

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-_____
U.S. Patent No. 9,399,060

PETITION FOR *INTER PARTES* REVIEW

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37 C.F.R. § 42.155

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LIST OF EXHIBITS

Exhibit No.	Document
1001	U.S. Patent No. 9,399,060 to Hausdorff <i>et al.</i> ("the '060 patent")
1002	Excerpts from the Prosecution History of the '060 patent
1003	Excerpts from the Prosecution History of US Patent Application No. 13/439,111
1004	Excerpts from the Prosecution History of US Patent Application No. 12/357,853
1005	Excerpts from the Prosecution History of US Patent Application No. 11/395,593
1006	US Provisional Application No. 60/669,605
1007	[Reserved]
1008	[Reserved]
1009	[Reserved]
1010	[Reserved]
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1068	[Reserved]

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1081	Beall <i>et al.</i> , "Pre- and Postvaccination Clonal Compositions of Invasive Pneumococcal Serotypes for Isolates Collected in the United States in 1999, 2001, and 2002," <i>J. Clin. Microbiol.</i> 44(3):999–1017 (2006)
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Exhibit No.	Document
1083	[Reserved]
1084	Declaration of Dennis L. Kasper, M.D.

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner" or "Merck") hereby requests *inter partes* review ("IPR") of claims 1 and 4-13 of U.S. Patent No. 9,399,060 ("the '060 Patent") (Ex. 1001), assigned to Wyeth LLC ("Patent Owner" or "Wyeth"). Petitioner has asserted, in a co-pending Petition for IPR of the '060 Patent, that the effective filing date of claims 1 and 4-13 is no earlier than January 22, 2009, and that those claims are invalid as anticipated by the prior art. However, as detailed herein and in the accompanying Declaration of Dennis L. Kasper, M.D. (a renowned researcher focusing on the development of human vaccines, including polysaccharide-protein conjugate vaccines) (Ex. 1084), even assuming *arguendo* an effective filing date of April 8, 2005 (the earliest possible priority date of the '060 Patent), there is a reasonable likelihood that Petitioner will prevail in establishing that claims 1 and 4-13 are invalid as obvious under pre-AIA § 103.

Conjugates of polysaccharides (sugars) to carrier proteins are commonly-used components of vaccines against disease-causing bacteria. To obtain wide-ranging coverage of various "serotypes" (*i.e.*, strains) of bacteria, conjugate vaccines are often "multivalent" (*i.e.*, include polysaccharides from multiple serotypes). For example, Patent Owner's prior art Prevnar[®] is a 7-valent pneumococcal conjugate vaccine with CRM₁₉₇ as the only carrier protein.

Sole independent claim 1 of the '060 Patent is directed to the natural progression of the prior art Prevnar[®] CRM₁₉₇-conjugate vaccine (targeting serotypes 4, 6B, 7F, 9V, 14, 18C, 19F and 23F) to additionally include at least serotype 3, which was well known in the art to be prevalent and a cause of serious disease. Claim 1 recites a composition with at least 8 immunogenic CRM₁₉₇-conjugates prepared from serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F.

The combination of the Prevnar 2001 (Ex. 1011) and Overturf 2002 (Ex. 1013) prior art references renders obvious the composition of sole independent claim 1. Prevnar 2001 discloses Patent Owner's immunogenic Prevnar[®] vaccine. Overturf 2002 discloses that Patent Owner was developing an 11-valent iteration of Prevnar[®] (featuring all 8 serotypes of claim 1 of the '060 Patent), with each polysaccharide conjugated to CRM₁₉₇. The inclusion of serotype 3 conjugated to CRM₁₉₇ in Overturf 2002 would have motivated a POSITA (with a reasonable expectation of success) to broaden the coverage of Prevnar[®] to include that conjugate.

The limitations of dependent claims 4-7 (at their narrowest, reciting aluminum phosphate adjuvant) and dependent claim 13 (reciting dose volume, polysaccharide amount and amount of aluminum phosphate) are directed to features of the prior art 7-valent Prevnar[®] vaccine; they reflect obvious features of an expanded iteration with at least 8 serotypes. And, claims 8-12 (broadly reciting

various additional antigens) would have been obvious in further view of Chiron 2003 (Ex. 1014) and Wyeth 2002 (Ex. 1015), which disclose that the claimed antigens can be added to a multivalent pneumococcal conjugate vaccine.

Finally, any secondary considerations that Patent Owner may allege will not overcome the strong evidence of obviousness based on prior art. There is no nexus between any alleged commercial success of Patent Owner's purported commercial embodiment (Prevnar 13[®]) and the claimed compositions; it was the prior art 7-valent Prevnar[®] that was a commercial success, and Prevnar 13[®] is its obvious next iteration. Moreover, in distinguishing the claimed compositions over the prior art during prosecution, Patent Owner relied on the purported immunogenicity against serotype 3; and yet, studies have demonstrated that Prevnar 13[®] does not provide significant protection against serotype 3. And, any alleged commercial success of Prevnar 13[®] is not commensurate with the scope of at least claims 1 and 4-13 that broadly cover virtually any multivalent immunogenic pneumococcal conjugate vaccine, which Patent Owner has not invented, disclosed or enabled, let alone practiced.

II. MANDATORY NOTICES

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are: Petitioner Merck Sharp & Dohme Corp., and Merck & Co., Inc.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner has filed two additional Petitions for *inter partes* review of the '060 Patent: IPR2017-01211 and IPR2017-01215. Petitioner has also filed two Petitions for post grant review ("PGR") of the '060 Patent: PGR2017-00016 and PGR2017-00017. Petitioner has filed a Petition for *inter partes* review of Patent Owner's US Patent No. 8,895,024: IPR2017-01194. Petitioner has filed three Petitions for *inter partes* review of Patent Owner's US Patent No. 8,562,999: IPR2017-00378, IPR2017-00380 and IPR2017-00390. Petitioner is unaware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding.

C. Lead and Backup Counsel and Service Info (37 C.F.R. § 42.8(b)(3)-(4))

Lead counsel is Arlene L. Chow (Reg. No. 47,489), Hogan Lovells US LLP, 875 Third Avenue, New York, NY 10022, Phone: 212-918-3000, Fax: 212-918-3100, and Email: arlene.chow@hoganlovells.com. Back-up counsel is: Ernest Yakob, Ph.D. (Reg. No. 45,893), Hogan Lovells US LLP, 875 Third Avenue, New York, NY 10022, Phone: 212-918-3000, Fax: 212-918-3100, and Email: ernest.yakob@hoganlovells.com.

Petitioner consents to electronic service.

III. PAYMENT OF FEES (37 C.F.R. §§ 42.15(b), 42.103)

Petitioner submits the required fees with this Petition. Please charge any additional fees required during this proceeding to Deposit Account No. 50-1349.

IV. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner respectfully submits that it has demonstrated, in co-pending Petitions for PGR of the '060 Patent (PGR2017-00016 and -00017), that the '060 Patent is a post-AIA patent containing at least one claim with an effective filing date of July 2, 2014. However, to the extent the Board determines that the '060 Patent is a pre-AIA patent (based on a claim of priority to a pre-AIA application), Petitioner certifies that the '060 Patent is available for IPR. Petitioner further certifies that it is not barred or estopped from requesting review on the grounds identified.

V. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner challenges claims 1 and 4-13 of the '060 Patent, and respectfully submits that the claims are unpatentable based on the following grounds:

Ground 1. Claims 1, 4-7 and 13 are unpatentable as obvious under pre-AIA § 103 over Prevnar 2001 (Ex. 1011) in view of Overturf 2002 (Ex. 1013) and the general knowledge of a POSITA.

Ground 2. Claims 8-10 and 12 are unpatentable as obvious under pre-AIA § 103 over Prevnar 2001 (Ex. 1011) in view of Overturf 2002 (Ex. 2013), Chiron 2003 (Ex. 1014) and the general knowledge of a POSITA.

Ground 3. Claim 11 is unpatentable as obvious under pre-AIA § 103 over Plevnar 2001 (Ex. 1011) in view of Overturf 2002 (Ex. 1013), Wyeth 2002 (Ex. 1015) and the general knowledge of a POSITA.

The above prior art references (including publication information) are summarized in Section VI.D *infra*; claim construction is addressed in Section VIII *infra*; and a detailed explanation of the grounds for unpatentability is provided in Section IX *infra*.

VI. BACKGROUND

A. State of the Art as of the Earliest Possible Priority Date of the '060 Patent, April 8, 2005

1. Polysaccharide-Protein Conjugates in Bacterial Vaccines

A vaccine prevents infectious diseases by priming the immune system prior to exposure to disease-causing organisms (*i.e.*, pathogens), such as bacteria, viruses or parasites. Ex. 1084, ¶ 23. When the source of infection is encapsulated bacteria (*i.e.*, bacteria covered in a shell of polysaccharides (which are polymers of sugars)), such as pneumococcus, the immune system often targets its response to the polysaccharides; this makes the polysaccharides attractive molecules for vaccines. *Id.*, ¶¶ 24-26.

Despite the successful use of bacterial polysaccharides to immunize adults and older children, polysaccharides were not very immunogenic in children under

2 years of age. *Id.*, ¶ 27 (citing Ex. 1020 at 18¹). Successful immunization of that particularly susceptible age group took place with bacterial proteins, *e.g.*, tetanus and diphtheria toxoids (inactivated toxins). *Id.* (citing Ex. 1021 at 6-7). Through conjugation to carrier proteins, a robust antibody-mediated response against the polysaccharides can be achieved in very young children. *Id.*, ¶¶ 28-30 (citing Ex. 1022; Ex. 1023; Ex. 1024 at 17-19; Ex. 1025).

Polysaccharide-protein conjugate vaccines had been commercialized for nearly two decades before April 8, 2005. *Id.*, ¶ 31. Numerous conjugate vaccines had been approved, including a vaccine against pneumococcus (Prevnar[®]). *Id.* (citing Ex. 1026 at 2; Ex. 1070; Ex. 1072; Ex. 1074; Ex. 1075 at 28, 38, 42; Ex. 1027 at 5-6; Ex. 1028 at 6). CRM₁₉₇ was commonly used as the carrier protein in many conjugate vaccines (*e.g.*, Vaxem HIB, HibTITER, Prevnar[®], Meningitec, Menjugate[®]). *Id.* (citing Ex. 1028 at 6; Ex. 1072; Ex. 1075 at 38, 42).

¹ Except for citation to patents and patent publication (which refer to the originally-published column and line numbers) and citation to the expert declaration of Dr. Kasper (which refers to paragraph numbers), this Petition cites to the page numbers added by Petitioners at the bottom of each Exhibit (and designated "PTAB PAGE ___/___").

2. Multivalent Polysaccharide-Protein Conjugate Vaccines

Strains of a species of extracellular bacteria, called "serotypes" or "serogroups," are characterized by the particular polysaccharides displayed on their surface. *Id.*, ¶ 34. For example, as of April 8, 2005, there were nearly 100 serotypes of pneumococcus. *Id.* (citing Ex. 1017 at 1). In general, antibodies are serotype-specific, recognizing the specific structure of a polysaccharide; antibodies against a polysaccharide from one serotype are generally not cross-protective against structurally-unrelated serotypes. *Id.* Because of this lack of cross-protection, vaccines are frequently multivalent, *i.e.*, they include polysaccharides from more than one serotype. *Id.*

There is a natural progression in the development of multivalent vaccines. *Id.*, ¶ 35. The earliest version utilizes the most prevalent polysaccharide serotypes. *Id.* Over time, later vaccine versions will incorporate additional clinically-relevant serotypes for broader protection. *Id.* An early pneumococcal polysaccharide vaccine (Pneumovax[®]) was licensed in 1977 and contained 14 serotypes. *Id.*, ¶ 40 (citing Ex. 1052). That 14-valent Pneumovax[®] was replaced with a 23-valent version (Pneumovax[®] 23) in 1983. *Id.* (citing Ex. 1053).

Because the pneumococcal polysaccharide vaccines were not immunogenic in young children, Patent Owner introduced a polysaccharide-protein conjugate vaccine (Prennar[®]) in 2000. *Id.* (citing Ex. 1033 at 3). Prennar[®] was a 7-valent

vaccine, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated to the CRM₁₉₇ carrier protein. *Id.*, ¶ 41 (citing Ex. 1011 at 2). Pneumococcal conjugate vaccines progressed to a 9-valent (adding serotypes 1 and 5), 11-valent (adding serotypes 3 and 7F), and the 13-valent (adding serotypes 6A and 19A) versions; a 13-valent iteration was approved and marketed as Prevnar 13[®] in 2010. *Id.*, ¶¶ 37, 42 (citing Ex. 1033 at 7). As of April 8, 2005, the field had identified the most prevalent and/or virulent serotypes of extracellular bacteria affecting young children; with respect to pneumococcus, the serotypes of Prevnar 13[®] were well-known, top candidates for a multivalent conjugate vaccine. *Id.*, ¶¶ 38, 42 (citing Ex. 1017 at 7; Ex. 1033 at 7; Ex. 1035 at 1; Ex. 1036 at 3).

3. Immunogenicity of Multivalent Polysaccharide-Protein Conjugate Vaccines

The characteristics of the immune response elicited by a vaccine reflect the likelihood that the vaccine will be successful at preventing disease. *Id.*, ¶ 43 (citing Ex. 1037 at 6). For example, demonstration of immunologic memory, *e.g.*, that antibody responses can be quickly and robustly recalled *in vivo* after re-exposure to the polysaccharide serotypes of the vaccine, is evidence that the immunity may persist for long periods of time and that antibody responses may be similarly fast and robust upon exposure to actual pathogens. *Id.* Likewise, if antibodies elicited by a vaccine are "functional" *in vitro*, *e.g.*, they are efficient mediators of bacterial death *in vitro*, one would expect such antibodies to prevent

actual infection *in vivo*. *Id.* The degree to which the vaccine elicits desired immune responses is referred to as "immunogenicity"; in the context of a multivalent conjugate vaccine, immunogenicity is assessed on a serotype-by-serotype basis. *Id.* (citing Ex. 1037 at 3).

