

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,

Petitioner

v.

WYETH LLC.,

Patent Owner

Case IPR2017-01215

Patent 9,399,060 B2

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

JENKS, *Administrative Patent Judge*.

DECISION

Denying Institution of *Inter Partes* Review

37 C.F.R. § 42.108

I. INTRODUCTION

Merck Sharp & Dohme Corp. and Merck & Co. Inc. (collectively “Petitioner”) filed a Petition requesting an *inter partes* review of claims 1–13 of U.S. Patent No. 9,399,060 B2 (Ex. 1001, “the ’060 patent”). Paper 2 (“Pet.”). Wyeth, LLC (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 8 (“Prelim. Resp.”).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon consideration of the arguments and evidence presented in the Petition and the Preliminary Response, we are not persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 1–13 of the ’060 patent. Accordingly, we do not institute an *inter partes* review of claims 1–13.

A. *Related Proceedings*

Petitioner identifies as related matters three prior Petitions for *inter partes* review of U.S. Patent No. 8,562,999 (“the ’999 patent”). Pet 5 (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.

Petitioner filed two requests for *inter partes* review and two requests for post-grant review of the ’060 patent. *See* Pet. 5; Cases IPR2017-01211, IPR2017-01223, PGR2017-00016, and PGR2017-00017. Petitioner also filed one request for *inter partes* review of related U.S. Patent No.

8,895,024. *See* Case IPR2017-01194. Concurrently herewith, we issue decisions in those related proceedings.

B. 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.”

The '060 patent 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. 3; Prelim. Resp. 10.

The polysaccharides are obtained from *S. pneumoniae* cell cultures that are harvested and then lysed to release cell-associated polysaccharides into the culture medium. *See 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 DMSO¹ 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 presence of sodium periodate. *Id.* at 16:39–47. While the serotype 19A polysaccharide activation process involves adding sodium acetate before reaching the oxidation step with sodium periodate. *Id.* at 21:19–22.

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

The '060 patent explains that the conjugation step involves lyophilizing the activated polysaccharide and then mixing in the lyophilized carrier CRM₁₉₇ protein² and reconstituting the dried components before adding the crosslinking agent. *Id.* at 14:7–12. The lyophilized polysaccharide and lyophilized CRM₁₉₇ 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. *See Id.* at 25:1–50, 26:28–52; *see* 16:58–67 (Example 4: Preparation of Serotype 3 Pneumococcal Saccharide CRM₁₉₇ Conjugate).

The '060 patent explains that the final immunogenic composition is formulated by combining the individual polysaccharide-CRM₁₉₇ protein conjugates. The formulation contains 2–2.2 µg of each saccharide, except for 6B at 4–4.4 µg, approximately 29 µg CRM₁₉₇ 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, *see id.* at 29:66–67.

C. *Illustrative Claim*

Claim 1, the sole independent claim of the '060 patent, is illustrative and is reproduced below:

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,

² CRM₁₉₇ (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 at 8:19–22.

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 CRM₁₉₇.

D. The Prior Art

Petitioner relies upon the following prior art references:

Prevnar 2001	Prevnar® entry from the 2001 (55th Edition) Physicians' Desk Reference	Ex. 1011
Sigurdardottir 2002	Sigurdardottir et al., <i>Immune response to octavalent diphtheria- and tetanus-conjugated pneumococcal vaccines is serotype- and carrier-specific: the choice for a mixed carrier vaccine</i> , 21 PEDIATR. INFECT. DIS. J. 548–54 (2002).	Ex. 1012
Chiron 2003	Contorni et al., WO 03/009869 A1, published Feb. 6, 2003.	Ex. 1014
Wyeth 2002	Zagursky et al., WO 02/083855 A2, published Oct. 24, 2002.	Ex. 1015
Huebner 2004	Huebner et al., <i>Long-term antibody levels and booster responses in South African children immunized with nonavalent pneumococcal conjugate vaccine</i> , 22 VACCINE 2696–2700 (2004).	Ex. 1016
Hausdorff 2002	Hausdorff et al., <i>Multinational study of pneumococcal serotypes causing acute otitis media in children</i> , 21 PEDIATR. INFECT. DIS. J. 1008–1016 (2002).	Ex. 1017

