommeren).

*12, *19–20. Also, the Board construed "about 18°C," and based on that claim construction, it concluded that all the challenged claims were unpatentable as anticipated by van Sommeren or rendered obvious by van Sommeren alone or in combination with other prior art references. *Id.* at *13, *22.

Genentech appeals. The Patent Office intervened pursuant to 35 U.S.C. § 143 to defend against Genentech's constitutionality challenge to IPRs as applied to the '799 patent because it issued on October 5, 2010, which is before the enactment of the AIA in 2011. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review the Board's legal determinations de novo, and the Board's factual findings underlying those determinations for substantial evidence. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding. *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938).

Anticipation is a question of fact that we review for substantial evidence. *In re Rambus, Inc.*, 753 F.3d 1253, 1256 (Fed. Cir. 2014). Obviousness is a question of law based on underlying factual findings, including "the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art, and any objective indicia of non-obviousness." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)).

I. ANTICIPATION BY WO '389

The Board determined that claims 1 and 5 are anticipated by WO '389. *'837 Decision*, 2018 WL 1187484, at *8. WO '389 teaches a method for purifying certain antibodies of the IgG class, which are proteins comprising the

C_H2/C_H3 region, including a step wherein HCCF is subject to protein A affinity chromatography. J.A. 511 at 2:37, 522 at 13:9–13. WO '389 Example 1 discloses a washing step after HCCF is applied to the chromatography column, whereupon the HCCF composition is washed with at least three column volumes of buffer before the antibody is eluted. J.A. 523 at 14:20–23. WO '389 teaches that "[a]ll steps are carried out at room temperature (18–25°C)." J.A. 522 at 13:13.

Claim 1, the sole challenged independent claim of the '799 patent, requires "subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10°C to about 18°C." '799 patent at claim 1. The temperature range disclosed in WO '389, "18–25°C," overlaps with the claimed range of "about 10°C to about 18°C," regardless of the construction of "about 18°C." Indeed, Genentech's own proposed construction for "about 18°C" embraces temperatures up to 19°C, which further reinforces the overlap with WO '389's disclosed temperature range.

A prior art reference that discloses an overlapping but different range than the claimed range can be anticipatory, even where the prior art range only partially or slightly overlaps with the claimed range. *See Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 870–71 (Fed. Cir. 2015) (affirming summary judgment of anticipation of patent claims for composition with "0.05 to 0.5% by weight of at least one saturated fatty acid amide" lubricant in view of a prior art reference disclosing the same class of lubricant in an overlapping range of "0.1 to 5 parts by weight," and the parties agreed that a measurement in "% by weight" was equivalent to one in "parts by weight"). Once the patent challenger has established, through overlapping ranges, its prima facie case of anticipation, "the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention." *Id.* at 871; *see also E.I. DuPont de Nemours & Co. v.*

Synvina C.V., 904 F.3d 996, 1008 (Fed. Cir. 2018) ("'where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence' of . . . criticality") (quoting *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013)). Here, the Board found that Genentech failed to establish that the claimed temperature range of "about 10°C to about 18°C" is critical to performing protein A chromatography. *'837 Decision*, 2018 WL 1187484, at *10–11. Genentech does not challenge the Board's finding as to criticality, and accordingly, whether or not the claimed temperature range achieves different performance results than WO '389's disclosed temperature range is not at issue on appeal. Appellee's Br. at 15.

