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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,

Petitioner

v.

WYETH LLC.,

Patent Owner

Case IPR2017-01211
Patent 9,399,060 B2

Before TONI R. SCHEINER, GRACE K. OBERMANN, and ULRIKE W. JENKS, Administrative Patent Judges.

OBERMANN, *Administrative Patent Judge.*

DECISION

Denying Institution of *Inter Partes* Review
35 U.S.C. § 314; 37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner filed a Petition for *inter partes* review of claims 1–13 of U.S. Patent No. 9,399,060 B2 (Ex. 1001, "the '060 patent"). Paper 1 ("Pet."). Patent Owner filed a timely Preliminary Response. Paper 8 ("Prelim. Resp."). Based on the information presented in the Petition and the Preliminary Response, we hold that Petitioner has not demonstrated that it is reasonably likely to prevail at trial in showing that at least one challenged claim of the '060 patent is unpatentable.

Accordingly, we deny the Petition.

A. Related Proceedings

Petitioner identifies two related requests for *inter partes* review that it filed in connection with the '060 patent. Pet. 5 (citing Cases IPR2017-01215 and IPR2017-01223). Concurrently herewith, we issue decisions in those two proceedings.

Petitioner also acknowledges that it filed two Petitions for post grant review of U.S. Patent No. 9,399,060 ("the '060 patent"). *Id*. (citing Cases PGR2017-00016 and PGR2017-00017). Concurrently herewith, we issue a consolidated decision in those two proceedings.

Petitioner identifies as related matters three prior Petitions for *inter partes* review of U.S. Patent No. 8,562,999 ("the '999 patent"). *Id*. at 6 (citing Cases IPR2017-00378, IPR2017-00380, and IPR2017-00390). The claims in the '999 patent are directed to formulations containing polysaccharide-protein conjugates. The Board instituted trial in those three proceedings on June 13, 2017.

The '060 Patent (Ex. 1001)

The '060 patent issued from Application No. 14/322,057 ("the '057 application"), filed on July 2, 2014. The '057 application is a continuation of Application No. 13/439,111, filed April 4, 2012, now U.S. Patent No. 8,808,708; which is a continuation of Application No. 12/357,853, filed January 22, 2009, now U.S. Patent No. 8,895,024; which is a continuation of Application No. 11/395,593, filed March 31, 2006, now abandoned; which claims the benefit of the filing date of U.S. Provisional Patent Application No. 60/669,605, filed April 8, 2005. We collectively refer to the non-provisional applications, filed prior to the '057 application, as "the non-provisional '060 parent applications." That history is important because the single ground of invalidity stated in the Petition is based on anticipation by Hausdorff 2006; therefore, this case turns on whether Petitioner establishes that claims 1–13 have an effective filing date that post-dates the applied reference. Pet. 7, 35–53.

The '060 patent, entitled "Multivalent Pneumococcal Polysaccharide-Protein Conjugate Composition," relates to an immunogenic composition comprising polysaccharide-protein conjugates containing capsular polysaccharides prepared from different *Streptococcus pneumoniae* serotypes. Ex. 1001, Abstract. The different serotypes represented in the immunogenic composition include serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. *Id*. We adopt the parties' convention and refer to the 13-valent pneumococcal conjugate as the "13vPnC" vaccine. *See, e.g.*, Pet. 1; Prelim. Resp. 10–11.

The polysaccharides are obtained from *S. pneumoniae* cell cultures that are harvested and then lysed to release cell-associated polysaccharides into the culture medium. *Id*. at 11:25–12:10. The polysaccharide containing lysate is clarified by continuous flow centrifugation followed by microfiltration. *Id*. at 12:25–27. The purification of the pneumococcal polysaccharide consists of several steps including: concentration/diafiltration operations, precipitation/elution, column chromatography, and depth filtration. *Id*. at 12:30–34. These steps are repeated for each individual serotype.