Petitioner also relies upon the Declaration of Dennis L. Kasper, M.D. (Ex. 1083).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–13 of the '060 patent on the following grounds (Pet. 7):

Claims Challenged	Basis	References
1, 4–7, 13	§ 103(a)	Prevnar 2001 in view of Sigurdardottir 2002
8–10, 12	§ 103(a)	Prevnar 2001 in view of Sigurdardottir 2002 and Chiron 2003
11	§ 103(a)	Prevnar 2001 in view of Sigurdardottir 2002 and Wyeth 2002
1–3	§ 103(a)	Hubner 2004 in view of Hausdorff 2002

II. ANALYSIS

A. Claim Construction

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).

Each party proposes a specific construction for the following term:

“Immunogenic”

Petitioner notes that the term “immunogenic” appears in the preamble of every claim, but nevertheless is limiting. Pet. 31;³ *see also id.* at 32 (“The

³ Except for citations to the Petition or Preliminary Response (which refer to the original page number), patents and patent publications (which refer to

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 consistent with the disclosure and prosecution history of the ’060 patent. Pet. 32, (Ex. 1083 ¶ 108).

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. 31 (citing Ex. 1083 ¶ 107). Petitioner contends that during prosecution Patent Owner stressed that “the claimed composition unexpectedly provides ‘a **robust** immune response with respect to serotype 3 polysaccharides while using CRM₁₉₇ for all serotypes, including serotype 3.’” Pet. 34 (citing Ex. 1002, 180 (emphasis added); *see also id.* at 181 (“the present inventors[] unexpectedly obtained robust immune results with regard to serotype 3 despite the failure of others”)); *see also* Ex. 1064, 1 (“The PCV13 toddler dose [i.e., a booster dose to assess immunologic memory] resulted in higher immune responses compared with infant-series doses”).

Petitioner’s position is that based on the ’060 specification disclosure and prosecution history, “the broadest reasonable interpretation limits the

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 Petitioners or Patent Owner at the bottom of each Exhibit.

claimed ‘immunogenic’ composition to one that ‘elicits immunologic memory and/or functional antibody with respect to each serotype of the vaccine, including serotype 3.’” *See* Pet 35 (citing Ex. 1083 ¶ 117).

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 CRM₁₉₇.’” Prelim. Resp. 8 (emphasis added) (citing Ex. 1001, 30:62–67). 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, 30:42–45).

Patent Owner explains that “[t]he OPA [response] is an important measure of functional immune response as opsonic activity has been shown

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).

to correlate with protection.” Prelim. Resp. 11 (citing Ex. 2012,⁵ 2; Ex. 2009,⁶ 3; Ex. 2018,⁷ 101). Measuring 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 CRM₁₉₇.” *Id.* (citing Ex. 1001, 29:60–64); *see id.* at 11–13 (citing Ex. 1001, 29:66–30:38, 30: 41–45, 30:47–50, 30:54–61, 30:63–67, Tables 5 and 6).

Patent Owner and Petitioner both cite the Yeh 2010 publication (Ex. 1064⁸) albeit each relies on a different portion of the reference in support of their respective claim interpretations. Specifically, Patent Owner acknowledges citing to Table 3 of the Yeh 2010 publication (Ex. 1064) during prosecution of the ’060 patent to support the position that “the inventors ‘unexpectedly discovered a robust immune response with respect to serotype 3.’” Prelim Resp. 13–14 (citing Ex. 1002, 180–181). “In Yeh 2010, the Infant Vaccination Series refers to the primary immunizations at 2, 4 and 6 months. EX 1064 at 2. This is before the booster dose (referred to by the authors as the ‘toddler dose’) [that] was administered at 12-15

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.