4. Carrier Induced Epitopic Suppression in Multivalent Conjugate Vaccines

As of April 8, 2005, there had been reports in the literature of "immune interference," where the contemporaneous administration of vaccines purportedly impacted antibody responses (either positively or negatively). *Id.*, ¶ 44. For example, some reports suggested that immunization with a large dose of a single carrier protein (*e.g.*, due to the presence of many polysaccharide serotypes conjugated to the carrier protein in a multivalent vaccine, or co-administration of two or more vaccines containing the carrier protein) could potentially suppress the antibody response against the polysaccharide component of the vaccine. *Id.* This is referred to as "carrier induced epitopic suppression" ("CIES"). *Id.*

Those reports of CIES did not impact the natural progression of multivalent vaccine development. *Id.*, ¶ 45. As of April 8, 2005, there were clear advantages to using a single carrier protein in a multivalent conjugate vaccine, *e.g.*, efficiency, cost, simplicity and minimization of the risk of adverse reactions. *Id.*, ¶ 46. Institutionally, there is also typically a preference for particular carrier proteins for which there is prior successful experience and know-how. *Id.*, ¶ 47. This is

evidenced by Patent Owner's consistent usage of CRM₁₉₇ as the single carrier protein in its own development efforts with respect to pneumococcal and other vaccines. *Id.* The prior art 7-valent Prevnar[®] (using CRM₁₉₇ as the only carrier protein) was itself an expanded form of earlier lower-valency compositions using CRM₁₉₇ as the only carrier protein. *Id.* (citing Ex. 1038 at 1). The next iteration was a prior art 9-valent vaccine, again using CRM₁₉₇ as the sole carrier protein. *Id.* (citing Ex. 1016 at 1; Ex. 1039 at 2). The prior art literature further indicated that Patent Owner was expanding its 9-valent pneumococcal conjugate vaccine to an 11-valent iteration with CRM₁₉₇ as the sole carrier protein. *Id.* (citing Ex. 1013 at 4; Ex. 1040 at 5).

Moreover, the literature as of April 8, 2005 indicated that CIES was not always observed when increasing the amount of a carrier protein; decreased antibody response due to CIES was not clinically relevant when other correlates of protection were still observed. *Id.*, ¶ 48. With respect to CRM₁₉₇, at least one study reported on the simultaneous administration of a 9-valent pneumococcal CRM₁₉₇-conjugate vaccine and a non-pneumococcal CRM₁₉₇-conjugate vaccine; the joint administration of a total of 45 µg of CRM₁₉₇ (more than double the 20 µg in Prevnar[®]) did not result in suppression. *Id.* (citing Ex. 1039 at 6-7). Similarly, co-administration of the 7-valent pneumococcal CRM₁₉₇-conjugate vaccine and a non-pneumococcal CRM₁₉₇-conjugate vaccine "produced no meaningful increase

or reduction in the concentration of pneumococcal or other vaccine antibodies." *Id.* (citing Ex. 1013 at 6; Ex. 1041 at 5). And, in a study (sponsored by Patent Owner) that did observe suppression of pneumococcal antibody responses in connection with increased amounts of carrier protein in a 7-valent pneumococcal CRM₁₉₇-conjugate vaccine, the authors concluded that "this may be clinically unimportant given that their [*i.e.*, the patients'] response to polysaccharide boosting suggested good priming [*i.e.*, memory]." *Id.* (citing Ex. 1042 at 8).

5. Use of Aluminum Adjuvants in Conjugate Vaccines

As of April 8, 2005, aluminum salts, such as aluminum phosphate and aluminum hydroxide, were the most commonly used adjuvants for enhancing the immunogenicity of human vaccines. *Id.*, ¶ 71. An adjuvant helps amplify the interaction between B-cells (or other antigen presenting cells) and helper T-cells, which is necessary for a robust IgG antibody response. *Id.* As of April 8, 2005, aluminum salt was an adjuvant in many licensed conjugate vaccines, including Prevnar[®] (aluminum phosphate). *Id.* (citing Ex. 1075 at 42).

B. The '060 Patent

Sole independent claim 1 of the '060 Patent is generally directed to a multivalent immunogenic pneumococcal CRM₁₉₇-conjugate vaccine. The pneumococcal serotypes of the claim "comprise" the 7 polysaccharide serotypes (*i.e.*, 4, 6B, 9V, 14, 18C, 19F, 23F) in Patent Owner's prior art Prevnar[®] vaccine

(also referred to in the '060 Patent specification as "7vPnC"), and "at least one additional serotype, wherein the additional serotype is serotype 3":

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 CRM₁₉₇.

Ex. 1001. Since "comprise" is an open-ended term, the broadest reasonable interpretation of claim 1 is that it is directed to any pneumococcal CRM₁₉₇-conjugate vaccine with any combination of pneumococcal serotypes (of which nearly 100 are presently known), so long as the composition includes the 8 serotypes recited in the claim and is immunogenic.

Despite the open-ended (*i.e.*, "comprise") scope of claim 1, the '060 Patent discloses only a vaccine with the 13 serotypes of 13vPnC. *See, e.g., id.* at 2:20-24. The '060 Patent provides no guidance with respect to an immunogenic vaccine with any other specific polysaccharide serotypes. Dependent claims 4-13 retain the open-endedness of claim 1 with respect to the number and identity of the "additional serotype[s]," and instead recite limitations regarding adjuvant (claims

4-7), additional antigens other than pneumococcal conjugates (claims 8-12), and dosage (claim 13). *Id.* at claims 4-13.

1. The '060 Patent Only Discloses Immunogenic Vaccines with the 13 Serotypes of 13vPnC

In contrast to the broad scope of claim 1, the specification of the '060 Patent discloses only an immunogenic composition with the 13 serotypes of 13vPnC. The Abstract of the '060 Patent summarizes the narrowly-tailored disclosure of the '060 Patent:

An immunogenic composition having 13 distinct polysaccharide-protein conjugates and optionally, an aluminum-based adjuvant, is described. Each conjugate contains a capsular polysaccharide prepared from a different serotype of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) conjugated to a carrier protein.

Id. The Summary of the Invention is the same:

[T]he present invention provides generally a multivalent immunogenic composition comprising 13 distinct polysaccharide-protein conjugates . . . More specifically, the present invention provides a 13-valent pneumococcal conjugate (13vPnC) composition comprising the seven serotypes in the 7vPnC vaccine (4, 6B, 9V, 14, 18C, 19F and 23F) plus six additional serotypes (1, 3, 5, 6A, 7F and 19A).

Id. at 2:13-24. Of the ~32 columns in the '060 Patent disclosure (excluding references and claims), ~16 columns provide details for preparing conjugates of

each of the 13 serotypes of 13vPnC (*id.* at 11:21-27:35), and ~5 columns are devoted to immunologic testing of 13vPnC (*id.* at 28:1-32:64). There is no corresponding disclosure for any other pneumococcal serotype. The only "additional serotypes" (of claim 1) disclosed in the specification are the 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A) of 13vPnC (*see, e.g., id.* at 2:63-65).

2. The Inventors of the '060 Patent Chose the 13 Serotypes of 13vPnC Based on Publicly Available Data

For the selection of the 13 serotypes of 13vPnC, the '060 Patent makes clear that the inventors relied on public data readily available to any POSITA - thus confirming the clear map in the prior art for the progression of pneumococcal serotypes from 7vPnC to the disclosed 13vPnC.

In the Background of the Invention, the '060 Patent explains that, 7vPnC "covers approximately 80-90%, 60-80%, and 40-80% of invasive pneumococcal disease (IPD) in the US, Europe, and other regions of the world, respectively." *Id.* at 1:43-46. The specification makes clear that the addition of 6 specific serotypes (1, 3, 5, 6A, 7F and 19A) to 7vPnC "would increase coverage for invasive disease to >90% in the US and Europe, and as high as 70%-80% in Asia and Latin America." *Id.* at 2:1-6.

