NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

MERCK SHARP & DOHME CORP.,
Appellant

v.

WYETH LLC,
Appellee

2018-2133, 2018-2134

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-00378, IPR2017-00380.

Decided: November 26, 2019

JEFFREY A. LAMKEN, MoloLamken LLP, Washington, DC, argued for appellant. Also represented by MICHAEL GREGORY PATTILLO, JR., BENJAMIN THOMAS SIROLLY; SARA MARGOLIS, New York, NY; ARLENE L. CHOW, Hogan Lovells US LLP, New York, NY; RYAN BOYD MCCRUM, Jones Day, Cleveland, OH; JENNIFER LORAINE SWIZE, Washington, DC.

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Before PROST, *Chief Judge,* DYK and WALLACH, *Circuit Judges.*

DYK, *Circuit Judge.*

Merck Sharp & Dohme Corp. ("Merck") appeals decisions of the Patent Trial and Appeal Board ("Board") declining to find claim 18 of U.S. Patent No. 8,562,999 ("the '999 patent") unpatentable as obvious. We vacate and remand for further proceedings.

BACKGROUND

The '999 patent, owned by Wyeth LLC ("Wyeth"), is directed to formulations for stabilizing polysaccharide-protein conjugate vaccines. These vaccines are derived from the capsular polysaccharides present on the surface of certain disease-causing bacteria. The human immune system can use these capsular polysaccharides to detect and identify different serotypes (i.e., strains) of a species of bacteria. Polysaccharide vaccines can be monovalent (comprising a single serotype), or multivalent (comprising multiple serotypes). For example, a 13-valent vaccine would contain polysaccharides from 13 different serotypes. Because these polysaccharides typically have low immunogenicity (i.e., ability to provoke an immune response), it is desirable to enhance the effectiveness of these vaccines by conjugating (i.e., bonding) the polysaccharides to a carrier protein with high immunogenicity. However, as the '999 patent explains, polysaccharide-protein conjugate vaccines aggregate (i.e., clump together) when exposed to silicone oil, a common lubricant used in vaccine storage containers. The invention described in the '999 patent is a formulation that inhibits silicone-induced aggregation by suspending the polysaccharide-protein conjugate in a mixture of (1) a pH-buffered saline solution and (2) an aluminum salt.

Claim 1, the sole independent claim of the '999 patent, recites a formulation comprising of: (1) a pH-buffered saline solution, (2) an aluminum salt, and (3) one or more polysaccharide-protein conjugates. Claim 18 recites a specific 13-valent pneumococcal polysaccharide conjugate with CRM_{197} as the sole carrier protein for use with the formulation recited in claim 1.

On December 1, 2016, Merck filed two petitions for *inter partes* review with the Board, challenging claims 1–6, 10, 11, 14, and 17–20 of the '999 patent. The Board instituted review of all challenged claims in two parallel proceedings, IPR2017-00378 ("the 378 IPR") and IPR2017-00380 ("the 380 IPR"). In each proceeding, the Board found all the challenged claims except one—claim 18—to be unpatentable as obvious. Claim 18 covers a 13-valent pneumococcal conjugate vaccine. In both proceedings, the Board rejected Merck's argument that the formulation recited by claim 18 was obvious in light of the prior art. Merck appeals the Board's decisions as to claim 18. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

"We review the Board's factual findings for substantial evidence and review its legal conclusions de novo." *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1280 (Fed. Cir. 2015). "The ultimate determination of obviousness under [35 U.S.C.] § 103 is a question of law based on underlying factual findings." *Id.*[1] "The presence or absence of a

[1] Congress amended § 103 when it enacted the Leahy-Smith America Invents Act ("AIA"). Pub. L. No. 112-29, § 3(b)(1), 125 Stat. 284, 285–87 (2011). However, because the application that led to the '999 patent has never contained (1) a claim having an effective filing date on or after March 16, 2013, or (2) a reference under 35 U.S.C. §§ 120, 121, or 365(c) to any patent or application

motivation to combine references in an obviousness determination is a pure question of fact." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016) (quoting *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014)). "The presence or absence of a reasonable expectation of success is also a question of fact." *Id.* (quoting *Par Pharm.*, 773 F.3d at 1196).

I

It is well established that "[t]he agency tribunal must make findings of relevant facts, and present its reasoning in sufficient detail that the court may conduct meaningful review of the agency action." *In re Lee*, 277 F.3d 1338, 1346 (Fed. Cir. 2002). "The [Board]'s own explanation must suffice for us to see that the agency has done its job and must be capable of being 'reasonably . . . discerned' from a relatively concise [Board] discussion." *In re NuVasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) (quoting *In re Huston*, 308 F.3d 1267, 1281 (Fed. Cir. 2002)).

On appeal, Merck argues that the Board's decisions here fail to provide a reasoned basis for upholding claim 18. For the reasons discussed below, we agree.