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

months.” Prelim Resp. 14. Petitioner cites to the portion of the Yeh 2010 disclosure directed to measuring the toddler dose response, and not to the infant dose response relied on by Patent Owner during prosecution, to formulate their claim construction. *Compare* Pet. 34, with Prelim Resp. 14. We agree with Patent Owner that Petitioner’s reliance on the toddler dose immunization as disclosed in Yeh 2010 is not a reasonable basis for concluding that “immunogenic memory” is a limitation that should be read into the claim.

We are persuaded, for purposes of this decision, that Patent Owner’s proposed construction is the broadest reasonable construction consistent with the specification of the ’060 patent and file history. Based on the record before us, we accept Patent Owner’s construction that “immunogenic,” in this context means “eliciting ‘higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM₁₉₇.’” Prelim. Resp. 8, *see id.* at 17.

For purposes of this decision and on this record, no other claim terms require express construction.

B. Obviousness over Prevnar 2001 (Ex. 1011) in view of Sigurdardottir 2002 (Ex. 1012)

Petitioner asserts that claims 1, 4–7, and 13 of the ’060 patent would have been obvious over the combination of Prevnar 2001 and Sigurdardottir 2002 in conjunction with the general knowledge of a person of ordinary skill in the art. Pet. 38–49. Patent Owner counter argues that Petitioner’s rationale relies on an improper claim construction. Specifically, Patent

Owner argues Petitioner does not take into account the “showing functional antibody activity” that is required by the claim term immunogenic. Prelim. Resp. 22. We agree with Patent Owner that the Petition is deficient because it analyzes the asserted prior art in the context of an overly broad construction of the term “immunogenic.”

Prevnar 2001

Prevnar 2001 is an entry in the Physicians’ Desk Reference and teaches that the vaccine composition is a pneumococcal 7-valent conjugate that contains capsular antigens of *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM₁₉₇ protein. Ex. 1011, 2. Each 0.5 ml dose provides 2 µg of each saccharide with the exception of serotype 6B for which 4 µg is included in the formulation. *Id.* Prevnar 2001 is indicated for the immunization of infants and toddlers ranging in age from 2–15 months. *Id.* at 3.

Sigurdardottir 2002

Sigurdardottir 2002 is a journal article that teaches the production of “two octavalent pneumococcal conjugate vaccines (serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to diphtheria toxoid (PncD) or tetanus protein (PncT).” Ex. 1012, 1. The article generally explains that “[s]erotype-specific polysaccharide antibodies provide protection against infection. Children <2 years of age are unable to produce protective antibodies to most of the polysaccharides which are T cell-independent antigens” and children in this age group are less efficient at mounting an immune response to polysaccharide only vaccines. *Id.* Sigurdardottir 2002 teaches immunizing infants with three primary vaccinations at 3, 4, and 6 months of age with a polysaccharide-protein conjugate vaccine. *Id.* at 3–4.

Following this vaccination schedule with the disclosed vaccine produced serotype-specific IgG responses to each of the serotypes included in the vaccine. *Id.* at 4. Antibody production responses were measured by ELISA assay. *Id.* at 2. The authors also measured response to a polysaccharide only booster immunization administered at 13 month, that is, 7 months after the last priming vaccination, and this booster showed good IgG response in this patient population as well. *Id.* at 4, Fig. 1.