The '060 Patent acknowledges Patent Owner's prior development of a 9-valent vaccine, which was "7vPnC plus serotypes 1 and 5" (*id.* at 6:23-25), and

cites to a 2002 publication (*id.* at 4:15-18), which discloses an "11-valent pneumococcal conjugate vaccine formulation, containing [9-valent] PCV-9 serotypes plus 3 and 7F (PCV-11)." Ex. 1017 ("Hausdorff 2002") at 2. That same Hausdorff 2002 publication identifies 6A and 19A as the next group of "major serotypes": "It appears that the serotypes represented in PCV-11, plus 6A and 19A, comprise all major serotypes in each age group studied." *Id.* at 7. Similarly, a 1999 paper, discussed in the '060 Patent, expressly discloses that future vaccines may include the 13 serotypes of 13vPnC: "The current experimental conjugate vaccines contain 7 (e.g., serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) or more serotypes. To increase the coverage for protection, additional serotypes (e.g., serotypes 1, 3, 5, 6A, 7F, and 19A) may be added to the conjugate vaccines in the future." Ex. 1035 at 1.

C. Prosecution History of the '060 Patent

The '060 Patent was filed on July 2, 2014, but it claims an earliest possible priority date of April 8, 2005, based on the filing date of US Provisional Application No. 60/669,605 ("the '605 Provisional"). Ex. 1006. The '060 Patent is also the last issued patent in a chain of non-provisional applications, all claiming priority back to the '605 Provisional. Exs. 1002-1005.

During prosecution of the '060 Patent, the claims were rejected over GSK prior art, which expressly disclosed, *inter alia*, 11- and 13-valent pneumococcal

conjugate vaccines with the same serotypes claimed in the '060 Patent, as well as CRM₁₉₇ as a carrier protein; according to the Examiner, there was nothing inventive about Patent Owner's choice of serotypes, nor the choice of CRM₁₉₇. Ex. 1002 at 141. To overcome the prior art, Patent Owner argued that it would not have been obvious to use CRM₁₉₇ as the single carrier for the claimed conjugates because: (1) unlike the claims of the '060 Patent, the particular GSK prior art that was cited by the Examiner did not disclose a single carrier for each of the conjugates, and (2) GSK's use of another single carrier, Protein D, in its "11-Pn-PD" vaccine (which included all of the serotypes of claim 1) failed to "exhibit[] significant immunogenicity with respect to serotype 3 polysaccharides." *Id.* at 179-181. Patent Owner argued that the inventors of the '060 Patent "unexpectedly discovered a robust immune response with respect to serotype 3 polysaccharides while using CRM₁₉₇ for all serotypes, including serotype 3." *Id.* at 180. The Examiner allowed the claims in response to Patent Owner's arguments. *Id.* at 208.

D. Prior Art

1. Prevnar 2001

Grounds 1-3 of this Petition rely on the Prevnar[®] entry from the 2001 (55th Edition) Physicians' Desk Reference ("Prevnar 2001"). Ex. 1011. Because Prevnar 2001 was published on or before January 4, 2001 (*id.* at 9), more than one year prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it

is prior art under pre-AIA § 102(b). Prevnar 2001 discloses FDA-approved product information for Patent Owner's Prevnar[®] vaccine, including in relevant part, its composition, dosing parameters, immunogenicity, and effect on concurrently-administered vaccines.

"Prevnar[™], Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein), is a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM₁₉₇ protein." *Id.* at 2. As of the publication date of Prevnar 2001, the 7 serotypes of Prevnar[®] "have been responsible for approximately 80% of invasive pneumococcal disease in children < 6 years of age in the United States." *Id.* at 3. The 7 polysaccharide serotypes are individually conjugated to CRM₁₉₇, after which "[t]he individual glycoconjugates are compounded to formulate the vaccine, Prevnar[™]." *Id.* at 2.

With respect to dosing, "[e]ach 0.5 mL dose is formulated to contain: 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of serotype 6B per dose (16 µg total saccharide); approximately 20 µg of CRM₁₉₇ carrier protein; and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant." *Id.*

Prevnar 2001 expressly discloses that "Prevnar[™] induces functional antibodies to all vaccine serotypes, as measured by opsonophagocytosis following

three doses." *Id.* at 3. It was also well known for years before April 8, 2005 that Prevnar[®] elicits immunologic memory and is protective with respect to each of its serotypes. *See, e.g.*, Ex. 1042 at 8; Ex. 1061 at 4.

Prevnar 2001 discloses the results of clinical studies assessing "[t]he immune response to routine vaccines when administered with Prevnar[™] (at separate sites)." Ex. 1011 at 4. With respect to concurrently-administered HibTITER *Haemophilus influenzae* type b conjugate vaccine (containing 25 µg of CRM₁₉₇ carrier protein), Prevnar 2001 cites (*id.*) to a 1999 study, which found no meaningful suppression of pneumococcal antibodies. Ex. 1041 at 5. Prevnar 2001 notes that "[s]ome suppression of *Haemophilus influenzae* type b (Hib) response was seen at the 4th dose, but over 97% of children achieved titers ≥ 1 µg/mL." Ex. 1011 at 4. In fact, in infants, concurrent administration of HibTITER resulted in "**enhancement**" of Hib polysaccharide PRP antibodies. *Id.* (emphasis added).

2. Overturf 2002

Grounds 1-3 rely on Overturf, "Pneumococcal Vaccination of Children," *Semin. Pediat. Infec. Dis.* 13(3):155-164 (2002) ("Overturf 2002"). Ex. 1013. Because Overturf 2002 was published in 2002, more than one year prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under pre-AIA § 102(b).

Overturf 2002 discloses a pneumococcal "11-valent vaccine," with "[p]urified polysaccharides conjugated to CRM₁₉₇"; the serotypes contained in the vaccine are "1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F." *Id.* at 4. Although Overturf 2002 mentions purported concerns regarding CIES with respect to "the addition of a larger number of serotypes" (*id.* at 8), Overturf 2002 explains that no meaningful suppression was observed with respect to Prevnar[®]:

Concurrent administration of pneumococcal conjugate vaccines with diphtheria and tetanus toxoids and pertussis (DTP), DTaP, or Hib conjugate vaccines produced **no meaningful increase or reduction in the concentration of pneumococcal or other vaccine antibodies**, including those to pertussis antigens (eg, pertussis toxin, fimbriae, 69 kd protein, fimbrial hemagglutinin), diphtheria or tetanus antitoxins, or the Hib polysaccharide.

Id. at 6 (emphasis added).

3. Chiron 2003

Ground 2 (concerning dependent claims 8-10 and 12) further relies on Chiron's International Patent Publication No. WO 03/009869 ("Chiron 2003"). Ex. 1014. Because Chiron 2003 was published on February 6, 2003, more than one year prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under pre-AIA § 102(b).

Chiron 2003 discloses saccharide-protein conjugate antigens, preferably with a CRM₁₉₇ carrier protein. *Id.* at 2:5, 3:20-23. The teachings of Chiron 2003

are preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus and meningococcus species. *Id.* at 6:32-35.

In addition to pneumococcal saccharide-protein conjugate antigens (*id.* at 2:15), Chiron 2003 discloses that "[t]he composition may comprise one or more of these bacterial . . . antigens":

- "a protein antigen from *N. meningitidis* serogroup B . . .";
- "an antigen from *Moraxella catarrhalis* . . ."

Id. at 2:9-10, 2:29, 3:14.

