UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME CORP.
Petitioner

v.

WYETH LLC
Patent Owner

_____

Case IPR2017-_____
U.S. Patent No. 9,399,060

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PETITION FOR *INTER PARTES* REVIEW

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1083	Declaration of Dennis L. Kasper, M.D.
1084	[Reserved]

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner" or "Merck") hereby requests *inter partes* review ("IPR") of claims 1-13 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 (and possibly claims 2 and 3, depending on their construed scope) 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. 1083), 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 1-13 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 CRM_{197} as the only carrier protein.

Sole independent claim 1 of the '060 Patent is directed to the natural progression of the prior art Prevnar® CRM_{197}-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 CRM_{197}-conjugates prepared from serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F.

The combination of the Prevnar 2001 (Ex. 1011) and Sigurdardottir 2002 (Ex. 1012) prior art references renders obvious the composition of sole independent claim 1. Prevnar 2001 discloses Patent Owner's immunogenic Prevnar® vaccine. Sigurdardottir 2002 discloses two immunogenic 8-valent conjugate vaccines (with the 7 serotypes of Prevnar® and serotype 3); both vaccines feature a single commonly-used carrier protein - either diphtheria toxoid or tetanus toxoid. In view of the promising data of Sigurdardottir 2002, a POSITA would have been motivated (with a reasonable expectation of success) to expand the coverage of Prevnar® to include serotype 3 conjugated to CRM_{197} carrier protein.

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.

While claims 1 and 4-13 require the addition of **at least serotype 3** to the 7-valent Prevnar®, dependent claim 2 recites a 13-valent composition with **exactly 6 serotypes (1, 3, 5, 6A, 7F, and 19A)** added to the 7-valent Prevnar®. Claim 2 thus corresponds to the only embodiment described in any detail in the '060 Patent, "13vPnC." (With respect to dependent claim 3, to the extent it is definite and amenable to a broadest reasonable interpretation, it is likewise limited to a 13-valent composition with the 13 serotypes of 13vPnC.) As was the case with the 8 serotypes recited in claim 1, the 13 serotypes of 13vPnC had been well-documented in the prior art literature as top candidates for a pneumococcal conjugate vaccine. To obtain the claims of the '060 Patent, Patent Owner argued during prosecution that the immunogenicity of 13vPnC - with each serotype conjugated to CRM_{197} carrier protein - was unexpected and surprising.

But Patent Owner cannot have it both ways. Claims 1 and 4-13 of the '060 Patent open-endedly include **any combination** of immunogenic CRM_{197}-conjugates (from nearly 100 pneumococcal serotypes), as long as the composition contains at least the 8 recited serotypes. Those claims include countless

compositions that Patent Owner has not invented or disclosed. Indeed, Patent Owner has taken the position - during proceedings challenging the validity of foreign counterparts, as well as during prosecution of other members of the '060 Patent family - that the immunogenicity of every multivalent conjugate vaccine (including 13vPnC) is wholly unpredictable. To the extent the full scope of open-ended claims 1 and 4-13 is enabled (the subject of a co-pending Petition for IPR of the '060 Patent), the 13-valent composition of claims 2 and 3 would have been obvious; a POSITA would necessarily have had a reasonable expectation of success expanding Patent Owner's next iteration of Prevnar® (a strongly-immunogenic 9-valent pneumococcal CRM_{197}-conjugate composition disclosed in Huebner 2004, Ex. 1016) to include 4 well-known, top candidates for a pneumococcal conjugate vaccine (disclosed in, *e.g.*, Hausdorff 2002, Ex. 1017).

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 is concurrently filing two additional Petitions for *inter partes* review of the '060 Patent. 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 1-13 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 Sigurdardottir 2002 (Ex. 1012) 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 Sigurdardottir 2002 (Ex. 1012), Chiron 2003 (Ex. 1014) and the general knowledge of a POSITA.

Ground 3. Claim 11 is unpatentable as obvious under pre-AIA § 103 over Prevnar 2001 (Ex. 1011) in view of Sigurdardottir 2002 (Ex. 1012), Wyeth 2002 (Ex. 1015) and the general knowledge of a POSITA.

Ground 4. Claims 1-3 are unpatentable as obvious under pre-AIA § 103 over Huebner 2004 (Ex. 1016) in view of Hausdorff 2002 (Ex. 1017) 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. 1083, ¶ 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 18[1]). 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

[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 __/__").

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). CRM_{197} 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).