Analysis

Petitioner asserts that Prevnar 2001 discloses a safe and effective 7-valent pneumococcal conjugate vaccine. Pet. 38. Sigurdardottir 2002 discloses two different pneumococcal vaccines that include serotype 3. *Id.* at 38–39. Because of “the inclusion of serotype 3 in Sigurdardottir 2002, an ordinary artisan would have been motivated to broaden the coverage of Prevnar® to include serotype 3.” *Id.* at 39. Petitioner asserts that both vaccines of Sigurdardottir 2002 are “immunogenic as required by the claims. Ex.1083, ¶ 160. . . . Both vaccines elicited immunologic memory with respect to each serotype in the vaccine (including serotype 3), as evidenced by ‘the strong responses to the PPS at 13 months, an age when children would normally not respond to native polysaccharides.’” *Id.* at 41 (citing Ex. 1083 ¶ 160). Petitioner concludes that an ordinary artisan “would have had a high level of confidence (and, at the very minimum, a reasonable expectation) that moving from diphtheria or tetanus toxoid to CRM₁₉₇ (mutant diphtheria toxin) carrier protein would not negate the immunogenicity of the Sigurdardottir 2002 vaccines.” *Id.* at 45 (citing Ex. 1083 ¶ 167).

We agree with Patent Owner that Petitioner's focus on IgG antibody production, the only response measured in Sigurdardottir 2002, without addressing the requirement that the "immunogenic" composition also induce a functional antibody response as measured for example by OPA is not sufficient to show that the combination of references renders the claims obvious. *See* Prelim. Resp. 20–40; *see above* Claim Construction. According to Patent Owner, "an increase in IgG antibody titer does not necessarily correlate with the production of functional antibodies that effectively neutralize the target antigen and is therefore not a confirmatory measurement of "immunogenicity" as properly interpreted." Prelim. Resp. 22. "Sigurdardottir 2002 merely shows an increase in IgG antibody titers without showing functional antibody activity," and Petitioner does not provide evidence "that the Sigurdardottir 2002 composition would possess any opsonophagocytic activity as measured by OPA" or any other measure of functional antibody activity. *Id.* We agree with Patent Owner's position.

On this record, we are not persuaded that Petitioner demonstrates that the claimed immunogenic (as construed above) composition would have been obvious over Prevnar 2001 and Sigurdardottir 2002 for the reasons discussed in detail on pages 20–40 of Patent Owner's Preliminary Response. Accordingly, we deny *inter partes* review because Petitioner has not established a reasonable likelihood it would prevail in showing claims 1, 4–7, and 13 of the '060 patent are unpatentable under 35 U.S.C. § 103(a).

C. *Obviousness over Prevnar 2001 (Ex. 1011) in view of Sigurdardottir 2002 (Ex. 1012) and Chiron 2003 (Ex. 1014)*

Petitioner asserts that claims 8–10 and 12 would have been obvious over Prevnar 2001, Sigurdardottir 2002, and Chiron 2003. Pet. 49–51. Patent Owner opposes Petitioner’s assertion. Prelim. Resp. 40–41.

Chiron 2003

Chiron 2003 is an international patent application that is directed to improving the stability of vaccines by including aluminum salt as adjuvants. Ex. 1014, Abstract. Chiron 2003 teaches using “carrier proteins [such as] bacterial toxins or toxoids, such as diphtheria or tetanus toxoids. The CRM₁₉₇ diphtheria toxoid as a carrier is particularly preferred. Other suitable carrier proteins include the *N. meningitidis* outer membrane protein.” *Id.* at 4. Chiron 2003 teaches that antigens include “a protein antigen or a saccharide antigen (optionally conjugated).” *Id.* at 3. Suitable antigens are protein antigens from *Neisseria* (e.g. *N. meningitidis*), an antigen from *Moraxella catarrhalis*, a saccharide antigen from *Haemophilus influenzae* B, as well as saccharide antigens from *Streptococcus pneumoniae*, among others. *Id.*

Analysis

Petitioner asserts that Chiron 2003 would have made it obvious to “include one or more antigens, such as *Moraxella catarrhalis*, in the 8-valent immunogenic CRM₁₉₇-conjugate vaccine” suggested by the combination with Prevnar 2001 and Sigurdardottir 2002. Pet. 49–51.