Aside from the overlapping range issue, the Board construed the limitation "subjecting a composition . . . to protein A affinity chromatography at a temperature in the range from about 10°C to about 18°C" as referring to the temperature of the composition *prior to and/or during* protein A affinity chromatography. *'837 Decision*, 2018 WL 1187484, at *8 (emphasis added). The Board found that WO '389's disclosed temperature range applies to all components used in the purification process, including the HCCF composition being purified. *'837 Decision*, 2018 WL 1187484, at *10. In that way, it found WO '389 discloses that *prior to* protein A affinity chromatography, the HCCF composition is at a temperature within the claimed range of "about 10°C to about 18°C." Additionally, the Board found that WO '389's disclosed composition's temperature reaches the claimed temperature range *during* protein A affinity chromatography. *'837 Decision*, 2018 WL 1187484, at *10. The Board read WO '389's teaching that "[a]ll steps are carried out at room temperature (18–25°C)" to mean that the apparatus of the chromatography column and column buffers are all within that temperature range. *Id.* Based on WO '389 Example 1's disclosure of washing the

composition with at least three column volumes of buffer, the Board inferred that the composition would reach "18–25°C" during the washing step, and thus be within the claimed temperature range. *Id.*

On appeal, Genentech argues that WO '389's statement that "[a]ll steps are carried out at room temperature (18–25°C)" refers *only* to the temperature of the laboratory where each step was performed, and *not* to the temperature of the HCCF composition applied to the chromatography column. Appellant's Br. at 33–34. Genentech contends this statement cannot be referring to the temperature of the HCCF composition because WO '389 discloses some "steps" being carried out where the composition was cold or frozen. J.A. 523–24 (disclosing that after the viral inactivation step "[t]he resulting solution is . . . held in sterile containers at 4°C, or frozen and held at -70°C"). Both parties' experts testified that HCCF comes from a bioreactor in which cells are typically cultured around 37°C. J.A. 1351–52 ¶ 77 (Dr. Cramer's testimony); J.A. 1531 (Dr. Przybycien's testimony). Both parties' experts also testified that WO '389 does not specify how long the HCCF was held before being subjected to protein A affinity chromatography. J.A. 1352 ¶ 78 (Dr. Cramer's testimony); J.A. 1554 (Dr. Przybycien's testimony). According to Genentech's expert, Dr. Cramer, efficiency is typically a goal of industrial processes, and absent an instruction to wait to allow the HCCF to cool to room temperature, a skilled artisan would have interpreted WO '389 as allowing the disclosed process to be performed with HCCF that was potentially warmer than room temperature. J.A. 1352 ¶ 78. Genentech contends that even if the laboratory was at "room temperature (18–25°C)," the HCCF composition need not have been. Appellant's Br. at 33.[3]

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[3] Although the dissent believes that WO '389's "room temperature" would not be understood to encompass

Hospira responds that WO '389 uses the term, "room temperature (18–25°C)," to describe the temperature for conducting protein A affinity chromatography, and all the components involved in that process, including the composition to be purified. Appellee's Br. at 29. According to Hospira's expert, Dr. Przybycien, in the field of antibody purification, absent contrary language, a skilled artisan would understand that experiments are being conducted at ambient temperature with all materials equilibrated in order to obtain robust scientific data. J.A. 946 ¶ 26. Based on WO '389's disclosure that the composition was cold or frozen after the viral inactivation step, Hospira contends that WO '389 specifically called out the temperature of the composition when requiring it to be at a temperature other than room temperature. Appellee's Br. at 31–32 (citing J.A. 523–24).

Here, substantial evidence supports the Board's finding that the HCCF subject to protein A affinity chromatography in WO '389 is within the claimed temperature range of claim 1. *'837 Decision*, 2018 WL 1187484, at *9–10. The Board reasoned that it would have been redundant to specifically call out the temperature of the HCCF during protein A affinity chromatography in light of WO '389's blanket statement to carry out all steps at "18–25°C." *Id.* at *9. The Board considered, but disagreed with, Dr. Cramer's interpretation of WO '389 as disclosing a process with HCCF that was warmer than "18–25°C" because his opinion was predicated on the view that the '799 patent is directed to large-scale, industrial processes, which it is not. *Id.* Further, Dr. Cramer testified that even for large-scale,