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 (Prevnar®) in 2000. *Id*. (citing Ex. 1033 at 3). Prevnar® was a 7-valent vaccine, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated to the CRM_{197} 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 CRM_{197} 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 CRM_{197} as the only carrier protein) was itself an expanded form of earlier lower-valency compositions using CRM_{197} as the only carrier protein. *Id.* (citing Ex. 1038 at 1). The next iteration was a prior art 9-valent vaccine, again using CRM_{197} 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 CRM_{197} 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 CRM_{197}, at least one study reported on the simultaneous administration of a 9-valent pneumococcal CRM_{197}-conjugate vaccine and a non-pneumococcal CRM_{197}-conjugate vaccine; the joint administration of a total of 45 μg of CRM_{197} (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 CRM_{197}-conjugate vaccine and a non-pneumococcal CRM_{197}-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 CRM_{197}-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 CRM_{197}-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 CRM_{197}.

Ex. 1001. Since "comprise" is an open-ended term, the broadest reasonable interpretation of claim 1 is that it is directed to any pneumococcal CRM_{197}-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.

Dependent claim 2 limits the "additional serotypes" of claim 1:

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

Id. As discussed with respect to claim construction below, claim 2 is limited to 13 different pneumococcal polysaccharide-CRM_{197} conjugates with the 13 serotypes of 13vPnC.

Similarly, claim 3 limits the conjugates of claim 1 to "consist of" 13 conjugates, but as discussed below with respect to claim construction, claim 3 is indefinite because of the irreconcilable recitation later in the claims that the serotypes "consist essentially of" (rather than "consist of") 13 serotypes:

> 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**.

Id. (emphasis added).

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.

Notably, the '060 Patent cites to numerous prior art publications showing the limited cross-protection between serotypes already included in 7-valent Prevnar® (6B and 19F) and non-vaccine serotypes 6A and 19A; this provided incentive for the latter's inclusion. Ex. 1001 at 4:60-5:29. For example, the data of Figure 1 of the '060 Patent is based on the data of a 2003 paper, disclosing a significant number of cases of pneumococcal invasive disease due to serotype 6A, even after vaccination with Prevnar® (which contains serotype 6B). Ex. 1061 at 5; *see* Ex. 1001 at 1:46-49.

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 CRM_{197} as a carrier protein; according to the Examiner, there was nothing

inventive about Patent Owner's choice of serotypes, nor the choice of CRM_{197}. Ex. 1002 at 141. To overcome the prior art, Patent Owner argued that it would not have been obvious to use CRM_{197} 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 CRM_{197} 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 (concerning claims 1 and 4-13) 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 CRM_{197} 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 CRM_{197} 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 CRM_{197}, 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, l8C, 19F, and 23F, and 4 μg of serotype 6B per dose (16 μg total saccharide); approximately 20 μg of CRM_{197} 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 CRM_{197} 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. Sigurdardottir 2002

Grounds 1-3 (concerning claims 1 and 4-13) further rely on 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," *Pediatr. Infect. Dis. J*. 21:548–54 (2002) ("Sigurdardottir 2002"). Ex. 1012. Because Sigurdardottir 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).

Sigurdardottir 2002 "demonstrate[s] the safety and immunogenicity of two monocarrier octavalent pneumococcal conjugate vaccines, PncD and PncT, in infants." *Id*. at 5. Both disclosed vaccines include polysaccharide serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F, but differ in the carrier protein to which the polysaccharides are linked; one vaccine includes diphtheria toxoid as the sole carrier protein, and the other includes tetanus toxoid. *Id*. at 2.

In the reported study, ~160 infants received a 3 dose primary vaccination of PncD or PncT 8-valent pneumococcal conjugate vaccine at age 3, 4 and 6 months *Id*. The infants received a fourth, booster dose at 13 months "with the same pneumococcal conjugate vaccine or a 23-valent pneumococcal polysaccharide vaccine." *Id*. Antibody responses "were measured at 3, 4, 6, 7, 13 and 14 months." *Id*. at 1. Both vaccines elicited immunologic memory with respect to each serotype in the vaccine (including serotype 3), as evidenced by "the strong responses to the PPS [*i.e.*, polysaccharide] at 13 months, an age when children would normally not respond to native polysaccharides." *Id*. at 6; *see also id*. at 4 ("Significant rises in specific IgG to **all serotypes** were induced by both vaccines after primary and booster vaccination (P<0.0001).") (emphasis added); *id*. ("Good booster responses (Table 3; Fig. 1) were observed in all four groups (P < 0.0001) 1 month after booster immunization at 13 months with either the same conjugate vaccine as used for the primary series or the polysaccharide vaccine.").

