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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 IPR2017-01223
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 and 4–13 of U.S. Patent No. 9,399,060 B2 (Ex. 1001, "the '060 patent"). Paper 1 ("Pet."). Wyeth, LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("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 and 4–13 of the '060 patent. For the reasons that follow, we do not institute an *inter partes* review on claims 1 and 4–13.

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 4 (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. 4; Cases IPR2017-01211, IPR2017-01215, 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, 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. 14; 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 were 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 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 CRM_{197} protein[2] and then 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. *See 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 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, *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

[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.

> 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}.

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
Overturf 2002	*Pneumococcal Vaccination of Children*, 13 Seminars in Pediatric Infectious Diseases 155-164 (2002)	Ex. 1013
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

Petitioner also relies upon the Declaration of Dennis L. Kasper, M.D. (Ex. 1084).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1, 4–13 of the '060 patent on the following grounds (Pet. 28–41):

Claims Challenged	**Basis**	**References**
1, 4–7, and 13	§ 103(a)	Prevnar 2001 in view of Overturf 2002
8–10 and 12	§ 103(a)	Prevnar 2001 in view of Overturf 2002 and Chiron 2003
11	§ 103(a)	Prevnar 2001 in view of Overturf 2002 and Wyeth 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. 24;[3] *see also id*. ("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

[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 Petitioners or Patent Owner at the bottom of each Exhibit.

uncontested proposition that "immunogenic" limits each challenged claim, because the proposition is consistent with the disclosure and prosecution history of the '060 patent. Pet. 24, (Ex. 1084, ¶ 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. 23–24 (citing Ex. 1084 ¶ 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 CRM_{197} for all serotypes, including serotype 3.'" Pet. 26 (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* Pet. 27 (citing Ex. 1064 at 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 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 27─28 (citing Ex. 1084, ¶ 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 CRM_{197}.'" Prelim. Resp. 8 (emphasis added)(citing Ex. 1001 at 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 at 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 to correlate with protection." Prelim. Resp. 11 (citing Ex. 2012[5] at 2; Ex. 2009[6] at 3; Ex. 2018[7] at 101). Measuring OPA response is supported by the '060 specification which compares "rabbit immune response to the

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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.

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 at 29:60–64); *see id*. at 11–13 (citing Ex. 1001 at 29:66–30:38, 30:41–45, 30:46–50, 30:54–61, 30:63–67, Tables 5 and 6).

Patent Owner and Petitioner both cite the Yeh 2010 publication (Ex. 1064[8]) 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 at 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') was administered at 12-15 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. 27, with Prelim Resp. 14. We agree with Patent Owner that Petitioner's reliance on the toddler dose immunization as disclosed in Yeah 2010 is not a reasonable basis for concluding that "immunogenic memory" is a limitation that should be read into the claim.

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

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 CRM_{197}.'" 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 Overturf 2002 (Ex. 1013)

Petitioner asserts that claims 1, 4–7, and 13 of the '060 patent would have been obvious over the combination of Prevnar 2001 and Overturf 2002. Pet. 28–38. Patent Owner contends that Petitioner's rationale does not establish a reasonable expectation that the combination "would be successful in yielding the claimed invention." Prelim. Resp. 18. We agree with Patent Owner that the Petition is deficient because it has not established a sufficient rationale from which to conclude that the disclosure in the prior art teaches a serotype 3 polysaccharide CRM_{197} conjugate that is "immunogenic" as claimed.

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 CRM_{197} protein. *See* Ex. 1011 at 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, and the total saccharide concentration is about 16 µg per dose. *Id*. The formulation includes approximately 20 µg of the CRM_{197} carrier protein, and 0.125 mg aluminum phosphate adjuvant per 0.5 ml dose. *Id*. Prevnar 2001 is indicated for the immunizations of infants and toddlers ranging in age from 2–15 months. *Id*. at 3.