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temperatures as low as 18°C, WO '389 expressly discloses a temperature range that includes 18°C. Thus, the Board reasonably read the temperature range of WO '389 to encompass temperatures as low as 18°C. Genentech does not contend otherwise.

industrial processes, he was not aware of any process where HCCF was applied directly into the chromatography column after being removed from the bioreactor and filtered. *Id.* at *10 (citing J.A. 1075 at 85:6–15). The Board instead credited Dr. Przybycien's testimony that no skilled artisan would contact 37°C HCCF to the chromatography column, and report having performed the step at "room temperature (18–25°C)" because using HCCF that was warmer than the chromatography column would raise the temperature of the entire system, making it impossible to conduct "[a]ll steps . . . at room temperature." *'837 Decision*, 2018 WL 1187484, at *10 (citing J.A. 947 ¶ 27). To the extent that the experts disagreed with each other, the Board reasonably chose to credit the testimony of Dr. Przybycien over the testimony of Dr. Cramer. *Id.* at *9–10. *See Yorkey v. Diab*, 601 F.3d 1279, 1284 (Fed. Cir. 2010) ("[T]he Board was well within its discretion to give more credibility to [one expert's] testimony over [another's] unless no reasonable trier of fact could have done so."). We discern no reversible error in that choice.

We are not persuaded by Genentech's arguments that this result is contrary to the case law. Appellant's Br. at 36. *Nidec Motor Corp. v. Zhongshan Board Ocean Motor Co.*, cited by Genentech, holds that a reference missing a limitation cannot anticipate even if a skilled artisan would "at once envisage" the missing limitation. 851 F.3d 1270, 1274–75 (Fed. Cir. 2017). We do not agree with Genentech's argument that there is a "missing limitation." As discussed above, the Board reasonably found that a skilled artisan would have understood that WO '389's disclosed composition is within the claimed temperature range prior to or during protein A affinity chromatography. "Anticipation is established when 'one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim [limitation] was disclosed in that single reference.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1338 (Fed. Cir. 2017) (quoting *Akamai Techs., Inc. v.*

Cable & Wireless Internet Servs., Inc., 344 F.3d 1186, 1192–93 (Fed. Cir. 2003)). That is the case here.

Genentech does not raise any arguments with respect to any other claim limitation, nor does it separately argue dependent claim 5. Thus, dependent claim 5 stands or falls together with independent claim 1. *See In re Kaslow*, 707 F.2d 1366, 1376 (Fed. Cir. 1983). We therefore conclude that substantial evidence supports the Board's finding that WO '389 anticipates claims 1 and 5 of the '799 patent.

II. OBVIOUSNESS GROUNDS BASED ON WO '389

The Board determined that claims 1 and 5 would have been obvious over WO '389; claims 1–3 and 5 would have been obvious in view of WO '389, Balint,[4] and Potier[5]; and claims 2–3 and 6–11 would have been obvious in view of WO '389, Balint, Potier and/or U.S. Patent 6,127,526. As with anticipation, Genentech challenges the Board's determination that WO '389's disclosed temperature range renders the claimed temperature range obvious.

If the relevant comparison between a disputed claim limitation and the prior art pertains to a range of overlapping values, "we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). We have said such an overlap creates a presumption of obviousness, and that the burden

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[4] Joseph P. Balint, Jr. and Frank R. Jones, *Evidence for Proteolytic Cleavage of Covalently Bound Protein A from a Silica Based Extracorporeal Immunoadsorbent and Lack of Relationship to Treatment Effects*, 16 TRANSFUS. SCI. 85 (1995), J.A. 578–87 (Balint).

[5] P. Potier et al., *Temperature-Dependent Changes in Proteolytic Activities and Protein Composition in the Psychrotrophic Bacterium Arthrobacter Globiformis $S_1$55*, 136 J. GEN. MICROBIOL. 283 (1990), J.A. 592–600 (Potier).

of production falls upon the patentee to come forward with pertinent evidence that the overlapping range would not have been obvious in light of the prior art. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006, 1008 (Fed. Cir. 2018) (collecting cases).