With respect to the potential effect of CIES on concomitant administration of diphtheria-conjugated pneumococcal and *H. influenzae* polysaccharides, the authors observed that responses to *H. influenzae* PRP polysaccharide were lower, but pneumococcal responses were not affected. *Id*. at 6 ("Concomitant administration of PRP-D did not result in lower pneumococcal antibodies in the PncD group, but PRP antibodies were lower than in the PncT group."). The authors noted that an enhanced response could likewise result: "[t]his influence of the protein carrier can be in both directions as an increased PRP response has been reported for *H. influenzae* type b vaccine when sharing CRM_{197} carrier with the Pnc conjugates." *Id*. The authors concluded that "[b]oth octavalent pneumococcal conjugates were safe and immunogenic in infants." *Id*. at 1.

Although Sigurdardottir 2002 references a "mixed-carrier" vaccine (*i.e.*, using both diphtheria and tetanus toxoids as carrier proteins in a single vaccine), that refers to a separate 11-valent vaccine that was in development (not the 8-valent vaccines assessed in Sigurdardottir 2002). *Id*. at 1, 6. Sigurdardottir 2002 did not report evidence of CIES; to the contrary, increasing the diphtheria toxoid load (due to the concomitantly-administered DTwP//PRP-D vaccine) did not impact the antibody responses with respect to the pneumococcal serotypes of the 8-valent conjugate vaccines. *Id*. at 6.

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 CRM_{197} 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.

5. Huebner 2004

Ground 4 (concerning claims 1-3) relies on Huebner *et al*., "Long-term antibody levels and booster responses in South African children immunized with nonavalent pneumococcal conjugate vaccine," *Vaccine* 22:2696-2700 (2004)

("Huebner 2004"). Ex. 1016. Because Huebner 2004 was published on February 19, 2004, 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).

Huebner 2004 presents immunogenicity data with respect to Patent Owner's next iteration of Prevnar®, a 9-valent pneumococcal CRM_{197}-conjugate vaccine that adds serotypes 1 and 5 to the 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) of Prevnar®; the 9-valent vaccine "was developed to include serotypes 1 and 5 that are important in developing countries." *Id*. at 1. Huebner 2004 reports that, like 7-valent Prevnar®, the 9-valent iteration elicits immunologic memory:

> Boosting at 18 months with polysaccharide vaccine produced higher antibody concentrations to all serotypes in children who had previously received conjugate vaccine compared to children who had not received the conjugate vaccine in infancy.

Id.

Children who previously received either a three-dose primary immunization with the 9-valent conjugate vaccine or placebo were boosted at 18 months of age with either the same 9-valent conjugate vaccine or a 23-valent polysaccharide-only vaccine (which included the serotypes of the 9-valent conjugate vaccine). *Id*. at 2. Children boosted with polysaccharide alone would only generate a robust antibody response if memory had previously been elicited by the 9-valent conjugate vaccine:

> Children who received polysaccharide at 18 months after a primary series of conjugate in infancy had significantly higher antibody levels 1 month later than did children who had not received the primary conjugate vaccine in infancy. Mean antibody levels were at least two-fold higher for all serotypes when the polysaccharide was used as a booster rather than as a primary immunogen.

Id. at 2-3.

The authors concluded that "the nonavalent pneumococcal conjugate vaccine given at 6, 10, and 14 weeks of age elicits significant and long-lasting antibody responses [*i.e.*, memory] which can be boosted with either the conjugate or polysaccharide vaccine." *Id*. at 4.

6. Hausdorff 2002

Ground 4 (concerning claims 1-3) further relies on Hausdorff *et al*., "Multinational study of pneumococcal serotypes causing acute otitis media in children," *Pediatr. Infect. Dis. J*. 21:1008-1016 (2002) ("Hausdorff 2002"). Ex. 1017. Because Hausdorff 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).

Hausdorff 2002 reports on the most prevalent pneumococcal serotypes isolated from over 3000 children in 11 countries worldwide with acute otitis media ("AOM," *i.e.*, infection of the middle ear), which is "by far the most common manifestation of disease caused by *Streptococcus pneumoniae*." *Id*. at 1, 4. One

major goal was "to identify the pneumococcal serotypes most responsible for AOM in children and relate those to specific vaccine formulations." *Id*. at 7.

With respect to known vaccine compositions, Hausdorff 2002 identifies the following 7-, 9-, and 11-valent conjugate vaccines:

> 7-valent pneumococcal conjugate vaccine formulation, containing serotypes 4, 6B, 9V, 14, 18C, 19F, 23F (PCV-7); 9-valent pneumococcal conjugate vaccine formulation, containing PCV-7 serotypes plus 1 and 5 (PCV-9); 11-valent pneumococcal conjugate vaccine formulation, containing PCV-9 serotypes plus 3 and 7F (PCV-11).