Claim 18 depends on claim 1, which recites:

> A formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) an aluminum salt and (iii) one or more polysaccharide-protein conjugates, wherein the formulation is comprised in a siliconized container means and inhibits aggregation induced by the siliconized container means.

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that ever contained such a claim, the pre-AIA § 103 applies. *See id.* § 3(n)(1), 125 Stat. at 293.

'999 patent, col. 31, ll. 7–12.

Claim 18 recites:

> The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises [13 different *S. pneumoniae* serotype polysaccharides conjugated to a CRM_{197} polypeptide].

'999 patent, col. 32, ll. 24–45.[2]

In the 378 IPR, Merck challenged claim 1 as obvious in light of International PCT Application No. WO 03/009869 ("Chiron"); Edward J. Smith, *Siliconization of Parenteral Drug Packaging Components* (1988) ("Smith"); and International PCT Application No. WO 2004/071439 ("Elan"). In the 380 IPR, Merck challenged claim 1 as obvious in light of Chiron and Annex I of the European Medicines Agency's European Public Assessment Report for Prevenar ("Prevenar"). In both proceedings, the Board made detailed findings that claim 1 was obvious in light of the cited references.[3] The Board also found that a skilled artisan "would have found it obvious to prepare Chiron's formulation [according to claim 1 and also] comprising the seven

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[2] The 13 serotypes are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

[3] The Board found that "Chiron teaches a formulation comprising the ingredients [pH-buffered saline solution, aluminum salt, and one or more polysaccharide-protein conjugate] recited in independent claim 1," J.A. 21, that "a person of ordinary skill in the art would have had reason to provide Chiron's formulation in a siliconized container means, and would have had a reasonable expectation of successfully doing so, as had been done with other . . . conjugate vaccines [identified by Chiron]," J.A. 29, and that "a person of ordinary skill in the art would have appreciated that Chiron's formulation inhibits aggregation induced by a siliconized container means," J.A. 32.

valent conjugate recited in claim 17." J.A. 37. Wyeth does not challenge either of these determinations on appeal.

In each proceeding, Merck also challenged dependent claim 18 as obvious in light of the previously cited references and in combination with an additional reference, Peña et al., *Present and Future of the Pneumonia Vaccination*, 24 Pediatrika 47 (2004) ("Peña"). Peña disclosed a study involving a 13-valent conjugate, but did not disclose conjugating with the CRM_{197} protein as required by claim 18.

The Board found that although Peña disclosed a "13-valent pneumococcal conjugate vaccine with the same serotypes recited by claim 18 that is described as being in an 'advanced phase of study,'" Merck failed to "direct [the Board] to any disclosure in Peña, or other evidence of record, further characterizing the vaccine or the study." J.A. 44 (citing J.A. 272, 992), *see also* J.A. 86. The Board stated that it was "unable to assess whether the study involved a formulation comprising each of the thirteen known serotypes conjugated to a CRM_{197} polypeptide, [the carrier protein] required by the claim, or if such an attempt was even considered, tried, and successful." *Id.* The Board concluded that Merck "ha[d] not provided a reason that a person of skill in the art would have modified Chiron's formulation to comprise a thirteen valent conjugate," and that "[Merck] ha[d] not provided sufficient evidence for [the Board] to determine whether a skilled artisan who endeavored to modify Chiron's formulation to yield a 13-valent pneumococcal conjugate vaccine with the same serotypes as in Peña would have had a reasonable expectation of successfully doing so." *Id.* at 44.

The Board found—and there is no dispute—that Peña discloses each of the 13 serotypes in claim 18. Merck's expert testified (without contradiction from Wyeth's expert) that early pneumococcal polysaccharide vaccines included 14-valent and 23-valent unconjugated vaccines which,

together, included all 13 serotypes, and that it would have been obvious to combine them. At oral argument in this court, Wyeth made little effort to counter Merck's contentions that each of the 13 serotypes was disclosed in the prior art and that there was motivation to combine the 13 serotypes into a single vaccine. Furthermore, Wyeth was unable to identify any expert testimony in the record suggesting that the 13-serotype combination was not obvious. On this record, Merck established that it was obvious to combine the 13 serotypes into a single vaccine.

Instead, the question was whether it was obvious to conjugate the 13 serotypes to the CRM_{197} protein in a single vaccine. The Board's decision rests on its finding that the study discussed in Peña did not show that "a formulation comprising each of the thirteen known serotypes conjugated to a CRM_{197} [protein] . . . was even considered, tried and successful." J.A. 44. Standing alone, this finding is insufficient to support a lack of motivation or a reasonable expectation of success. Obviousness, unlike anticipation, does not require a prior art successful formulation. *See Par Pharm.*, 773 F.3d at 1198. Here, there was conflicting evidence as to motivation and reasonable expectation of success—evidence not discussed by the Board.