The ’060 patent explains that the purified polysaccharides are chemically activated with sodium periodate so that they are able to chemically interact with the carrier protein in order to form a glycoconjugate. *Id*. at 8:1–3. The ’060 patent explains that “different serotype saccharides follow different pathways for activation (hydrolysis or no hydrolysis prior to [sodium periodate] activation) and conjugation (aqueous or DMSO[1] reactions).” *Id*. at 24:9–12. For example, the ’060 patent explains that for the serotype 1 polysaccharide the chemical activation involves treating the purified polysaccharide with sodium carbonate to achieve partial deacetylation, followed by neutralization, and finally oxidation in the presence of sodium periodate. *Id*. at 13:50–56. For the serotype 3 polysaccharide the chemical activation process involves treating the purified polysaccharide with acetic acid to hydrolyze the polysaccharide, followed by adding sufficient magnesium chloride to achieve a final concentration of 0.1M, before proceeding to the oxidation step in the

[1] “DMSO” is dimethylsulfoxide. Ex. 1001, 19:14.

presence of sodium periodate. *Id*. at 16:39–47. The serotype 19A polysaccharide activation process involves adding sodium acetate before reaching the oxidation step with sodium periodate. *Id*. at 21:19–22.

The ’060 patent explains that the conjugation step involves lyophilizing the activated polysaccharide and then mixing in the lyophilized carrier CRM_{197} protein[2] and reconstituting the dried components before adding the crosslinking agent. *Id*. at 14:7–12. The lyophilized polysaccharide and lyophilized CRM_{197} protein are reconstituted in either DMSO or in an aqueous buffer before proceeding to the conjugation reaction with sodium cyanoborohydride to obtain the polysaccharide-protein conjugate. *Id*. at 25:1–50, 26:28–52; *see* 16:58–67 (Example 4: Preparation of Serotype 3 Pneumococcal Saccharide CRM_{197} Conjugate).

The ’060 patent specification explains that the final immunogenic composition is formulated by combining the individual polysaccharide-CRM_{197} protein conjugates. The formulation contains 2–2.2 µg of each saccharide, except for 6B at 4–4.4 µg, approximately 29 µg CRM_{197} carrier protein; 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant, as well as sodium chloride and sodium succinate buffer as excipient. *Id*. at 3:9–15, 29:60–30:41.

[2] CRM_{197} (Wyeth, Sanford, N.C.) is a non-toxic variant (i.e., toxoid) of diphtheria toxin isolated from cultures of *Corynebacterium diphtheria* strain C7 (β197) grown in casamino acids and yeast extract-based medium. Ex. 1001, 8:19–22.

Illustrative Claims

Claims 1 and 2, reproduced below, illustrate the subject matter:

> 1. A multivalent immunogenic composition comprising polysaccharide-protein conjugates and a physiologically acceptable vehicle, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein, wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional serotype, wherein the additional serotype is serotype 3, and wherein the carrier protein is CRM_{197}.
>
> 2. The immunogenic composition of claim 1, wherein the additional serotypes consist of serotypes 1, 3, 5, 6A, 7F and 19A.

Ex. 1001, 35:16–26.

Evidence Relied Upon

The Petition asserts the following reference as prior art:

1. Hausdorff et al., U.S. Pat. Pub. 2006/0228380 A1 (Oct. 12, 2006) ("Hausdorff 2006") (Ex. 1018).

The Petition is supported by a declaration of Dennis L. Kasper, M.D. Ex. 1082. Based on Dr. Kasper's statement of qualifications and curriculum vitae, for the purposes of this decision, we hold that he is qualified to opine from the perspective of a person of ordinary skill at the time of the invention. *See* Ex. 1082 ¶¶ 4–12 (Dr. Kasper's statement of qualifications); *see also* Ex. 1082, Exhibit A (Dr. Kasper's curriculum vitae).

The Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–13 of the '060 patent on the single ground of anticipation under 35 U.S.C. § 102(b) based on the disclosure of Hausdorff 2006. Pet. 7.

II. ANALYSIS

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 136 S. Ct. 2131, 2142 (2016). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Broadest Reasonable Interpretation of "Immunogenic"

Each party proposes a specific construction for the term "immunogenic." Petitioner asserts that the term, which appears in the preamble of every claim, is limiting. Pet. 29[3] ("The fact that the preamble of every claim recites an 'immunogenic' composition underscores the intended limiting nature of the term"). "Patent Owner agrees with Petitioner that the term is a limitation notwithstanding that it appears in the preamble of the claim." Prelim. Resp. 7. We accept the uncontested proposition that "immunogenic" limits each challenged claim, because the proposition is

[3] Except for citations to the Petition or Preliminary Response (which refer to the original page number), patents and patent publications (which refer to the originally published column and line numbers or paragraph number), and citations to the declaration of Dr. Kasper (which refers to paragraph numbers), this Decision cites to the page numbers added by Petitioner or Patent Owner at the bottom of each Exhibit.

consistent with the disclosure and prosecution history of the ’060 patent. Pet. 29–30 (citing Ex. 1082 ¶¶ 108–115).