Overturf 2002 (Ex. 1013)

Overturf 2002 is a review article discussing pneumococcal vaccination in children generally. Ex. 1013, Title, Abstract. Children with underlying disease or immune defects such as those "with asplenia or splenic dysfunction, metabolic disorders, loss or failure of immunoglobulin production, other severe B-lymphocytc dysfunction" are at "increased risk of acquiring invasive pneumococcal disease." *Id*. at 1. Overturf 2002 acknowledges that there are two commercially available "purified capsular polysaccharide pneumococcal vaccines" and each contains polysaccharide of serotype 3. *Id*. at 3. Overturf 2002 explains that

> [t]he poor immunogenicity of polysaccharide vaccines in young children [those under 2] is caused by the T lymphocyte-independent characteristic of polysaccharide antigens, which not only causes a failure of primary responses in infants and young children . . . . In addition to poor quantitative responses, functional or qualitative responses as measured by opsonization also may be poor.

Id. at 4. Overturf 2002 teaches using protein conjugate vaccine in children under 2 years of age, and lists several conjugate vaccines in development. *Id*., *see* Table 4. Table 4 is reproduced below:

Table 4. Pneumococcal Conjugate Vaccines in Development

Vaccine Conjugate	*Serotypes Contained in Vaccine*	*Manufacturer*	*Clinical Trial Status*
Purified polysaccharides conjugated to CRM_{197}	Nanovalent vaccine: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F	Wyeth Lederle Vaccines, Philadelphia, PA	Phase III
Purified polysaccharides conjugated to CRM_{197}	11-valent vaccine: 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Wyeth Lederle Vaccines, Philadelphia, PA	Preclinical
Purified polysaccharides conjugated to outer membrane protein of *N. menigitidis*	Heptavalent vaccine: 4, 6B, 9V, 14, 18C, 19F, 23F	Merck & Co, Inc, West Point, PA	Preclinical

NOTE. Other vaccine combinations or conjugates that have been tested in phase II and III studies include conjugates in addition to tetanus and diphtheria toxoids and combinations of pneumococcal antigens ranging from monovalent preparations (6B) to pentavalent (6B, 14, 18C, 19F, and 23F), hepatavalent (PCV7), nanovalent (PCV7 plus serotypes 1 and 5), and 11-valent (nanovalent plus 3 and 7V) combinations.
Abbreviation: CRM, cross-reacting material.

Table 4 shows several vaccines that are in clinical or preclinical stages, only one of the vaccines listed includes serotype 3 in the formulation. Specifically, Table 4 shows an 11-valent vaccine containing purified polysaccharides from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F conjugated to CRM_{197}. *Id*. Overturf 2002 indicates that "[p]reliminary trials of numerous conjugate vaccines are being conducted or recently have been completed (Table 4)." *Id*. (citing Ex. 2013[9]). Overturf 2002 concludes that "[t]he serological antipolysaccharide antibody correlate of protection against pneumococcal infection is poorly defined," and developing precise correlates would facilitate development of future polysaccharide vaccine compositions. *Id*. at 8.

Analysis

Petitioner asserts that Prevnar 2001 discloses a safe and effective 7-valent pneumococcal conjugate vaccine. Pet. 29. According to Petitioner

[9] American Academy of Pediatrics, Committee on Infectious Diseases, *Policy Statement: Recommendations for the Prevention of Pneumococcal Infections, Including the Use of Pneumococcal Conjugate Vaccine (Prevnar), Pneumococcal Polysaccharide Vaccine, and Antibiotic Prophylaxis*, 106 PEDIATRICS 362366 (2000) (Ex. 2013).

"Overturf 2002 discloses that Patent Owner was developing an 11-valent iteration of Prevnar (including all 8 serotypes of claim 1 of the '060 Patent), in which each polysaccharide was conjugated to CRM_{197}." *Id*. Petitioner asserts that the motivation to include serotype 3 into a conjugate vaccine is based on "the prevalence of serotype 3, its association with serious disease, and its inclusion in the Pneumovax® 23 polysaccharide vaccine." *Id*. Petitioner concludes that "[b]ased on the inclusion of a serotype 3 CRM_{197} conjugate in Overturf 2002, a POSITA would have been motivated to broaden the coverage of Prevnar® to include at least serotype 3 conjugated to CRM_{197}." *Id*.

Patent Owner counter argues that Prevnar 2001 "neither discloses nor suggests adding a serotype 3 polysaccharide conjugate" to the formulation. Prelim. Resp. 19. Patent Owner contends that "Overturf 2002 does not teach or suggest that the purported, 11-valent vaccine [in preclinical studies] was immunogenic, and Petitioner has not provided any evidence that the 11-valent vaccine [disclosed in Overturf 2002] was ultimately demonstrated to be immunogenic." *Id*. at 20, *see also* 21 (stating that none of the art cited by Petitioner "provides any data whatsoever establishing immunogenicity or confirming even the existence of the allegedly developed 11-valent pneumococcal CRM_{197}-conjugate vaccine.").