One way in which the patentee may rebut the presumption of obviousness is by showing "that there is something special or critical about the claimed range." *Id.* The presumption of obviousness applies here, and the Board found that Genentech failed to establish criticality for the claimed temperature range. *'837 Decision*, 2018 WL 1187484, at *18. On appeal, Genentech does not argue that this Board finding lacks substantial evidence. Appellee's Br. at 15.

Another way in which the presumption can be rebutted is by showing that a process parameter, such as temperature, was not recognized as "result-effective." *DuPont*, 904 F.3d at 1006 (citing *Applied Materials*, 692 F.3d at 1295). "The idea behind the 'result-effective variable' analysis is . . . that a person of ordinary skill would not always be motivated to optimize a parameter 'if there is no evidence in the record that the prior art recognized that [that] particular parameter affected the result.'" *Id.* at 1008 (quoting *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977)). But where the prior art recognizes that the process parameter affects the relevant property or result, then the process parameter is "result-effective." *Id.* at 1009.

The Board found that a skilled artisan would have recognized that the temperature for conducting protein A affinity chromatography was a result-effective variable. *'837 Decision*, 2018 WL 1187484, at *18. The Board found that it was recognized in the prior art at the time of the invention that leaching was caused by proteolysis of matrix-bound protein A (as illustrated in Balint and other prior art references), and that proteolysis was affected by temperature (as illustrated in Potier). *Id.*; *see id.* at *19; J.A. 594,

596 (Potier demonstrating that the extent of protein degradation caused by proteolysis increased with temperature). Moreover, the Board found that a skilled artisan would have expected that lowering temperature would reduce proteolysis of matrix-bound protein A, and consequently, would reduce protein A leaching. *Id.* at *17; *see id.* at *19.

"The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of . . . ranges is the optimum combination." *Peterson*, 315 F.3d at 1330. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (citing *In re Aller*, 220 F.2d 454, 456 (1955)). The Board reasonably found that a skilled artisan would have been motivated to optimize the temperature given the teachings of the prior art, and that given the ease with which temperature can be varied, finding an optimal temperature range would have been nothing more than routine experimentation. *'837 Decision*, 2018 WL 1187484, at *18–19.

On appeal, Genentech does not appear to contest that temperature is a result-effective variable in the claimed process. Instead, Genentech argues that the desire to reduce protein A leaching applies *only* to the large-scale, industrial purification of therapeutic antibodies for clinical applications, because non-clinical applications do not involve concerns about product purity that require the elimination of leached protein A. Appellant's Br. at 41. Genentech further contends that chilling HCCF for large-scale, industrial processes would have been inconvenient, costly, and impractical. Appellant's Br. at 45.

Hospira responds that it would be desirable to reduce protein A leaching for non-clinical applications because protein A leaching degrades chromatography columns, reducing their usable capacity and life span. Appellee Br. at

46 (citing J.A. 932). The Board correctly noted that neither the challenged claims nor the disclosure of WO '389 are limited to large-scale, industrial processes. *'837 Decision*, 2018 WL 1187484, at *9. The evidence in the record supports the Board's finding that the temperature of the chromatography column could be readily controlled. We hold that substantial evidence supports the Board's conclusion that it would have been routine experimentation to explore the temperature dependence of protein A leaching. Genentech has not shown that the Board's factual findings are unsupported by substantial evidence.

The Board considered Genentech's evidence of objective indicia of nonobviousness but found it to be unpersuasive. *'837 Decision*, 2018 WL 1187484, at *19. Genentech alleged industry praise and recognition by others in the field based on the selection of a presentation relating to the claimed method at the American Chemical Society's National Meeting in 2005. Genentech contends that the fact that its research was selected for presentation undermines the Board's conclusion that the claimed method would have been the obvious result of "routine optimization." Appellant's Br. at 52–53. Hospira responds, and we agree, that Genentech fails to establish a nexus between the objective indicia and the claimed method because there was no evidence that the presentation was selected due to the claimed method. Appellee Br. at 53. Substantial evidence supports the Board's decision to accord little weight to Genentech's evidence of objective indicia.