Petitioner proposes that the broadest reasonable interpretation of “immunogenic” is a composition “that ‘elicits immunologic memory and/or functional antibody with respect to each serotype of the vaccine, including serotype 3.’” Pet. 32 (citing Ex. 1082 ¶ 117). Petitioner argues that Patent Owner “emphasized immunogenicity in the specification, and relied on it during prosecution history to gain allowance of the claims over a prior art vaccine.” Pet. 28–29 (citing Ex. 1082 ¶¶ 108); *see id*. at 29–30 (citing Ex. 1001, 4:26–47; Ex. 1002, 180–181 (disclosures in the ’060 patent and its prosecution history; Ex. 1082 ¶¶ 109–115 (Dr. Kasper’s testimony)).

Patent Owner counter argues that “immunogenic” means “eliciting ‘higher serum IgG titers **and** overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM_{197}.’” Prelim. Resp. 8 (emphasis added) (citing Ex. 1001, 30:63–67). Patent Owner further contends that Petitioner “does not identify anything in the specification or prosecution history that supports [inserting] the ‘**and/or**’ aspect” into the requirements of the immunogenic composition. *Id*. at 17 (emphasis added).

Patent Owner explains that “[n]either the specification nor the prosecution history supports including ‘immunologic memory’ within the definition of immunogenic. . . . While in some contexts a definition of immunogenicity can include memory, adding a test for memory that is not described or contemplated in the ’060 patent is not reasonable.” Prelim. Resp. 9. Instead, Patent Owner submits that “immunogenic” as recited in

the claims "is based on two tests: antigen specific ELISA[4] for measuring serum IgG concentration and opsonophagocytic assay (OPA) for antibody function." *Id*. (citing Ex. 1001, 28:11–14, 30:42–46).

Patent Owner further explains that "[t]he OPA [response] is an important measure of functional immune response as opsonic activity has been shown to correlate with protection." Prelim. Resp. 11 (citing Ex. 2012,[5] 2; Ex. 2009,[6] 3; Ex. 2018,[7] 101). We are persuaded that measuring an OPA response is supported by the '060 specification, which compares "rabbit immune response to the polysaccharides contained in the vaccine, after immunization with the thirteen polysaccharide serotypes with or without conjugation to the carrier protein CRM_{197}." *Id*. (citing Ex. 1001, 29:60–64); *see* Ex. 1001, 29:66–30:38, 30:41–45, Tables 5 and 6 (relevant disclosures); Prelim. Resp. 11–12 (discussing import of those disclosures).

In an attempt to show that the applicants, during patent prosecution, invoked immunologic memory as a criterion for demonstrating

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[4] ELISA (acronym): (Biochemistry) enzyme-linked immunosorbent assay: an immunological technique for accurately measuring the amount of a substance, for example in a blood sample. The Free Dictionary, http://www.thefreedictionary.com/ELISA (last visited Oct. 8, 2017).
[5] J. Eskola, *Polysaccharide-based pneumococcal vaccines in the prevention of acute otitis media*, 19 VACCINE S78–S82 (2001).
[6] L. Jodar et al., *Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants*, 21 VACCINE 3265–3272 (2003).
[7] *WHO Expert Committee on Biological Standardization*, WHO, Geneva 2005.

immunogenicity, Petitioner directs us to a passage in Yeh 2010 (Ex. 1064[8]) but fails to show sufficiently that the passage was cited during prosecution. Pet. 31–32 (citing Ex. 1064, 1); Prelim. Resp. 13–14. Patent Owner, by contrast, identifies persuasive evidence that the applicants, during patent prosecution, expressly used the term "immunogenic" to describe the property of eliciting "higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM_{197}." Prelim. Resp. 14–15 (quoting Ex. 1005, 145). Based on the information presented in the Petition and the Preliminary Response, we find that Petitioner directs us to insufficient evidence that the applicants, during patent prosecution, equated "immunogenic" with the property of eliciting immunogenic memory alone. Pet. 28–32; Prelim Resp. 7–17 (and citations to the record therein).

On this record, Patent Owner's proposed interpretation of "immunogenic" is the broadest reasonable construction consistent with the specification of the '060 patent and its prosecution history. Based on the record before us, therefore, we accept Patent Owner's construction that "immunogenic," in the context of the challenged claims, means "eliciting 'higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM_{197}.'" Prelim. Resp. 8. No other claim terms require express construction for the purposes of this decision.