4. Wyeth 2002

Ground 3 (concerning dependent claim 11) further relies on Patent Owner's International Patent Publication No. WO 2002/083855 ("Wyeth 2002"). Ex. 1015. Because Wyeth 2002 was published on October 24, 2002, more than one year prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under pre-AIA § 102(b).

Wyeth 2002 is cited in the specification of the '060 Patent as disclosing "[e]xamples of *Streptococcus pneumoniae* proteins suitable for inclusion" in "[t]he compositions of this invention." Ex. 1001 at 11:4-9. Wyeth 2002 discloses that its purported invention "addresses the need for *Streptococcus pneumoniae* immunogenic compositions that effectively prevent or treat most or all of the disease caused by serotypes of *Streptococcus pneumoniae*." Ex. 1015 at 23:27-29.

In particular, Wyeth 2002 discloses pneumococcal polypeptides (including proteins) "that are secreted, exposed, membrane associated or surface localized on *Streptococcus pneumoniae*, and thus serve as potential antigenic polypeptides in immunogenic compositions." *Id.* at 23:32-24:1. Wyeth 2002 further discloses "combination immunogenic compositions . . . provided by combining one or more of the polypeptides of the invention with one or more known *S. pneumoniae* . . . polysaccharide-protein conjugates, including, but not limited to . . . the 7-valent pneumococcal polysaccharide-protein conjugate vaccine." *Id.* at 96:17-22.

VII. LEVEL OF ORDINARY SKILL IN THE ART

The claims of the '060 Patent are generally directed to multivalent immunogenic pneumococcal conjugate vaccines that include at least the 7 serotypes of Prevnar[®] and serotype 3. Ex. 1084, ¶ 102. Therefore, a POSITA would have been an individual or team with Ph.D. degrees in the biological and chemical sciences and at least 3 years of work experience, or an M.D. degree and at least 6 years of work experience, developing conjugate vaccines, including specifically growing sufficient quantities of bacteria, extracting, purifying and analyzing bacterial polysaccharides, conjugating polysaccharides to a carrier protein (and analyzing the conjugates), and performing immunologic testing. *Id.*

VIII. CLAIM CONSTRUCTION

Petitioner submits that the term "immunogenic" (recited in every claim) requires construction. Likewise, the limitation in sole independent claim 1 regarding the number and identity of the claimed serotypes - "wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional serotype, wherein the additional serotype is serotype 3" - should be construed. Because the '060 Patent has not expired and will not expire before a final written decision is entered in this proceeding, each claim term is construed based on "its broadest reasonable construction [a/k/a broadest reasonable interpretation] in light of the specification of the patent in which it appears."² 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). In AIA post-grant proceedings, the broadest reasonable interpretation standard also takes into account Patent Owner's statements and arguments during prosecution history. *See, e.g., Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015).

A. "immunogenic"

Every claim of the '060 Patent recites an "immunogenic" composition. Ex. 1001. The broadest reasonable interpretation of that term is "elicits immunologic

² Petitioner reserves the right to argue for different claim constructions in district courts, where a different claim construction standard applies.

memory and/or functional antibody with respect to each serotype of the vaccine, including serotype 3." Ex. 1084, at ¶ 107.

As detailed below, although the term "immunogenic" appears in the claim preambles, Patent Owner repeatedly emphasized immunogenicity in the specification, and relied on it during prosecution history to gain allowance of the claims over a prior art vaccine that purportedly failed to elicit immunologic memory or functional antibody with respect to serotype 3. Ex. 1084, ¶ 108; *see, e.g., Rotatable Techs. LLC v. Motorola Mobility LLC*, 567 F. App'x 941, 943 (Fed. Cir. 2014) ("The specification is replete with references to [the preamble language] 'selectively rotating,' underscoring the importance of the feature to the claimed invention. . . . Further the prosecution history shows 'clear reliance on the preamble' to distinguish the claimed invention from the prior art") (internal citations omitted); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1347 (Fed. Cir. 2002) ("[B]oth the specification and prosecution history indicate that the phrase 'rich in glucosinolates' helps to define the claimed invention and is, therefore, a limitation of claim 1"). The fact that the preamble of every claim recites an "immunogenic" composition underscores the intended limiting nature of the term. Ex. 1084, ¶ 108; *see, e.g., Poly-Am., L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) (emphasizing that "the entire preamble 'blown-film textured liner' is restated in each of the patent's seven claims").

In the specification of the '060 Patent and during prosecution, Patent Owner conceded that GSK had disclosed a prior art 11-valent pneumococcal conjugate vaccine ("11-Pn-PD") with (1) the 8 polysaccharide serotypes recited in claim 1 (including serotype 3), and (2) each of the 11 total polysaccharide serotypes conjugated to protein D carrier proteins. Ex. 1001 at 4:26-42; Ex. 1002 at 180. Patent Owner stressed the importance of immunogenicity. Ex. 1001 at 4:43-47; Ex. 1002 at 180-181. More specifically, Patent Owner argued that 11-Pn-PD suffered from a deficiency with respect to the immune response against serotype 3 - the failure to elicit immunologic memory or functional antibody (both important correlates of protection) - which the purported invention of the '060 Patent allegedly overcame.³ Ex. 1084, ¶¶ 109-115.

In alleging that the 11-Pn-PD vaccine did not generate immunologic memory, Patent Owner cited to a 2004 GSK-sponsored study (Ex. 1037), arguing

³ Importantly, Patent Owner did not (and could not) argue that 11-Pn-PD failed to elicit significant antibody production for all serotypes, including serotype 3. *See, e.g.*, Ex. 1037 at 3 ("significantly higher antipneumococcal PS IgG concentrations for all vaccine serotypes after 3 doses of Pn-PD at 7 months"). Patent Owner's argument instead focused on more direct correlates of protection, generation of immunologic memory and functional antibody, as the baseline of acceptable immunogenicity. Ex. 1084, ¶ 110.

that "no priming effect [*i.e.*, immunologic memory] was observed for serotype 3 . . ." Ex. 1001 at 4:26-32; Ex. 1002 at 180; *see also* Ex. 1056 at 38 ("failed to induce significant immunogenic memory"); Ex. 1062 at 2 ("failed to exhibit sufficient immune response, in particular with regard to immunologic memory"). Patent Owner also stressed that GSK's prior art 11-Pn-PD vaccine did not elicit functional antibody, citing to a 2001 meeting abstract (Ex. 1063), and arguing that "opsonophagocytic assay (OPA) results [*i.e.*, measurements of functional antibody] . . . failed to show antibody responses for serotype 3 at levels comparable to other tested serotypes." Ex. 1001 at 4:32-38; Ex. 1002 at 180; *see also* Ex. 1063 ("Except for serotype 3, opsonophagocytic anti-Pn GMTs were 4 to 50-fold higher in subjects who received 11-Pn-PD than in controls").

In purported contrast to the prior art, 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." Ex. 1002 at 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") (emphasis added). In support, Patent Owner cited a 2010 paper that purports to show the generation of both immunologic memory and functional antibody for all serotypes, including serotype 3, in response to vaccination with Patent Owner's alleged commercial embodiment:

PCV13 also elicited **functional** opsonophagocytic activity comparable with that elicited by PCV7. For the 6 additional serotypes in PCV13, PCV13 elicited binding and **functional** antibody levels notably greater than those in PCV7 recipients. . . . The PCV13 toddler dose [*i.e.*, a booster dose to assess **immunologic memory**] resulted in higher immune responses compared with infant-series doses.

Ex. 1064 at 1 (emphasis added). In view of Patent Owner's arguments, the Examiner allowed the claims of the '060 Patent. Ex. 1002 at 208.