Patent Owner recognizes that Chiron 2003 discloses numerous combinations of bacterial and viral antigens, but argues “there is no explicit suggestion to combine a pneumococcal antigen conjugate with a conjugate

using another antigen.” Prelim. Resp. 40. The focus of Chiron 2003 is on *Neisseria meningitides*. *Id.* Patent Owner points out that “Chiron 2003 fails to remedy the deficiencies of Sigurdardottir 2002 to show OPA” response. *Id.*

We agree with Patent Owner that Petitioner has not demonstrated a reasonable likelihood of prevailing at trial in showing that claims 8–10 and 12 would have been obvious over Prevnar 2001, Sigurdardottir 2002, and Chiron 2003 in conjunction with any general knowledge of an ordinary artisan. Chiron 2003 does not address the deficiency in the combination of Prevnar 2001 and Sigurdardottir 2002, namely, that there is no correlation between IgG plasma values and functional antibody activity as shown with an OPA assay or any other functional antibody assay. In other words, showing IgG production only addresses half of the “immunogenic” limitation as claimed.

Accordingly, we determine that Petitioner has not established a reasonable likelihood it would prevail in showing claims 8–10 and 12 of the ’060 patent are unpatentable under 35 U.S.C. § 103(a).

D. Obviousness over Prevnar 2001 (Ex. 1011) in view of Sigurdardottir 2002 (Ex. 1012), Wyeth (Ex. 1015)

Petitioner asserts that claim 11 would have been obvious over Prevnar 2001, Sigurdardottir 2002, and Wyeth 2002. Pet. 51–52. Patent Owner opposes Petitioner’s assertion. Prelim. Resp. 41.

Wyeth 2002

Wyeth 2002 is an international application that relates to *S. pneumoniae* open reading frames that encode polypeptide antigens,

polypeptides, preferably antigenic polypeptides. Ex. 1015, 1. Wyeth 2002 teaches immunogenic compositions that combine one or more of the *S. pneumoniae* polypeptides “with one or more known *S. pneumoniae* polysaccharides or polysaccharide-protein conjugates, including, but not limited to, the currently available 23-valent pneumococcal capsular polysaccharide vaccine and the 7-valent pneumococcal polysaccharide-protein conjugate vaccine.” *Id.* at 97.

Analysis

Petitioner asserts that a person of ordinary skill in the art would have been motivated with a reasonable expectation to successfully incorporate one or more *S. pneumoniae* polypeptides with an 8-valent pneumococcal polysaccharide-protein conjugate vaccine based on the combination of Prevnar 2001 and Sigurdardottir 2002. Pet. 51. This is especially true, in Petitioner’s view, because Wyeth 2002 expressly suggests including the polypeptide with the 7-valent pneumococcal polysaccharide-protein conjugate vaccine. *Id.* at 52.

Patent Owner opposes this position as “Wyeth 2002 fails to remedy the deficiencies of Sigurdardottir 2002 to show OPA” response. Prelim. Resp. 41.

We agree with Patent Owner that Petitioner has not sufficiently shown, on this record, a reasonable likelihood of prevailing that claim 11 would have been obvious over Prevnar 2001, Sigurdardottir 2002, and Wyeth 2002. For the same reasons discussed above, Petitioner advances insufficient evidence to show persuasively that there is correlation between IgG antibody production and production of functional antibody as measured by an OPA assay or any other functional antibody assay. Wyeth 2002 also

does not establish that IgG production correlates with function based on an OPA assay or any other functional antibody assay and, thereby, Petitioner fails to show sufficiently that the inclusion of Wyeth 2002 would have led one to an “immunogenic” composition that results in both antibody production as measured by IgG ELISA and a functional antibody response to the immunogen as required by the claims.

Accordingly, we determine that Petitioner has not established a reasonable likelihood it would prevail in showing claim 11 of the '060 patent is unpatentable under 35 U.S.C. § 103(a).

E. Obviousness Over Huebner 2004 (Ex. 1016) in view of Hausdorff 2002 (Ex. 1017)

Petitioner asserts that claims 1–3 would have been obvious over Huebner 2004 in view of Hausdorff 2002. Pet. 52–62. Patent Owner opposes Petitioner’s assertion. Prelim. Resp. 42–48.