[8] Yeh et al., *Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine in Infants and Toddlers*, 126 PEDIATRICS e493–e505 (2010).

Challenge Based on Anticipation by Hausdorff 2006

Petitioner challenges claims 1–13 of the '060 patent as anticipated by Hausdorff 2006 (Ex. 1018). Pet. 47. We expressly decline to reach the merits of whether the disclosure of Hausdorff 2006 anticipates the invention of claims 1–13, because Petitioner fails to establish adequately that the applied reference qualifies as prior art.

Criticality of Effective Filing Date

The central dispute surrounds the effective filing date of claims 1–13, and whether it precedes the October 12, 2006, publication date of Hausdorff 2006. Petitioner asserts that the effective filing date is January 22, 2009.[9] *Id*. at 35–46. Patent Owner counters that claims 1–13 are entitled to claim priority through the '060 parent applications, which were filed as early as April 8, 2005. Prelim. Resp. 6–7, 20–21 (citing Ex. 1001, 1:8–17 (claiming priority based on earlier filing dates of the '060 parent applications)). For reasons that follow, we are not persuaded that Petitioner is reasonably likely to prevail at trial in showing that the effective filing date of claims 1–13 falls after the filing date of Hausdorff 2006. Given that circumstance, Petitioner cannot show sufficiently that Hausdorff 2006 qualifies as prior art with regard to the invention of claims 1–13. Accordingly, we deny the Petition as to the anticipation ground on that basis alone.

[9] Petitioner here appears to select the filing date of the '853 application. *See* Ex. 1001 (related application data). Elsewhere, however, Petitioner directs us to the April 8, 2005, filing date of the '605 parent application. Pet. 15.

Enablement and Undue Experimentation

In Petitioner's view, the disclosures of the '060 parent applications fail to enable claims 1–13; therefore, according to Petitioner, claims 1–13 are not entitled to claim priority through those applications. Pet. 36–46. Specifically, Petitioner argues that claim 1, upon which the other claims depend, is "open-ended" and, therefore, embraces multivalent immunogenic compositions having any number of the "nearly 100 pneumococcal serotypes" identified at the time of the invention—"so long as the composition includes the eight serotypes recited in the claim." Pet. 37. Petitioner argues that none of the '060 parent applications inform "how to construct a large fraction of the immunogenic pneumococcal conjugates captured by claim 1"; therefore, according to Petitioner, those applications fail to enable claim 1. *Id*. at 38 (citing Ex. 1082 ¶ 129). Petitioner also contends that the '060 patent applications "provide no guidance as to the number and identity of serotypes that could be added to 13vPnC." *Id*. at 37.

The Petition is deficient, however, for failure to show sufficiently that a person of ordinary skill in the art could not identify the structure of any particular serotype without undue experimentation. Our reviewing court instructs that undue experimentation is analyzed by applying the factors set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Petitioner unpersuasively argues that the *Wands* factors are "illustrative, not mandatory." Pet. 37 (citing *Amgen, Inc. v. Chugai Pharm. Co*., 927 F.2d 1200, 1213 (Fed. Cir. 1991)). For reasons stated by Patent Owner, notwithstanding the *Amgen* decision, the *Wands* factors are applicable in this case. Prelim. Resp. 23–24. Petitioner's failure to adequately address the *Wands* factors supports denial of the Petition.

The *Wands* factors require an analysis that is focused on the guidance and working examples presented in the disclosure of the patent application at issue.[10] Instead of providing a cogent analysis grounded in the *Wands* factors, including any guidance or working examples set forth in the '060 parent applications, Petitioner generally refers to statements regarding unpredictability previously made by Patent Owner during prosecution of foreign counterparts of the '060 patent, as well as statements made during domestic prosecution of a related patent application, which, Patent Owner counters, "are taken out of context." Prelim. Resp. 27; *see* Pet. 38–40, 44. The Petition fails to explain satisfactorily how those statements regarding unpredictability of arriving at the claimed invention from the prior art rise to the level of admissions pertaining to the disclosures of the '060 parent applications to enable the subject matter of any challenged claim. Nor does the Petition provide adequate reasons why those statements substitute for an analysis tethered to the *Wands* factors.