Id. at 2.

Two of the most frequently isolated pneumococcal serotypes were serotypes 6A and 19A, representing 7.3% and 6.6% of all datasets, respectively. *Id*. at 5. Hausdorff 2002 observes that, "[i]t appears that the serotypes represented in PCV-11, plus 6A and 19A, comprise all major serotypes in each age group studied." *Id*. at 7.

Apart from pneumococcal serotypes, Hausdorff 2002 also reports that non-pneumococcal pathogens (including *Moraxella catarrhalis*) are frequently isolated alongside pneumococci. *Id*. at 5.

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. 1083, ¶ 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, as should the scope of dependent claims 2 and 3 with respect to the number and identity of the claimed serotypes. 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 memory and/or functional antibody with respect to each serotype of the vaccine, including serotype 3." Ex. 1083, ¶ 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. 1083, ¶ 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

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

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. 1083, ¶ 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. 1083, ¶¶ 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 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; s*ee also* Ex. 1063

[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. 1083, ¶ 110.

("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 CRM_{197} 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. 1083, ¶ 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. 1083, ¶ 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. 1083, ¶ 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*.

C. Claim 2

Petitioner submits that the broadest reasonable interpretation of claim 2 is "the immunogenic composition of claim 1, wherein the claimed polysaccharide-protein conjugates consist of 13 different pneumococcal polysaccharide-CRM_{197} conjugates, wherein the polysaccharide serotypes consist of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F." Ex. 1083, ¶ 119.

The above construction follows the plain and ordinary meaning of the claim language (which was present in the claims as filed in the '060 Patent and was not discussed during prosecution history). *Id*., ¶ 120. Claim 1 requires at least 8 pneumococcal polysaccharide-CRM_{197} conjugates with "different" serotypes - the 7 serotypes of Prevnar® and "at least one additional serotype" (that must include serotype 3). *Id*. Claim 2 specifies that the "additional serotypes consist of serotypes 1, 3, 5, 6A, 7F and 19A"; thus, Claim 2 is restricted to a 13-valent immunogenic CRM_{197}-conjugate vaccine with the 7 serotypes of Prevnar® and additional serotypes 1, 3, 5, 6A, 7F, and 19A. *Id*. The above construction is

consistent with the 13vPnC composition, the only disclosed immunogenic composition (other than the prior art 7vPnC) in the '060 Patent. *Id*.

D. Claim 3

In a co-pending PGR proceeding, Petitioner has asserted that claim 3 is invalid as indefinite. Ex. 1083, ¶ 121. However, to the extent the Board deems the claim amenable to construction, Petitioner submits that the claim must be limited to 13 conjugates prepared separately from the 13 recited serotypes. *Id.*

In claim 3, the recitation of serotypes that "consist essentially of" the 13 recited serotypes is irreconcilable with the earlier limitation that the claimed composition is exactly 13 conjugates. *Id*., ¶ 122. The claim plainly recites that "said polysaccharide-protein conjugates **consist of** 13 distinct polysaccharide-protein conjugates" (emphasis added), unequivocally limiting the number of conjugates to exactly 13. *Id*. Furthermore, each conjugate contains "a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein," and the claim identifies the 13 specific serotypes of Patent Owner's 13vPnC composition. *Id*. The specification of the '060 Patent explains in no uncertain terms that the individual polysaccharide serotypes are conjugated to a carrier protein in separate processes:

> In the present invention, capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F of *Streptococcus pneumoniae*. **These pneumococcal conjugates are**

> **prepared by separate processes** and formulated into a single dosage formulation. . . . Once activated, **each capsular polysaccharide is separately conjugated to a carrier protein** to form a glycoconjugate.

Ex. 1001 at 7:59-8:5 (emphasis added). It follows that the claim must be limited to 13 conjugates with the recited 13 serotypes. Ex. 1083, ¶ 122.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

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

The Prevnar 2001 (Ex. 1011) and Sigurdardottir 2002 (Ex. 1012) 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. 1083, ¶ 158. Based on the combination of the Prevnar 2001 and Sigurdardottir 2002 references, it would have been obvious for a POSITA to arrive at the immunogenic pneumococcal CRM_{197}-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.*

As detailed below, 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. Sigurdardottir 2002 discloses 2 distinct 8-valent pneumococcal

conjugate vaccines, each with the 7 serotypes of Prevnar® plus serotype 3 (as claimed); both vaccines feature a single commonly-used carrier protein - either diphtheria toxoid or tetanus toxoid. Both 8-valent vaccines of Sigurdardottir 2002 are immunogenic as required by the claim, since they elicit immunologic memory for each vaccine serotype, **including serotype 3**. (Sigurdardottir 2002 squarely contradicts Patent Owner's argument during prosecution that a multivalent conjugate vaccine with a single carrier protein that was immunogenic against all serotypes of the vaccine, including serotype 3, was absent in the prior art.)