We agree with the Patent Owner that Petitioner has not shown, on this record, a reasonable likelihood of prevailing that claims 1, 4–7, and 13 would have been obvious over Prevnar 2001 and Overturf 2002. Petitioner merely directs us to Table 4 in Overturf 2002 and intimates that the composition disclosed in that table is a progression from Patent Owner's Prevnar® vaccine and an artisan "would have understood that the conjugates

were prepared individually, as was the case with Prevnar®" and that composition would thereby also be immunogenic. *Id*. at 32 (citing Ex. 1084 ¶ 146), *see also id*. 31 ("reasonable expectation that the disclosed 11-valent CRM_{197}-conjugate vaccine would be immunogenic. EX. 1084, ¶143").

Overturf 2002 teaches an 11-valent vaccine that is a CRM_{197} conjugate vaccine and includes serotype 3 as one of the polysaccharides conjugated to the carrier protein. There is no indication in Overturf 2002 of how the individual polysaccharides are attached to the carrier protein, or that the composition had been tested. *See* Prelim Resp. 20. The '060 patent, however, explains that "different serotype saccharides follow different pathways for activation (hydrolysis or no hydrolysis prior to [sodium periodate] activation) and conjugation (aqueous or DMSO reactions)." Ex. 1001 at 24:9–12. In other words, the '060 patent explains that the same conjugation protocol does not work for every polysaccharide.

Petitioner's conclusion that the 11-valent CRM_{197}-conjugate vaccine disclosed in Overturf 2002 is an extension of Patent Owners Prevnar® vaccine rests on unsupported opinions of Dr. Kasper. For example, without citing any objective proof, Dr. Kasper opines that "[b]ecause the 11-valent CRM_{197}-conjugate vaccine of Overturf 2002 was a progression from Patent Owner's Prevnar® vaccine, a POSITA would have understood that the conjugates were prepared individually, as was the case with Prevnar®." Pet. 32 (citing Ex. 1084 ¶ 146). Similarly Petitioner's position that "the 11-valent CRM_{197}-conjugate vaccine [of Overturf 2002] would be immunogenic" is also based on an unsupported opinion of Dr. Kasper. *Id*. at 31 (citing Ex. 1084 ¶ 143).

Petitioner contends that the inclusion of serotype 3 in a vaccine formulation would have been obvious because this serotype was known to cause serious disease. *See* Pet. 33 (citing 1084 ¶ 147). Nevertheless, even accepting that the ordinary artisan would have been motivated "to broaden the coverage of Prevnar® with at least serotype 3 conjugated to CRM_{197}" as asserted by Petitioner (*see* Pet. 33 (citing Ex. 1083 ¶¶ 147–148, and Ex. 1012), it does not necessarily follow that one would have had a reasonable expectation that the composition would be "immunogenic" as claimed. On that front, Dr. Kasper opines that because "two distinct 8-valent conjugate compositions were immunogenic with respect to serotype 3" there is a reasonable expectation that serotype 3 conjugated to CRM_{197} would also be immunogenic. Ex. 1084 ¶ 148 (citing Sigurdardottir 2002 (Ex. 1012[10])). A review of Sigurdardottir 2002 shows that the reference teaches immunizing infants with three primary vaccinations at 3, 4, and 6 months of age with a polysaccharide-protein conjugate vaccine. Ex. 1012, 3–4. Following this vaccination schedule with the disclosed vaccine produced serotype-specific IgG responses, as measured by ELISA assay, for each of the serotypes included in the vaccine. *Id*. at 4. However, Petitioner points to no evidence that the compositions relied upon by Dr. Kasper in the declaration were tested for the production of a functional antibody response. Therefore, the compositions taught in Sigurdardottir 2002 do not provide evidence for Petitioner's assertion that any serotype 3 conjugated to a protein carrier is

[10] Sigurdardottir et al., *Immune response to octavalent diphtheria- and tetanus-conjugated pneumococcal vaccines is serotype- and carrier-specific: the choice for a mixed carrier vaccine*, 21 PEDIATR. INFECT. DIS. J. 548–554 (2002).

immunogenic as claimed, i.e., showing higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM_{197}. Dr. Kasper's declaration has not identified any other evidence that provides a reasonable basis to conclude that any serotype 3 protein conjugate would be immunogenic.