Petitioner's arguments relating to undue experimentation, moreover, rest on unsupported opinions of Dr. Kasper. For example, without citing any objective proof, Dr. Kasper opines that "[m]erely generating conjugates of serotypes of unknown polysaccharide structure would have required months of undue experimentation" and, for many serotypes, that endeavor "would have taken years." Pet. 43 (Ex. 1082 ¶ 139). We agree with Patent Owner

[10] Petitioner lists the *Wands* factors without addressing them adequately: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Pet. 36 (quoting *In re Wands*, 858 F.2d at 737).

that neither Dr. Kasper nor Petitioner directs us to objective support for that naked opinion. Prelim. Resp. 24 (citing Ex. 1082 ¶ 139; Pet. 43). One's expertise, even when draped with a skilled-artisan veil, does not entitle a naked opinion to much weight. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations" is sufficient to "render the testimony of little probative value in a validity determination.").

Further, as Patent Owner observes, even if we accept Dr. Kasper's "unsubstantiated calculation" regarding the length of time it would have taken an ordinary artisan to generate conjugated serotypes, Petitioner's argument fails because "neither Dr. Kasper nor Petitioner explains why such experiments would be undue." Prelim. Resp. 25; *see Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013) ("Unsubstantiated statements indicating that experimentation would be 'difficult' and 'complicated' are not sufficient" to show that the "experimentation would be undue."). The test for enablement is "not merely quantitative." *PPG Indus. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (citation omitted). On the contrary, "a considerable amount of experimentation is permissible, if it is merely routine." *Id*.

Dr. Kasper's opinion that claim 1 "covers over **4 million** possible combinations," when one selects additional serotypes from among "the top 30 most prevalent serotypes," does not withstand scrutiny. Pet. 37 (citing Ex. 1082 ¶ 128). Even Petitioner acknowledges that, at least as early as 1983, three serotypes (25, 16, and 24F) were recognized as most prevalent and, therefore, would have been understood as leading "candidates for a pneumococcal vaccine." Pet. 41–42. Dr. Kasper does not explain "why

generating conjugates for three serotypes would amount to undue experimentation." Prelim. Resp. 25. Further, of the "nearly 100 distinct pneumococcal serotypes" that "had been identified" at the time of the invention, there is agreement that 66 structures were known and only "34 serotypes [structures] had not yet been reported." Pet. 41 (citing Ex. 1055; Ex. 1060, 4–9); Prelim Resp. 25.

Critically lacking in the Petition, moreover, is any showing that "the conjugation chemistry known in the prior art or taught in the '060 specification," which is essentially identical to the disclosures of the '060 parent applications, "would not work for these and other serotypes." *Id*. And the Petition lacks cogent argument sufficient to persuade us that Patent Owner was required to disclose in the '060 parent applications every possible additional serotype that would have been immunogenic when conjugated with CRM_{197}. *In re Goffe*, 542 F.2d 564, 567 (C.C.P.A. 1976) ("To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials . . . would not serve the constitutional purpose of promoting progress in the useful arts."); *see In re Fuetterer*, 319 F.2d 259, 266 (C.C.P.A. 1963) (holding that to ask otherwise, would require the patent applicant "to do research on the 'literally thousands' of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented, and is not claiming, colloid suspending agents but . . . a combination.").

Dr. Kasper's conclusory statements do not support adequately Petitioner's argument pertaining to undue experimentation, in view of the guidance and working examples reflected in the '060 parent applications,

which describe how to conjugate serotypes to CRM_{197} and, further, disclose tests to determine whether a resulting composition is immunogenic. Ex. 1001, 4:23–33:4.[11] On this record, and in the context of that disclosure, Petitioner fails to establish that claims 1–13 lack enablement in the '060 parent applications. Pet. 35–46. The examples set forth in the '060 parent applications provide adequate guidance enabling "the generation and characterization of a representative multivalent composition of the granted claims." Prelim. Resp. 21; Ex. 1001, 11:25–28:67 (Examples 1–16).

Under the circumstances, Petitioner cannot show adequately that Hausdorff 2006 is a prior art publication that anticipates any challenged claim.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that any claim of U.S. Patent 9,399,060 B2 is unpatentable.

IV. ORDER

It is

ORDERED that the Petition is *denied* and no trial is instituted.

[11] The parties agree that the non-provisional '060 parent applications share essentially the same written description as the '060 patent. Pet. 3; Prelim. Resp. 7. Accordingly, for ease of reference, we cite to the '060 patent disclosure when assessing whether the disclosure of any '060 parent application enables or supports the claims identified by Petitioner.

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