Based on the inclusion of serotype 3 in Sigurdardottir 2002, a POSITA would have been motivated to broaden the coverage of Prevnar® to include serotype 3. 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 CRM_{197} protein as the single carrier protein in an expanded Prevnar® vaccine. Indeed, Patent Owner had already developed a 9-valent CRM_{197} pneumococcal conjugate vaccine (adding serotypes 1 and 5), and the literature had reported that Patent Owner was developing an 11-valent CRM_{197} pneumococcal conjugate vaccine as well (adding serotypes 3 and 7F).

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

conjugated to CRM_{197}) would be immunogenic, based on the successes of the 7-valent Prevnar and the compositions of Sigurdardottir 2002 (which include serotype 3). Concerns over CIES would not have discouraged development of the 8-valent CRM_{197}-conjugate vaccine. Patent Owner's prior art 7- and 9-valent CRM_{197}-conjugate vaccines, and Sigurdardottir 2002's 8-valent diphtheria-conjugate vaccine, were each safe and immunogenic. And, increases in amount of carrier protein in Prevnar 2001 and Sigurdardottir 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 CRM_{197} Protein)," which includes "saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM_{197} 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.

Sigurdardottir 2002 discloses two 8-valent pneumococcal conjugate vaccines - both of which include serotype 3; both vaccines are immunogenic as required by the claims. Ex. 1083, ¶ 160. In the 8-valent vaccines of Sigurdardottir 2002, "[t]he eight serotypes, 3, 4, 6B, 9V, 14, 18C, 19F and 23F, were conjugated to either diphtheria toxoid (PncD vaccine) or tetanus protein (PncT vaccine)." Ex. 1012 at 2. Both vaccines elicited immunologic memory with respect to each serotype in the vaccine (including serotype 3), as evidenced by "the strong responses to the PPS at 13 months, an age when children would normally not respond to native polysaccharides." *Id*. at 6; *see also id*. at 4 ("Significant rises in specific IgG to **all serotypes** were induced by both vaccines after primary and booster vaccination (P<0.0001)."") (emphasis added); *id*. ("Good booster responses (Table 3; Fig. 1) were observed in all four groups (P < 0.0001) 1 month after booster immunization at 13 months with either the same conjugate vaccine as used for the primary series or the polysaccharide vaccine.").

b. "polysaccharide-protein conjugates"

The disclosed vaccines in both Prevnar 2001 and Sigurdardottir 2002 include polysaccharide-protein conjugates. Ex. 1083, ¶ 161. Prevnar 2001 discloses that "[t]he polysaccharides are chemically activated to make saccharides which are directly conjugated to the protein carrier CRM_{197} to form the glycoconjugate." Ex. 1011 at 2. Sigurdardottir 2002 discloses "two octavalent

pneumococcal conjugate vaccines contain[ing] capsular polysaccharides of serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F conjugated with either diphtheria toxoid . . . or tetanus protein . . ." Ex. 1012 at 2.

c. "and a physiologically acceptable vehicle,"

The disclosed vaccines in both Prevnar 2001 and Sigurdardottir 2002 include a physiologically acceptable vehicle. Ex. 1083, ¶ 162. 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 Sigurdardottir 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. 1083, ¶ 162.

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 Sigurdardottir 2002 are prepared individually, each with a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae*. *Id.*, ¶ 163. 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 CRM_{197} protein." Ex. 1011 at 2; *see also id*. ("The individual glycoconjugates are compounded to formulate the vaccine, Prevnar™.").

For the pneumococcal conjugate vaccines of Sigurdardottir 2002, a POSITA would understand that each conjugate includes a polysaccharide from a different pneumococcal serotype conjugated to the particular carrier protein. Ex. 1083, ¶ 164. A previous report confirms this:

> The PncD vaccine . . . was an octavalent pneumococcal conjugate vaccine containing 3μg of capsular PS of the serotypes 3, 4, 6B, 9V, 14, 18C, 19F, and 23F **each conjugated individually** to a diphtheria toxoid. PncT vaccine . . . contained 1 μg of capsular PS from **each of the eight serotypes conjugated to a tetanus toxoid**.