During prosecution of other members of the '060 Patent family (each of which is incorporated by reference in its entirety in the '060 Patent), Patent Owner repeatedly emphasized that its "multivalent immunogenic composition" is immunogenic with respect to **each** of the polysaccharide serotypes of the composition. Ex. 1084, ¶ 116. For example, Patent Owner argued for the patentability of a claim (Ex. 1005 at 63 (claim 18)), which was similar to (if not broader than) the claims of the '060 Patent. Patent Owner argued that an unexpected feature of the claimed composition was "the ability of a multivalent conjugate composition comprising more than seven individual polysaccharide conjugates to elicit immunogenic responses to **each** of its component polysaccharide serotypes (claims 18-24)." Ex. 1005 at 144 (emphasis added).

Given the disclosure in the '060 Patent specification, as well as Patent Owner's clear and unambiguous representations to the Patent Office, 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." Ex. 1084, ¶ 117.

B. "wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional serotype, wherein the additional serotype is serotype 3"

Petitioner submits that, although the disclosure of the '060 Patent does not support an immunogenic composition with more than the 13 disclosed pneumococcal polysaccharide serotypes, the broadest reasonable interpretation of sole independent claim 1 is that it is open-ended with respect to the number "additional serotypes" that can be included. Ex. 1084, ¶ 118. The broadest reasonable interpretation of "wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional serotype, wherein the additional serotype is serotype 3" - which uses the open-ended phrases "comprise" and "at least" - is: "the serotypes must include at least serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F." *Id.*

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Claims 1, 4-7 and 13 Are Invalid as Obvious over Prevnar 2001 in View of Overturf 2002 and the General Knowledge of a POSITA

The Prevnar 2001 (Ex. 1011) and Overturf 2002 (Ex. 1013) prior art references both disclose multivalent pneumococcal conjugate vaccine compositions, and a POSITA would have considered both references when

developing a multivalent pneumococcal conjugate vaccine composition. Ex. 1084, ¶ 141. Based on the combination of the Prevnar 2001 and Overturf 2002 references, it would have been obvious for a POSITA to arrive at the immunogenic pneumococcal CRM₁₉₇-conjugate composition of sole independent claim 1, which merely requires the addition of at least serotype 3 to the 7 serotypes of Patent Owner's prior art Prevnar[®] vaccine. *Id.* The Prevnar 2001 reference discloses that the 7-valent Prevnar[®] is immunogenic for each of the serotypes in the vaccine, and it is safe and effective. 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 CRM₁₉₇.

Based on the inclusion of a serotype 3 CRM₁₉₇ conjugate in Overturf 2002, a POSITA would have been motivated to broaden the coverage of Prevnar[®] to include at least serotype 3 conjugated to CRM₁₉₇. And, further motivation was provided by the prevalence of serotype 3, its association with serious disease, and its inclusion in the Pneumovax[®] 23 polysaccharide vaccine. A POSITA also would have been motivated to continue using the safe and effective CRM₁₉₇ protein as the single carrier protein in an expanded Prevnar[®] vaccine as specifically recited in Overturf 2002.

A POSITA would also have had a reasonable expectation that an 8- to 11-valent iteration of Prevnar[®] (including the original 7 serotypes, serotype 3 and

potentially serotypes 1, 5 and/or 7F, each conjugated to CRM₁₉₇) would be immunogenic, based on the success of the 7-valent Prevnar[®] and the disclosure in Overturf 2002 that Patent Owner itself was pursuing an 11-valent iteration with CRM₁₉₇ as the sole carrier protein. Concerns over CIES would not have discouraged development of the 8- to 11-valent CRM₁₉₇-conjugate vaccine. Patent Owner's prior art 7- and 9-valent CRM₁₉₇-conjugate vaccines were each safe and immunogenic. And, increases in the amount of carrier protein in Prevnar 2001 and Overturf 2002 (by co-administering non-pneumococcal conjugate vaccines) did not suppress antibody responses against the pneumococcal polysaccharides.

1. Claim 1

a. "A multivalent immunogenic composition comprising"

Prevnar 2001 discloses a "Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein)," which includes "saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM₁₉₇ protein." Ex. 1011 at 2. Prevnar 2001 expressly discloses that "Prevnar[™] induces functional antibodies to all vaccine serotypes, as measured by opsonophagocytosis following three doses." *Id.* at 3. It was also well known for years before April 8, 2005 that Prevnar[®] elicits immunologic memory and is protective with respect to each of its serotypes. *See, e.g.,* Ex. 1042 at 8; Ex. 1061 at 4.

Overturf 2002 discloses a pneumococcal "11-valent vaccine," with "[p]urified polysaccharides conjugated to CRM₁₉₇"; the serotypes contained in the vaccine are "1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F." Ex. 1013 at 4. Based on Overturf 2002, a POSITA would have had a reasonable expectation that the disclosed 11-valent CRM₁₉₇-conjugate vaccine would be immunogenic. Ex. 1084, ¶ 143.

b. "polysaccharide-protein conjugates"

The disclosed vaccines in both Prevnar 2001 and Overturf 2002 include polysaccharide protein conjugates. Ex. 1084, ¶ 144. Prevnar 2001 discloses that "[t]he polysaccharides are chemically activated to make saccharides which are directly conjugated to the protein carrier CRM₁₉₇ to form the glycoconjugate." Ex. 1011 at 2. Overturf discloses "[p]urified polysaccharides conjugated to CRM₁₉₇." Ex. 1013 at 4.

c. "and a physiologically acceptable vehicle,"

The disclosed vaccines in both Prevnar 2001 and Overturf 2002 include a physiologically acceptable vehicle. Ex. 1084, ¶ 145. As an initial matter, the '060 Patent discloses that "[e]xamples of [physiologically acceptable] vehicles include, but are not limited to, water, buffered saline, polyols (e.g., glycerol, propylene glycol, liquid polyethylene glycol) and dextrose solutions." Ex. 1001 at 8:56-59. Since the vaccines of Prevnar 2001 and Overturf 2002 are injected intramuscularly,

a POSITA would have understood that they were provided in a physiologically acceptable vehicle such as water or buffered saline. Ex. 1084, ¶ 145.

- d. "wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein,"**

The conjugates of both Prevnar 2001 and Overturf 2002 are prepared individually, each with a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae*. Ex. 1084, ¶ 146. Prevnar 2001 discloses that Prevnar[®] is "a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM₁₉₇ protein." Ex. 1011 at 2; *see also id.* ("The individual glycoconjugates are compounded to formulate the vaccine, Prevnar[™]."). Because the 11-valent CRM₁₉₇-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[®]. Ex. 1084, ¶ 146. Moreover, it was well-known that conjugates of distinct serotypes are prepared individually to ensure inclusion of accurate amounts of each polysaccharide and more reproducible polysaccharide to protein ratios in each conjugate. *Id.*

- e. **"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"**

The 11-valent vaccine of Overturf 2002 includes serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to CRM₁₉₇. Ex. 1013 at 4. Prevnar 2001 discloses a 7-valent vaccine with all of the claimed serotypes, other than serotype 3. Ex. 1011 at 2. Based on the inclusion of serotype 3 in Overturf 2002, a POSITA would have been motivated (with a reasonable expectation of success) to broaden the coverage of Prevnar[®] with at least serotype 3 conjugated to CRM₁₉₇. Ex. 1084, ¶ 147. As conceded by Patent Owner during the prosecution of the '024 Patent, there was a "high motivation in the vaccine art" to create "a complex, multivalent conjugate vaccine that provides effective protection against all *S. pneumoniae* serotype polysaccharides incorporated in the vaccine (including serotype 3)." Ex. 1004 at 198. In that regard, it was well-known in the art that serotype 3 was prevalent and a cause of serious disease. Ex. 1084, ¶ 147.