The Board next determined that claims 2–3 and 6–11 would have been obvious over WO '389, Balint, Potier and/or U.S. Patent 6,127,526. Genentech does not separately argue the dependent claims and relies on the arguments it raised for anticipation and obviousness over WO '389. Thus, the dependent claims stand or fall together with the independent claim 1. *See Kaslow*, 707 F.2d at 1376. We therefore conclude that the Board did not err in concluding that claims 1–3 and 5–11 of the '799 patent

would have been obvious over WO '389 alone or in combination with other prior art references.

IV. OTHER ISSUES

Genentech also argues that because the Board erred in construing "about 18°C," the claims are not anticipated by van Sommeren nor obvious over grounds that include van Sommeren. Because we have determined that the Board did not err in concluding that all of the challenged claims are unpatentable on grounds based on WO '389, we need not reach the arguments involving van Sommeren. *See* Oral Arg. at 2:01–2:50, *Genentech, Inc. v. Hospira, Inc.*, No. 2018-1933 (Fed. Cir. Aug. 5, 2019), http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2018-1933.mp3.

Finally, we address Genentech's challenge that retroactive application of IPR to a patent issued prior to passage of the AIA constitutes a violation of the Fifth Amendment's Takings Clause.[6] We recently addressed this issue in *Celgene Corp. v. Peter*, 931 F.3d 1342, 1356–63 (Fed. Cir. 2019). As we explained, pre-AIA patents were issued subject to both district court and Patent Office validity proceedings. *Id.* at 1359. Though IPR differs from district court and pre-AIA Patent Office reexamination proceedings, we held that those differences were not sufficiently substantive or significant such that a "constitutional issue" is created when IPR is applied to pre-AIA patents. *Id.* at 1362; *see also id.* at 1358 & n.13 (affirming that our prior decisions ruling that retroactive application of reexamination does not violate the Fifth Amendment, the Seventh

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[6] To the extent Genentech intends to separately raise a due process challenge, the limited conclusory assertions it presented are "insufficient to preserve the issue for appeal." *See Trading Techs. Int'l, Inc. v. IBG LLC*, 921 F.3d 1378, 1385 (Fed. Cir. 2019).

Amendment, or Article III "control the outcome" of similar challenges to IPR).

Like the patent at issue in *Celgene*, when the '799 patent issued, patentees already expected that their patents could be challenged in district court and "[f]or forty years" had expected that "the [Patent Office] could reconsider the validity of issued patents on particular grounds, applying a preponderance of the evidence standard." *Id.* at 1363. Accordingly, application of IPR to Genentech's patent, on grounds that were available for Patent Office reconsideration when the patent was issued and under the same burden of proof, does not create a constitutional issue, and we reject Genentech's constitutional challenge.

CONCLUSION

We have considered Genentech's remaining arguments but find them unpersuasive. For the foregoing reasons, we *affirm* the decision of the Board.

AFFIRMED

United States Court of Appeals for the Federal Circuit

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UNITED STATES,
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Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-01837.

NEWMAN, *Circuit Judge*, dissenting.

I respectfully dissent, for the court finds the claims of U.S. Patent 7,807,799 ("the '799 patent") invalid for anticipation or obviousness, although no prior art shows the claimed method, or suggests that it should be attempted or that it might be successful. The court presents a hindsight determination that this apparently simple solution to a difficult problem is anticipated and obvious, although it was not known or obvious to the scientists who were attempting to solve the problem of leaching contamination, and the experts for both sides agreed that the solution presented in the '799 patent was new to them.