Ex. 1068 at 2 (emphasis added). 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. Ex. 1083, ¶ 164.

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"

Each of the vaccines of Sigurdardottir 2002 include serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F. Ex. 1012 at 2. Prevnar 2001 discloses a 7-valent vaccine with all of the claimed serotypes, other than serotype 3. Ex. 1011 at 2. Based on the reported safety and immunogenicity of Sigurdardottir 2002, including with

respect to serotype 3, a POSITA would have been motivated (with a reasonable expectation of success) to broaden the coverage of Prevnar® with at least serotype 3. Ex. 1083, ¶ 165. As conceded by Patent Owner during the prosecution of the '024 Patent (a parent of the '060 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. *Id*. And, a POSITA would have had a reasonable expectation of success of creating an immunogenic serotype 3 conjugate, given the disclosure of Sigurdardottir 2002, in which two distinct 8-valent conjugate compositions were immunogenic with respect to serotype 3. *Id*.; Ex. 1012.

f. "wherein the carrier protein is CRM_{197}."

The only carrier protein in Prevnar 2001 is CRM_{197}; it would have been obvious to likewise use CRM_{197} when expanding Prevnar® to include serotype 3. Ex. 1083, ¶ 166. CRM_{197} 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 CRM_{197} pneumococcal conjugate vaccine

(adding serotypes 1 and 5), and the literature had reported that Patent Owner was developing an 11-valent CRM_{197} pneumococcal conjugate vaccine as well (adding serotypes 3 and 7F). *See, e.g.*, Ex. 1016; Ex. 1039; Ex. 1013 at 4; Ex. 1040 at 5.

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, as were the 8-valent conjugate vaccines of Sigurdardottir 2002. Ex. 1083, ¶ 167. A POSITA would have had a high level of confidence (and, at the very minimum, a reasonable expectation) that moving from diphtheria or tetanus toxoid to CRM_{197} (mutant diphtheria toxin) carrier protein would not negate the immunogenicity of the Sigurdardottir 2002 vaccines. *Id*. CRM_{197} 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-valent pneumococcal CRM_{197}-conjugate vaccine; Patent Owner had already developed a safe and immunogenic 9-valent iteration of Prevnar® (with the 7 original serotypes plus serotypes 1 and 5). *Id*.; *see, e.g.*, Ex. 1016. Likewise, the 8-valent diphtheria-conjugate vaccine of Sigurdardottir was immunogenic. Ex. 1083, ¶ 168. And, in both Prevnar 2001 and Sigurdardottir 2002, although antibody responses were somewhat reduced in concurrently administered non-pneumococcal CRM_{197}-conjugate vaccines, antibody responses

against the pneumococcal polysaccharides were not meaningfully affected. Ex. 1011 at 4 (*see also* Ex. 1041 at 5); Ex. 1012 at 6. To the extent open-ended claim 1 is deemed enabled (in a co-pending IPR), 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. 1083, ¶ 168.

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. 1083, ¶ 169.

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. 1083, ¶ 170.

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. 1083, ¶ 171.

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. 1083, ¶ 172.

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, l8C, 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]

Ex. 1011 at 2; *see* Ex. 1083, ¶ 173. 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. 1083, ¶ 174.

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

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

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. 1083, ¶ 176.

B. Claims 8-10 and 12 Are Invalid as Obvious over Prevnar 2001 in View of Sigurdardottir 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 CRM_{197}-conjugate vaccine (discussed above, based on Prevnar 2001 and Sigurdardottir 2002). Ex. 1083, ¶ 177. 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 CRM_{197} 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 CRM_{197}-conjugate vaccine (discussed above, based on Prevnar 2001 and Sigurdardottir 2002). Ex. 1083, ¶ 178.

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 CRM_{197}-conjugate vaccine (discussed above, based on Prevnar 2001 and Sigurdardottir 2002). Ex. 1083, ¶ 179.

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 CRM_{197}-conjugate vaccine (discussed above, based on

Prevnar 2001 and Sigurdardottir 2002). Ex. 1083, ¶ 180. 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 CRM_{197} 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 Prevnar 2001 in View of Sigurdardottir 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 CRM_{197}-conjugate vaccine (discussed above, based on Prevnar 2001 and Sigurdardottir 2002). Ex. 1083, ¶ 181. 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. Claims 1-3 Are Invalid as Obvious over Huebner 2004 in View of Hausdorff 2002 and the General Knowledge of a POSITA

Dependent claim 2 limits the immunogenic composition of independent claim 1 to a 13-valent pneumococcal CRM_{197}-conjugate vaccine with serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Ex. 1083, ¶ 182. With respect to claim 3, as discussed above, it is indefinite; but to the extent it is definite, it is limited to 13 conjugates with the same 13 serotypes as in claim 2. *Id*.