A POSITA would have had a reasonable expectation of success of creating an immunogenic serotype 3 conjugate. *Id.*, ¶ 148. Patent Owner's argument to the contrary during prosecution is belied by at least one study, in which two distinct 8-valent conjugate compositions were immunogenic with respect to serotype 3. *Id.*; Ex. 1012.

f. "wherein the carrier protein is CRM₁₉₇."

The only carrier protein in Prevnar 2001 is CRM₁₉₇; it would have been obvious to likewise use CRM₁₉₇ when expanding Prevnar[®] to include at least serotype 3, as disclosed in Overturf 2002. Ex. 1084, ¶ 149. CRM₁₉₇ was well-known to be a safe and effective carrier protein, as evidenced by its use in Prevnar[®] and other vaccines (such as Vaxem Hib, Menjugate and Patent Owner's HibTITER and Meningitec vaccines). Ex. 1028 at 6; Ex. 1072; Ex. 1075 at 38, 42. Indeed, it was well-known that Patent Owner had already developed a 9-valent CRM₁₉₇ pneumococcal conjugate vaccine (adding serotypes 1 and 5). *See, e.g.*, Ex. 1016; Ex. 1039.

A POSITA would have had a reasonable expectation that an 8-valent iteration of Prevnar[®] (including the original 7 serotypes and serotype 3) would be immunogenic, based on the success of the 7-valent Prevnar[®] and the disclosure in Overturf 2002 that Patent Owner itself was pursuing an 11-valent iteration with CRM₁₉₇ as the sole carrier protein. Ex. 1084, ¶ 150. CRM₁₉₇ was known to be safe and effective carrier protein, and it had already been approved for (and effective in) the 7-valent Prevnar[®] and other vaccines. *Id.*

Finally, purported concerns of CIES would not have deterred a POSITA from developing an 8- to 11-valent pneumococcal CRM₁₉₇-conjugate vaccine. *Id.*, ¶ 151. Overturf 2002 expressly discloses an 11-valent iteration of Prevnar[®], and

Patent Owner had already developed a safe and immunogenic 9-valent iteration of Prevnar[®] (with the 7 original serotypes plus serotypes 1 and 5). *See, e.g.*, Ex. 1016. In Prevnar 2001, although antibody responses were somewhat reduced in concurrently administered non-pneumococcal CRM₁₉₇-conjugate vaccines, antibody responses against the pneumococcal polysaccharides were not meaningfully affected. Ex. 1011 at 4; *see also* Ex. 1041 at 5. Overturf 2002 likewise explains that no meaningful suppression was observed with Prevnar[®]:

Concurrent administration of pneumococcal conjugate vaccines with diphtheria and tetanus toxoids and pertussis (DTP), DTaP, or Hib conjugate vaccines produced **no meaningful increase or reduction in the concentration of pneumococcal or other vaccine antibodies**, including those to pertussis antigens (eg, pertussis toxin, fimbriae, 69 kd protein, fimbrial hemagglutinin), diphtheria or tetanus antitoxins, or the Hib polysaccharide.

Ex. 1013 at 6 (emphasis added). To the extent open-ended claim 1 is deemed enabled (in co-pending IPR2017-01211), any contention by Patent Owner - that CIES renders the expansion of a 7-valent conjugate vaccine to an 8-valent conjugate vaccine non-obvious - lacks any merit. Ex. 1084, ¶ 152.

2. Claim 4

- a. "The immunogenic composition of claim 1, further comprising an adjuvant."**

The vaccine of Prevnar 2001 includes "0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant." Ex. 1011 at 2. It would have been obvious to rely on the same adjuvant in an expanded vaccine to boost immunogenicity. Ex. 1084, ¶ 153.

3. Claim 5

- a. "The immunogenic composition claim 4, wherein the adjuvant is an aluminum-based adjuvant."**

The vaccine of Prevnar 2001 includes "0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant." Ex. 1011 at 2. It would have been obvious to rely on the same adjuvant in an expanded vaccine to boost immunogenicity. Ex. 1084, ¶ 154.

4. Claim 6

- a. "The immunogenic composition of claim 5, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide."**

The vaccine of Prevnar 2001 includes "0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant." Ex. 1011 at 2. It would have been obvious to rely on the same adjuvant in an expanded vaccine to boost immunogenicity. Ex. 1084, ¶ 155.

5. Claim 7

- a. "The immunogenic composition of claim 6, wherein the adjuvant is aluminum phosphate."**

The vaccine of Prevnar 2001 includes "0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant." Ex. 1011 at 2. It would have been obvious to rely on the same adjuvant in an expanded vaccine to boost immunogenicity. Ex. 1084, ¶ 156.

6. Claim 13

- a. "The immunogenic composition of claim 1, wherein the composition is formulated as a single 0.5 ml dose comprising 2.2 µg of each polysaccharide, except for 6B at 4.4 µg, and 125 µg aluminum phosphate adjuvant."**

The dosage details of claim 13 would have been obvious over Prevnar 2001, which discloses:

Each 0.5 mL dose is formulated to contain: 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of serotype 6B per dose (16 µg total saccharide); . . . and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant.⁴

⁴ The '060 Patent makes clear that the claimed "125 µg aluminum phosphate adjuvant" refers to the amount of elemental aluminum present in 0.5 mg of aluminum phosphate: "The present invention further provides that any of the immunogenic compositions administered is a single 0.5 mL dose formulated to

Ex. 1011 at 2; *see* Ex. 1084, ¶ 157. It would have been obvious to apply the same dosage parameters in an 8-valent iteration of Prevnar[®], especially since Patent Owner had already done so with its 9-valent iteration. Ex. 1069 at 3; *see* Ex. 1084, ¶ 158.

The specification of the '060 Patent concedes that the claimed dosage is "similar" to that of Prevnar[®], which "has shown desirable safety, immunogenicity, and efficacy against IPD in the 2 µg saccharide dose level for serotypes 4, 9V, 14, 18C, 19F and 23F, and at the 4 µg dose for 6B." Ex. 1001 at 10:32-38. There is no significance in the slight difference between 2.2 µg of the claims and 2 µg in Prevnar[®] (as well as 4.4 µg in the claims vs. 4 µg in Prevnar[®]); the '060 Patent itself uses the two dosages interchangeably for the disclosed 13-valent composition. *See, e.g., id.* at 3:9-15; 10:24-28; 29:63-65; *see* Ex. 1084, ¶ 160.

contain . . . 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant . . ." Ex. 1001 at 3:9-15.