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 Overturf 2002 for the reasons discussed in detail on pages 19–31 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) over Prevnar 2001 and Overturf 2002.

C. Obviousness over Prevnar 2001 (Ex. 1011) in view of Overturf 2002 (Ex. 1013) and Chiron 2003 (Ex. 1014)

Petitioner asserts that claims 8–10 and 12 would have been obvious over Prevnar 2001, Overturf 2002, and Chiron 2003. Pet. 39–41. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 31–32.

Chiron 2003

Chiron 2003 is a WO 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 CRM_{197} 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

Claims 8–10 and 12 depend directly or indirectly from claim 1, and further require inclusion of additional antigens—specified and unspecified--in the composition. 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 CRM_{197}-conjugate vaccine" suggested by the combination with Prevnar 2001 and Overturf 2002. Pet. 39.

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. 31–32. We agree with Patent Owner that Chiron 2003 "provides no evidence or data for the combination of these antigens" or guidance that the combination would produce an immunogenic composition as claimed. Prelim. Resp. 32.

Accordingly, we deny *inter partes* review because Petitioner has not demonstrated a reasonable likelihood of prevailing at trial in showing that claims 8–10 and 12 of the '060 patent would have been obvious over Prevnar 2001, Overturf 2002, and Chiron 2003.

D. Obviousness over Prevnar 2001 (Ex. 1011) in view of Overturf 2002 (Ex. 1013) and Wyeth (Ex. 1015)

Petitioner asserts that claim 11 would have been obvious over Prevnar 2001, Overturf 2002, and Wyeth 2002. Pet. 41. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 32–33.

Wyeth 2002

Wyeth 2002 is a WO application that relates to *S. pneumoniae* open reading frames that encode polypeptide antigens that are surface localized on *Streptococcus pneumoniae*. 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

Claim 11 depends from claim 1 and recites that the composition further comprises one or more proteins from *S. pneumoniae*. Petitioner asserts that a person of ordinary skill in the art would have been motivated with a reasonable expectation of successfully incorporating one or more *S. pneumoniae* polypeptides into an 8-valent pneumococcal polysaccharide-protein conjugate vaccine based on the combination of Prevnar 2001 and Overturf 2002. Pet. 41. This is especially true, in Petitioner's view, because Wyeth 2002 expressly suggests including one or more polypeptides of the invention with the 7-valent pneumococcal polysaccharide-protein conjugate vaccine. Pet. 41 (citing Ex. 1015, 96:17–22).

Patent Owner opposes this position because the combination of references does not provide "any guidance as to how to solve the problem of making a high-valent vaccine composition comprising a serotype 3-CRM_{197} conjugate," Prelim. Resp. 33.

Wyeth 2002 is not relied upon by Petitioner to address any deficiency in the combination of Prevnar 2001 and Overturf 2002, namely, that the combination fails to disclose an immunogenic serotype 3 polysaccharide conjugate to CRM_{197} as claimed. Petitioner intimates that "[b]ecause the 11-valent CRM_{197}-conjugate vaccine of Overturf 2002 was a progression from Patent Owner's Prevnar® vaccine" the composition is structurally the same and would thereby reasonably be immunogenic. Pet. 32 (citing Ex. 1084 ¶ 146); *see also id*. at 31 (citing Ex. 1084 ¶ 143). For the same reasons discussed above, Petitioner advances insufficient evidence to show that the serotype 3 CRM_{197} conjugate of Overturf 2002 is immunogenic as claimed because there is no evidence in the record that the product is structurally the same as the conjugate of the '060 patent. Petitioner fails to sufficiently show 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 as measured for example by OPA response or any other method of measuring functional antibody response.

Accordingly, we deny *inter partes* review because Petitioner has not demonstrated a reasonable likelihood of prevailing at trial in showing that claim 11 of the '060 patent would have been obvious over Prevnar 2001, Overturf 2002, and Wyeth 2002.

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 and 4–13 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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