The '799 patent describes the complexities of obtaining and purifying biological products such as antibodies, in the purity and on the scale needed for medicinal use. The patent describes a procedure called "protein A affinity chromatography," and its known use with biological materials. The patent describes the problem that the inventors encountered due to leaching of the protein A. The inventors described their discovery of the cause of the leaching, and the solution they found. This solution is not shown or suggested in the prior art—yet is deemed anticipated or obvious by my colleagues.

The '799 invention

The '799 patent is directed to the separation and purification of specified antibodies from the harvested cell culture fluid. Protein A affinity chromatography was a known tool for purifying antibodies. '799 patent col. 20, ll. 6–7. Protein A has "the ability to bind proteins which have a C_H2/C_H3 region." *Id.* at col. 4, ll. 20–25. In protein A affinity chromatography, the antibody containing "a C_H2/C_H3 region may be reversibly bound to, or adsorbed by, the protein A," the protein A extracts the antibody from its cell culture fluid, and the pure antibody is eluted. *Id.* at col. 4, ll. 27–47; *Id.* at col. 1, ll. 56–66. "Dynamic capacity" of protein A affinity chromatography "depends on many factors, including the type of protein A affinity chromatography media, the antibody concentration in the load, the column temperature and column length, the buffer, conductivity, and pH of the load, and the flow rate." J.A. 1312.[1]

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[1] This scientific article, authored by an inventor of the '799 patent, discusses protein A affinity chromatography for purification of biologicals. Fahrner et al., *The Optimal Flow Rate and Column Length for Maximum*

Genentech states that in its commercial-scale process for preparing specified antibodies, it was found that small but unacceptable amounts of protein A had leached from the column and contaminated the eluted antibody. Although the prior art describes possible procedures for removing any contaminating protein A, the Genentech inventors testified, and the experts for both sides agreed, these procedures were not effective for these antibodies. The Genentech research team "spent months trying to solve the leached protein A problem, under significant commercial pressure." J.A. 1436. "The research team eventually observed that . . . leaching might be caused by proteolysis" leading to "a series of experiments using reduced temperature and protease inhibitors." J.A. 1435.

Thus the inventors found the solution of temperature reduction, as described and claimed in the '799 patent. The retrospective simplicity of the solution apparently led the Board to find it obvious to them, despite the undisputed testimony that no reference suggests this solution to the contamination problem here encountered, as the experts for both sides acknowledged. On this appeal, Hospira offers no contradictory evidence, prior art, or argument.

Nonetheless, the Board held this novel method to be anticipated and obvious, although not described or suggested in the prior art; and my colleagues agree.

The prior art temperature range does not show or suggest the '799 invention

Claim 1 of the '799 patent states the temperature and other limitations for conduct of the claimed method:

> 1. A method of purifying a protein which comprises a C_H2/C_H3 region, comprising subjecting

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Production Rate of Protein A Affinity Chromatography, 21 Bioprocess Engineering 287 (1999)), J.A. 1312–17.

> a composition comprising said protein to protein A affinity chromatography at a temperature in the range from about 10 º C. to about 18 º C.

'799 patent col. 35, ll. 44–47.

The '799 patent specification describes the invention as "a method of purifying a protein which comprises a C_H2/C_H3 region, comprising reducing the temperature of a composition comprising the protein and one or more impurities subjected to protein A affinity chromatography in the range from about 3º C. to about 20º C., wherein protein A leaching is reduced." *Id.* at col. 2, ll. 22–27. The specification further states: "Preferably, the method comprises reducing the temperature of the composition subjected to the protein A affinity chromatography, e.g. where the temperature of the composition is reduced below room temperature, for instance in the range from about 3º C. to about 20º C., e.g. from about 10º C. to about 18º C." *Id.* at col. 18, ll. 4–9.