But, Patent Owner cannot have it both ways. Claims 1 and 4-13 of the '060 Patent open-endedly include **any combination** of immunogenic CRM_{197}-conjugates (from nearly 100 pneumococcal serotypes), as long as the composition contains at least the 8 recited serotypes. *Id*., ¶ 183. Those claims include countless compositions that Patent Owner has not invented or disclosed. *Id*. Indeed, Patent Owner has taken the position - during proceedings challenging the validity of foreign counterparts, as well as during prosecution of other members of the '060 Patent family - that the immunogenicity of every multivalent conjugate vaccine (including 13vPnC) is wholly unpredictable. *See, e.g.*, Ex. 1066 at 7 ("Without

conducting actual experiments, it is not possible to predict whether a combination of certain pneumococcal polysaccharides with certain conjugate protein(s) would become a successful immunogenic vaccine or not."); Ex. 1056 at 19, 30; Ex. 1067 at 16; Ex. 1004 at 128, 199, 200. To the extent the full scope of open-ended claims 1 and 4-13 is enabled (the subject of a co-pending Petition for IPR of the '060 Patent), the 13-valent composition of claims 2 and 3 must have been obvious; a POSITA would necessarily have had a reasonable expectation of success expanding Patent Owner's next iteration of Prevnar® (a strongly-immunogenic 9-valent pneumococcal CRM_{197}-conjugate composition disclosed in Huebner 2004, Ex. 1016) to include 4 well-known, top candidates for a pneumococcal conjugate vaccine (disclosed in, *e.g.*, Hausdorff 2002, Ex. 1017). *Id*.

1. Claim 1

a. "A multivalent immunogenic composition comprising"

Huebner 2004 (Ex. 1016) describes Patent Owner's prior art 9-valent pneumococcal CRM_{197}-conjugate vaccine that adds serotypes 1 and 5 to the 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) of Prevnar®, and demonstrates that the vaccine is immunogenic, as it elicits immunologic memory. Ex. 1083, ¶ 184; Ex. 1016 at 4 ("In conclusion, the nonavalent pneumococcal conjugate vaccine given at 6, 10, and 14 weeks of age elicits significant and long-lasting antibody responses

[*i.e.*, memory] which can be boosted with either the conjugate or polysaccharide vaccine.").

Hausdorff 2002 reports on the most prevalent pneumococcal serotypes causing acute otitis media worldwide, with a major goal being to "relate those to specific vaccine formulations." Ex. 1017 at 7. In that regard, Hausdorff 2002 identifies the following 7-, 9-, and 11-valent well-known conjugate vaccine compositions:

> 7-valent pneumococcal conjugate vaccine formulation, containing serotypes 4, 6B, 9V, 14, 18C, 19F, 23F (PCV-7); 9-valent pneumococcal conjugate vaccine formulation, containing PCV-7 serotypes plus 1 and 5 (PCV-9); 11-valent pneumococcal conjugate vaccine formulation, containing PCV-9 serotypes plus 3 and 7F (PCV-11).

Id. at 2. Hausdorff 2002 observes that, "[i]t appears that the serotypes represented in PCV-11, plus 6A and 19A, comprise all major serotypes in each age group studied." *Id.* at 7.

b. "polysaccharide-protein conjugates"

Huebner 2004 and Hausdorff 2002 disclose polysaccharide-protein conjugate vaccines. Ex. 1083, ¶ 186. Huebner 2004 discloses a "9-valent pneumococcal vaccine containing serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F conjugated to CRM197-diphtheria protein cross reacting molecule." Ex. 1016 at 1. Similarly, Hausdorff 2002 discloses, *inter alia*, an "11-valent pneumococcal

conjugate vaccine formulation, containing PCV-9 serotypes [i.e., the serotypes of Huebner 2004] plus 3 and 7F (PCV-11) ". Ex. 1017 at 2.

c. "and a physiologically acceptable vehicle,"

The disclosed vaccine in both Huebner 2004 and Hausdorff 2002 include a physiologically acceptable vehicle. Ex. 1083, ¶ 187. 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 8:59-62. A POSITA would have understood that the vaccines of Huebner 2004 and Hausdorff 2002 are injected intramuscularly, and so, they were provided in a physiologically acceptable vehicle such as water or buffered saline. Ex. 1083, ¶ 187.