Huebner 2004

Huebner 2004 is a journal article reviewing response levels to a 9-valent pneumococcal conjugate vaccine containing serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F. Ex. 1016, Abstract. The polysaccharides included in this 9-valent vaccine were conjugated to CRM₁₉₇-diphtheria protein. *Id.* at 1. Huebner 2004 teaches that the majority of the vaccinated children had antibody levels of >0.15 µg/ml. *Id.* at 2. The study population included infants at 6, 10, and 14 weeks of age. *Id.* Boosting the children at 18 month with a polysaccharide vaccine resulted in a quick antibody response. *Id.* at 3.

Hausdorff 2002

Hausdorff 2002 is a journal article that is a retrospective study analyzing nine datasets collected between 1994 and 2000. Ex.1017, Abstract. The datasets relied on in the analysis are all listed in Table 1 of the article. *See* Ex.1017, 3. Figure 2, not shown here, is a graphic representation of pneumococcal serotypes circulating in the population and shows that the circulating serotypes vary from country to country. *Id.* at 6. The figure depicts the percentage of pneumococcal serotypes isolated from middle ear fluid that would be targeted the by the various vaccines formulations available at the date the article was published. *Id.* In other words, the figure shows the theoretical contributions PCV-9 and PCV-11 pneumococcal conjugate vaccines would have on preventing disease in each country. Figure 2 also shows that there are changes in pneumococcal serotypes isolated from middle ear fluid based on the patient age group. *Id.* In the article, PCV-9 is an abbreviation for PCV-7 plus serotypes 1 and 5; PCV-11 is an abbreviation for PCV-9 plus serotype 3 and 7F. *Id.* at 2. The 7-valent pneumococcal conjugate vaccine (PCV-7) includes serotypes 4, 6B, 9V, 14, 18C, 19F, 23F). *Id.* The article indicates that the PCV-11 vaccines were in clinical trials at the time of the Hausdorff 2002 publication. *Id.* at 6.

Analysis

Petitioner asserts that the “9-valent pneumococcal CRM₁₉₇-conjugate vaccine [of Huebner 2004] . . . adds serotypes 1 and 5 to the 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) of Prevnar®, and demonstrates that the vaccine is immunogenic, as it elicits immunologic memory.” Pet. 53 (citing Ex. 1083 ¶ 184). Hausdorff 2002 “observes that, ‘[i]t appears that the serotypes represented in PCV-11 [(representing serotypes 1, 3, 4, 5, 6B, 7F

9V, 14, 18C, 19F, 23F)], plus 6A and 19A, comprise all major serotypes in each age group studied.” *Id.* at 54. Petitioner concludes that a person of ordinary skill in the art “would have had a reasonable expectation of success of creating an immunogenic serotype 3 conjugate, given the disclosure in Hausdorff 2002 of an 11-valent conjugate vaccine that includes serotype 3.” *Id.* at 56–57 (citing Ex. 1083 ¶ 190).

Patent Owner contends that Hausdorff 2002 does not show “immunogenicity” as required by the claims, *i.e.*, producing IgG as shown by ELISA and showing functional antibody as measured for example by an OPA response. *See* Prelim. Resp. 43. Patent Owner’s additional position is that the vaccines used in the Hausdorff 2002 publication are not CRM₁₉₇ conjugates as intimated by Petitioner. *See Id.*

Eskola 2001, the publication Hausdorff 2002 cites for support that the 11-valent conjugate is in “clinical trials” (*see* EX1017 at 6, reference “19”), mentions two 11-valent conjugates (neither of which used CRM₁₉₇ as required by the claims): (1) an 11-valent mixed carrier (diphtheria toxoid/tetanus toxoid (“DT/TT”)) conjugate by Aventis Pasteur; and (2) an 11-valent Hi Protein conjugate by SB Bio.