Even if we assume that the Board found that Peña itself did not suggest conjugating the 13-valent combination with CRM_{197}, the Board found that Chiron identified CRM_{197} as a "particularly preferred" carrier protein. J.A. 19. Merck's expert testified that "[o]ne of the studies cited in [Peña] describes the 9-valent version of the vaccine as being conjugated to only the single CRM_{197} carrier," J.A. 697, and Wyeth's expert conceded that the prior art disclosed "Wyeth's 9-valent conjugate vaccine in which the carrier protein is CRM_{197}," J.A. 6098. But the parties' experts differed as to the 11-valent conjugate vaccine. Merck's expert testified that that "it had been reported in the literature that, prior to 2004, Wyeth's . . . 11-valent conjugate vaccine[] used only CRM_{197} as a carrier protein."

J.A. 697. On the other hand, Wyeth's expert stated that none of the references "provide any citations or references to describe or even confirm the existence of the 11-valent pneumococcal CRM_{197} conjugate vaccine allegedly being developed by Wyeth," and that "[i]n fact, the two 11-valent vaccines in development at the time were Sanofi's mixed carrier vaccine and GSK's protein D carrier vaccine." J.A. 6098–99. Merck's expert testified that "as of April 26, 2006, [the priority date of the '999 patent,] a [skilled artisan] would have found it obvious to select the 13 conjugates recited in [Peña] (each conjugated to CRM_{197}) for a polysaccharide-protein conjugate vaccine." J.A. 698. Wyeth's expert testified to the contrary that Peña "would not have lead a [skilled artisan] to conclude that the 7-valent conjugate vaccine . . . could be expanded to the 13-valent pneumococcal polysaccharide single-carrier CRM_{197} conjugate vaccine of claim 18 with a reasonable expectation of success." J.A. 6098.

Merck's expert, relying on a memorandum purportedly drafted by Ireland's Environmental Protection Agency, testified that "Wyeth applied for a facility license to produce the 13-valent conjugate vaccine . . . around 2003," and that the memorandum noted that "CRM_{197} would be the only carrier protein for the . . . 13-valent version[] of the vaccine." J.A. 698 (citing J.A. 1253). However, the Board declined to rely on that memorandum, stating that it was "cumulative to previously submitted evidence, or related to issues disposed upon other bases." J.A. 48.

The parties' differences primarily concerned whether a skilled artisan would have been dissuaded from using a single carrier protein (i.e. CRM_{197}) due to "immune interference," a phenomenon that may result in decreased immunogenicity in multivalent vaccines with a sole carrier protein. Merck argues that the immune interference issue is irrelevant, quoting the Board's claim construction of the term "polysaccharide-protein conjugate[]" as not requiring "any specific level of immunogenicity for the composition."

J.A. 10. However, this issue is relevant to whether a skilled artisan would have been motivated to conjugate the 13 serotypes with CRM_{197} as a sole carrier protein. "If all elements of a claim are found in the prior art, as is the case here, the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references . . . ." *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.").

On the issue of immune interference, Wyeth's expert testified that "[a] [person of ordinary skill in the art] would have had significant concerns expanding the formulation of [the 7-valent] Prevenar [prior art reference] because of the possible loss of immunogenicity due to 'immune interference' when developing a 13-valent conjugate vaccine," and that "[v]accine development researchers believed that mixed-carrier [i.e., multiple different] conjugates provided the most reasonable technical solution for increasing the number of polysaccharide serotypes in a multivalent conjugate vaccine." J.A. 6090–91. On the other hand, Merck's expert testified that he "strongly disagree[d]" with the assertion that "concerns over 'immune interference' would have dissuaded a [person having ordinary skill in the art] from pursuing a 13-valent formulation in which each polysaccharide is conjugated to [only] CRM_{197}." J.A. 699.

Despite these clearly disputed factual issues, the Board simply did not address the evidence as to whether someone skilled in the art would have been motivated to combine the 13 serotypes into a CRM_{197} conjugate or whether the potential loss of immunogenicity would have dissuaded someone skilled in the art from making such a combination. The fact that Peña did not disclose such a combination fails to answer this central question, and an

explanation was particularly necessary given the Board's finding that the use of CRM_{197} was obvious with the 7-valent conjugate in claim 17—which also uses CRM_{197} as a sole carrier protein. We conclude that the Board's decision is too cryptic to survive judicial review.

Under these circumstances, "we have consistently vacated and remanded for further proceedings." *In re Van Os*, 844 F.3d 1359, 1362 (Fed. Cir. 2017). We therefore vacate the Board's obviousness findings with respect to claim 18, and remand for further consideration of the parties' arguments and evidence as to (1) motivation to combine and (2) reasonable expectation of success and, if the Board finds a sufficient motivation to combine and reasonable expectation of success, other issues such as secondary considerations.[4] We do not reach Merck's remaining arguments.

VACATED AND REMANDED

COSTS

No Costs.

[4] The Board in its decision did not consider the Ireland Environmental Protection Agency memorandum. On remand, the Board should consider these documents and their probative value.