**B. Claims 8-10 and 12 Are Invalid as Obvious over
Prevnar 2001 in View of Overturf 2002,
Chiron 2003 and the General Knowledge of a POSITA**

1. Claim 8

- a. "The immunogenic composition of claim 1, wherein the composition further comprises one or more antigens."**

Based on Chiron 2003 (Ex. 1014), it would have been obvious to include one or more antigens, such as *Moraxella catarrhalis*, in the 8-valent immunogenic CRM₁₉₇-conjugate vaccine (discussed above, based on Prevnar 2001 and Overturf 2002). Ex. 1084, ¶ 161. The teachings of Chiron 2003 are preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus and meningococcus species, and Chiron 2003 discloses saccharide-protein conjugate antigens, preferably with a CRM₁₉₇ carrier protein. Ex. 1014 at 2:5, 3:20-23, 6:32-35. In addition to pneumococcal saccharide-protein conjugate antigens (*id.* at 2:15), Chiron 2003 discloses that "[t]he composition may comprise one or more . . . bacterial . . . antigens," including "an antigen from *Moraxella catarrhalis* . . ." *Id.* at 2:29, 3:14.

2. Claim 9

- a. "The immunogenic composition according to claim 8, wherein said one or more antigens is from a bacteria other than *Streptococcus pneumoniae*."**

As explained for claim 8, it would have been obvious, based on Chiron 2003 (Ex. 1014), to include one or more antigens, such as *Moraxella catarrhalis*, in the

8-valent immunogenic CRM₁₉₇-conjugate vaccine (discussed above, based on Prevnar 2001 and Overturf 2002). Ex. 1084, ¶ 162.

3. Claim 10

- a. "The immunogenic composition according to claim 9, wherein said bacteria is selected from the group consisting of nontypable *Haemophilus influenza*, *Moraxella catarrhalis* and *Alloiococcus otitidis*."**

As explained for claim 8, it would have been obvious, based on Chiron 2003 (Ex. 1014), to include one or more antigens, such as *Moraxella catarrhalis*, in the 8-valent immunogenic CRM₁₉₇-conjugate vaccine (discussed above, based on Prevnar 2001 and Overturf 2002). Ex. 1084, ¶ 163.

4. Claim 12

- a. "The immunogenic composition of claim 1, wherein the composition further comprises one or more proteins from *Neisseria meningitidis* type B."**

Based on Chiron 2003 (Ex. 1014), it would have been obvious to include one or more antigens, such a protein(s) from *Neisseria meningitidis* type B, in the 8-valent immunogenic CRM₁₉₇-conjugate vaccine (discussed above, based on Prevnar 2001 and Overturf 2002). Ex. 1084, ¶ 164. The teachings of Chiron 2003 are preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus and meningococcus species, and Chiron 2003 discloses saccharide-protein conjugate antigens, preferably with a CRM₁₉₇ carrier protein. Ex. 1014 at 2:5, 3:20-23, 6:32-35. In addition to pneumococcal

saccharide-protein conjugate antigens (*id.* at 2:15), Chiron 2003 discloses that "[t]he composition may comprise one or more . . . bacterial . . . antigens," including " a protein antigen from *N. meningitidis* serogroup B . . ." *Id.* at 2:9-10, 3:14.

**C. Claim 11 Is Invalid as Obvious over
Pevnar 2001 in View of Overturf 2002,
Wyeth 2002 and the General Knowledge of a POSITA**

1. Claim 11

- a. "The immunogenic composition of claim 1, wherein the composition further comprises one or more proteins from *Streptococcus pneumoniae*."**

Based on Wyeth 2002 (Ex. 1015), it would have been obvious to include one or more proteins from *Streptococcus pneumoniae* in the 8-valent immunogenic CRM₁₉₇-conjugate vaccine (discussed above, based on Pevnar 2001 and Overturf 2002). Ex. 1084, ¶ 165. Wyeth 2002 is cited in the specification of the '060 Patent as disclosing "[e]xamples of *Streptococcus pneumoniae* proteins suitable for inclusion" in "[t]he compositions of this invention." Ex. 1001 at 11:4-9. Indeed, Wyeth 2002 discloses "combination immunogenic compositions . . . provided by combining one or more of the polypeptides [including proteins] of the invention with one or more known *S. pneumoniae* . . . polysaccharide-protein conjugates, including, but not limited to, . . . the 7-valent pneumococcal polysaccharide-protein conjugate vaccine." Ex. 1015 at 96:17-22.

D. Secondary Considerations

To the extent Patent Owner argues that secondary considerations support a finding of non-obviousness with respect to the challenged claims, Petitioner reserves the right to address any such arguments in Petitioner's Reply. However, any secondary considerations that Patent Owner may allege will not overcome the strong evidence of obviousness based on prior art. Ex. 1084, ¶ 166.

There is no nexus between any alleged commercial success of Patent Owner's purported commercial embodiment (Prevnar 13[®]) and the claimed compositions; it was the prior art 7-valent Prevnar[®] that was a commercial success, and Prevnar 13[®] is its obvious next iteration. *Id.*, ¶ 167. Moreover, in distinguishing the claimed compositions over the prior art during prosecution, Patent Owner relied on the purported immunogenicity against serotype 3; and yet, studies have demonstrated that Prevnar 13[®] does not provide significant protection against serotype 3. *Id.*, ¶ 168; *see, e.g.*, Ex. 1077 at 1; Ex. 1078 at 1. Finally, any alleged commercial success of Prevnar 13[®] is not commensurate with the scope of at least claims 1 and 4-13 that broadly cover virtually any multivalent immunogenic pneumococcal conjugate vaccine, which Patent Owner has not invented, disclosed or enabled, let alone practiced. Ex. 1084, ¶ 169.

X. CONCLUSION

Petitioner respectfully submits that it has established a reasonable likelihood that it will prevail as to the obviousness of claims 1 and 4-13 of the '060 Patent.

Petitioner respectfully requests that this Petition be granted, *inter partes* review be instituted, and claims 1 and 4-13 of the '060 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: March 31, 2017

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CLAIM LISTING APPENDIX

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 CRM₁₉₇.

2. The immunogenic composition of claim 1, wherein the additional serotypes consist of serotypes 1, 3, 5, 6A, 7F and 19A.

3. The immunogenic composition of claim 1, wherein said polysaccharide-protein conjugates consist of 13 distinct polysaccharide-protein conjugates, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein, and wherein the serotypes consist essentially of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

4. The immunogenic composition of claim 1, further comprising an adjuvant.

5. The immunogenic composition claim 4, wherein the adjuvant is an aluminum-based adjuvant.
6. The immunogenic composition of claim 5, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide.
7. The immunogenic composition of claim 6, wherein the adjuvant is aluminum phosphate.
8. The immunogenic composition of claim 1, wherein the composition further comprises one or more antigens.
9. The immunogenic composition according to claim 8, wherein said one or more antigens is from a bacteria other than *Streptococcus pneumoniae*.
10. The immunogenic composition according to claim 9, wherein said bacteria is selected from the group consisting of nontypable *Haemophilus influenzae*, *Moraxella catarrhalis* and *Alloiococcus otitidis*.

11. The immunogenic composition of claim 1, wherein the composition further comprises one or more proteins from *Streptococcus pneumoniae*.
12. The immunogenic composition of claim 1, wherein the composition further comprises one or more proteins from *Neisseria meningitidis* type B.
13. The immunogenic composition of claim 1, wherein the composition is formulated as a single 0.5 ml dose comprising 2.2 µg of each polysaccharide, except for 6B at 4.4 µg, and 125 µg aluminum phosphate adjuvant.

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §42.24(d), the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,399,060 contains, as measured by the word processing system used to prepare this paper, 8,969 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,399,060, along with all exhibits and other supporting documents, was served on March 31, 2017, by FedEx overnight (Saturday) delivery at the following address:

Pfizer Inc.
Attn: Legal Patent Department, Chief IP Counsel
235 East 42nd Street
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which is the correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 9,399,060.

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