Id. at 43–44. Because “Hausdorff 2002 does not point to any data showing that an 11-valent vaccine had in fact demonstrated immunogenicity,” Patent Owner contends that the combination with Huebner 2004 would not demonstrate “immunogenicity” as required by the claims. *Id.* at 43.

We agree with Patent Owner that the serotype 3 vaccines described in Hausdorff 2002 are not conjugated to CRM₁₉₇ as required by the claims. *See* Prelim Resp. 43–44 (citing Ex. 2012, Table 2). Table 2 of Ex. 2012 is reproduced below:

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Table 2
 Pneumococcal conjugate vaccines in clinical trials

Vaccine	Pneumococcal PSs	Carrier protein	Manufacturer
PncOMPC	4, 6B, 9V, 14, 18C, 19F, 23F	Meningococcal OMP	MRL
PncCRM	1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F	CRM197 protein	WLVP
PncDT	3, 6B, 14, 18C 1, 4, 5, 7F, 9V, 19F, 23F	Diphtheria toxoid, tetanus toxoid	Aventis Pasteur
PN-DP	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Hi protein	SB-Bio

The table shows that the vaccines that incorporate serotype 3 polysaccharide are not conjugated to CRM₁₉₇ but instead are conjugated to diphtheria toxoid/tetanus toxoid or Hi Protein. Ex. 2012, 2. Thus, serotype 3 vaccines described in Hausdorff 2002 are not the same compositions currently claimed. Nor does Petitioner sufficiently show, on this record, that one would have reasonably expected, in view of the disclosures of the applied prior art references, to attain an “immunogenic” composition (as construed above) when the polysaccharides, including serotype 3, are instead conjugated to CRM₁₉₇.

As previously discussed, we agree with Patent Owner’s claim construction that an “immunogenic” composition produces an immune response that elicits *both* an IgG response as measured by ELISA and a functional response as measured for example by an OPA response to the immunogen. *See above II. A, Claim Construction.* On this record we are not persuaded that Petitioner has established one of ordinary skill in the art would have had a reason to include serotype 3 in a multivalent vaccine, and would have had a reasonable expectation of success. *See Pet. 54–55 (citing Ex. 1083 ¶ 186); see also id. at 57 (“a POSITA would have had a reasonable expectation that a 10-valent CRM₁₉₇-conjugate vaccine (adding serotype 3) would be immunogenic as well” (citing Ex. 1083 ¶ 192)).*

We find, rather, as Patent Owner argues, that “Huebner 2004 provides no data at all concerning functional antibody activity and certainly no data from an OPA” response. Prelim. Resp. 42. Vaccines including serotype 3 have not been found to produce functional antibody (see above section *II. B*). Patent Owner directs us to evidence that “[t]he 11-valent Hi Protein conjugate in Eskola 2001 is the ‘protein D’ conjugate described in the ’060 patent and prosecution history as being unsuccessful with respect to serotype 3.” Prelim Resp. 44 (citing Ex. 1001, 4:23–47; Ex. 1002, 180–181). The evidence presented by Patent Owner sufficiently rebuts Petitioners unsubstantiated position that, at the time of the invention, there was a reasonable expectation of success in producing a serotype 3 vaccine that elicits both an IgG immune response and an OPA response.

On this record, we are not persuaded that Petitioner demonstrates that the claimed immunogenic (as construed above) composition would have been obvious over Huebner 2004 and Hausdorff 2002 for the reasons discussed in detail on pages 42–48 of Patent Owner’s Preliminary Response.

Accordingly, we determine that Petitioner has not established a reasonable likelihood it would prevail in showing claims 1–3 of the ’060 patent are unpatentable under 35 U.S.C. § 103(a).

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–13 of U.S. Patent 9,399,060 B2 are unpatentable under 35 U.S.C. § 103(a).

IV. ORDER

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

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Application 9,399,060 B2

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