The Board discarded this description, stating that it was merely a "preferred embodiment," whereby the Board "decline[d] to rewrite claim 1." *Hospira, Inc. v. Genentech, Inc.*, No. IPR2016-01837, 2018 WL 1187484, at *6 (P.T.A.B. Mar. 6, 2018) ("Board Op."). The Board stated that "understanding the claim language may be aided by the explanations contained in the written description, [but] it is important not to import into a claim limitations that [which is] not a part of the claim," quoting *SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004)), the Board apparently ignoring that claim 1, and all the claims, explicitly require "a temperature in the range from about 10 º C. to about 18 º C." *See* Board Op. at *6. The Board's statement that it "decline[d] to rewrite claim 1" is puzzling, for claim 1 as written is limited to the preferred embodiment.

The '799 patent specification describes the protein A affinity chromatography of 12,000 liters of cell culture fluid, chilled to "15 +/– 3º C," supporting the temperature limit of "about 18 º C" in the claims. '799 patent col. 21, ll. 4–8.

The Board cited the prosecution history of a related patent, and found that Genentech "limited the meaning of 'about' in the term 'about 18 ºC' to at least ±>2 ºC, but less than ±4º C." Board Op. at *7. Genentech amended the upper limit of its claims from "20ºC" to "about 18ºC" in view of a reference that showed affinity chromatography at "about 22ºC." J.A. 733–43, 740. The Board recited that "self-serving statements in the prosecution" are "accord[ed] little weight." Board Op. at *7. To the contrary, statements during prosecution are a primary resource and rigorous commitment in construing patent claims. *Phillips v. AWH Corp.,* 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc). The Board's construction that the range of "about 10 º C. to about 18 º C." reads on the prior art is not supported in fact or law.

The Board cited, and my colleagues discuss, two principal references. The scientific article of van Sommeren[2] includes data for protein A affinity chromatography performed at the standard of ambient temperature. The article compares results at "ambient temperature (AT) (20–25 ºC)" with results in a cold room at 4 ºC. J.A. 570. Based on this reference, the Board reasoned that 20–25ºC "overlaps with [its] construction of 'about 18º C.' as having an upper bound of 21 ºC." Board Op. at *12. Thus the

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[2] van Sommeren et al., *Effects of Temperature, Flow Rate and Composition of Binding Buffer on Adsorption of Mouse Monoclonal IgG$_1$ Antibodies to Protein A Sepharose 4 Fast Flow*, 22(2) Preparative Biochemistry 135 (1992), J.A. 555–74 ("van Sommeren").

Board held the '799 patent claims anticipated or obvious in view of van Sommeren.

The other principal reference, WO '389,[3] shows protein A chromatography in which "[a]ll steps are carried out at room temperature (18–25 °C)." J.A. 522. The WO '389 application recognizes that protein A may leach from the column, and states that its removal from the eluent may require "hydrophobic interaction chromatography." J.A. 512–13 ("Although Protein A affinity column chromatography is widely used, it is also appreciated that elution of antibody from such columns can result in leaching of residual Protein A from the support. . . . It has now been surprisingly discovered that HIC [hydrophobic interaction chromatography] can be usefully employed to remove contaminating Protein A."). Genentech points to the advantages of its method, in contrast with the WO '389 teaching of the need to conduct another chromatographic procedure to remove the contaminating Protein A.

The experts for both sides agreed that the WO '389 application's room temperature of 18–25°C refers to the ambient temperature, not the temperature of the chilled material in the column. J.A. 1350–53, 1547–48. Nonetheless, the PTAB and now my colleagues hold that this "room temperature" range anticipates the '799 patent's chilled range of 10°C–18°C, ignoring the significantly different results in the recited ranges. The general understanding of room temperature is in the range of 21°C–25°C (69°F –77°F), as the experts for both sides testified. J.A. 1346–50, 1599–1600. The '799 patent specification shows 15±3°C as the basis for the 18°C limit in the claims. No reference contemplates or suggests or hints that chilling below room temperature for the affinity chromatographic process

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[3] International Patent Application Publication No. WO 95/22389 A1, J.A. 508–54 ("WO '389").

would eliminate the contaminating leaching of the protein A.

WO '389's lower edge of 18ºC does not anticipate the chilled range of 10ºC–18ºC. The abutment at 18ºC between the claimed chilled temperature range and room temperature does not produce anticipation of the lower range. Anticipation requires that the same invention, including all claim limitations, was previously described. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.,* 851 F.3d 1270, 1274–75 (Fed. Cir. 2017) (holding that precedent "does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them."). Neither party's expert testified that the prior art showed that lowering the temperature below the norm of protein A affinity chromatography would eliminate leaching of protein A.

It was conceded that no reference showed or suggested the solution that was here discovered, and no expert witness acknowledged this practice. Hospira's expert testified:

> Q. . . . Are you aware of anyone prior to July of 2003 doing protein A chromatography at a reduced temperature using a jacketed column and/or a chilling tank?
>
> A. I have not seen that.

J.A. 1667–68.

The '799 patent specification describes that by conducting the affinity chromatography in the range of 10ºC–18ºC, substantially all of the leaching of protein A is prevented. However, my colleagues hold that the mention of 18ºC as the lower boundary of room temperature anticipates the claimed range of 10ºC–18ºC—and that this ends the inquiry. That is not the law of anticipation. An anticipating reference must describe the entirety of the claimed subject matter. "Anticipation is established when 'one skilled in

the art would reasonably understand or infer from the prior art reference's teaching that every claim [limitation] was disclosed in that single reference.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1338 (Fed. Cir. 2017) (quoting *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1192–93 (Fed. Cir. 2003)).

My colleagues nonetheless find the mention of a "room temperature" lower edge of 18ºC in the 18–25ºC range to be a fatal anticipation of the claimed 10ºC–18ºC range, despite the absence of identity of these ranges, despite the different results at the lower range, and despite the significance of the purity of the eluted antibody.

Precedent does not support my colleagues' finding of anticipation, for precedent requires that to anticipate, the prior art must describe the same invention. *See id.*; *King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1274 (Fed. Cir. 2010) ("[A] claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." (internal quotation marks omitted)). The prior art does not show the 10ºC–18ºC range, and the specification supports the distinction with description of the different characteristics of the cooled material. Nothing in the prior art suggested that the leaching of protein A could be prevented by lowering the temperature, with no adverse effect on the efficacy of the affinity purification, and no loss of the purified antibody.

The experts for both sides agreed that the prior art does not show or suggest that this 10ºC–18ºC temperature range would produce the favorable results that were achieved. Contrary to my colleagues' reasoning, this is not simply a matter of selecting the optimum temperature within a taught temperature range for conducting a known procedure. Neither the cooled temperature range nor the result of cooling the material subjected to protein A affinity chromatography is shown or suggested in the prior art.

Nor is the question whether it would be easy to experiment at varying temperatures, as my colleagues suggest. Maj. Op. at 13 ("The Board reasonably found that a skilled artisan would have been motivated to optimize the temperature given the teachings of the prior art, and that given the ease with which temperature can be varied, finding an optimal temperature range would have been nothing more than routine experimentation."). However, the question is not whether it would have been easy to cool the material to the 10°C–18°C range; the question is whether it would have been obvious to do so. Contrary to the Board's and the court's view, this is not a matter of optimizing a known procedure to obtain a known result; for it was not known that cooling the material for chromatography would avoid contamination of the purified antibody with leached protein A.

The Board's holding that the '799 method is anticipated by van Sommeren and WO '389 is devoid of support by substantial evidence, for the only evidence was that these are different procedures conducted under different conditions to achieve different purposes.

The Board and this court err in holding the '799 patent claims invalid on the grounds of anticipation and obviousness, for no prior art shows or suggests the claimed procedure.