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 Huebner 2004 and Hausdorff 2002 are prepared individually, each with a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae*. *Id.*, ¶ 188. 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.* Indeed, the underlying 7-valent Prevnar® vaccine was "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 CRM_{197} protein." Ex. 1011 at 2 (emphasis added); *see also id.* ("The individual glycoconjugates are compounded to formulate the vaccine, Prevnar™.").

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"

A POSITA would have been motivated (with a reasonable expectation of success) to expand the well-known immunogenic 9-valent pneumococcal CRM_{197}-conjugate composition of Huebner 2004 (with serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F) by adding at least serotype 3, as disclosed in Hausdorff 2002. Ex. 1083, ¶ 189. Hausdorff 2002 discloses an 11-valent pneumococcal conjugate vaccine, adding serotypes 3 and 7F to the 9 serotypes of Huebner 2004. *Id*.; Ex. 1017 at 2.

As conceded by Patent Owner during the prosecution of the '024 Patent (a parent of the '060 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. 1083, ¶ 190.

And, a POSITA would have had a reasonable expectation of success of creating an immunogenic serotype 3 conjugate, given the disclosure in Hausdorff 2002 of an 11-valent conjugate vaccine that includes serotype 3 (as well the other serotypes recited in the claim). *Id*.

f. "wherein the carrier protein is CRM_{197}."

When expanding the 9-valent iteration of Prevnar® to include serotype 3, it would have been obvious to continue the successful use of CRM_{197} carrier protein. Ex. 1083, ¶ 191. CRM_{197} was well-known to be safe and effective, as evidenced by its use in 7-valent Prevnar®, the 9-valent vaccine of Huebner 2004 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. In fact, the literature had already reported that Patent Owner was developing an 11-valent pneumococcal CRM-conjugate vaccine as well (adding serotypes 3 and 7F). Ex. 1013 at 4; Ex. 1040 at 5.

Given the strong immunogenicity exhibited for all 9 pneumococcal serotypes of the Huebner 2004 vaccine (Ex. 1016 at 3), a POSITA would have had a reasonable expectation that a 10-valent CRM_{197}-conjugate vaccine (adding serotype 3) would be immunogenic as well. Ex. 1083, ¶ 192. Again, Patent Owner was already reported to have been developing an 11-valent pneumococcal CRM_{197}-conjugate vaccine (including serotype 3). Ex. 1013 at 4; Ex. 1040 at 5.

And, contrary to Patent Owner's argument during prosecution, a POSITA would not have been discouraged from pursuing a multivalent conjugate vaccine that included serotype 3; for example, Sigurdardottir 2002 discloses 8-valent immunogenic pneumococcal conjugate vaccines that include serotype 3 and only a single carrier protein (either diphtheria or tetanus toxoid). Ex. 1012 at 2, 4, 6; *see* Ex. 1083, ¶ 192.

Reports of CIES as of April 8, 2005 would not have deterred a POSITA from pursuing a 13-valent conjugate vaccine with CRM_{197} as the single carrier protein. Ex. 1083, ¶ 193. As discussed above at Section VI.A.4, there were clear advantages to using a single carrier protein. *Id*. Moreover, the literature as of April 8, 2005 indicated that CIES was not always observed when increasing the amount of a carrier protein, and that decreased antibody response due to CIES was not clinically relevant when other correlates of protection are still observed. *Id*.; Ex. 1039 at 6-7; Ex. 1013 at 6; Ex. 1041 at 5; Ex. 1042 at 8. (Importantly, the claim does not require any particular amount of carrier protein, and merely expanding a 9-valent composition to include serotype 3 does not require adding large amounts of carrier protein. Ex. 1083, ¶ 193.)

2. Claim 2

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

Huebner 2004 (Ex. 1016) describes Patent Owner's prior art 9-valent pneumococcal CRM_{197}-conjugate vaccine, which (like the previous 7-valent Prevnar) elicited immunologic memory. Ex. 1083, ¶ 194. It would have been obvious, based on Hausdorff 2002 (Ex. 1017), to further expand the 9-valent vaccine of Huebner 2004 to a 13-valent vaccine with the claimed serotypes. Ex. 1083, ¶ 194.

The 9-valent vaccine of Huebner 2004 was itself a progression from Patent Owner's previous 7-valent Prevnar®, which incorporated serotypes 4, 6B, 9V, 14, 18C, 19F and 23F; the vaccine of Huebner 2004 adds serotypes 1 and 5, while continuing to use CRM_{197} as the single carrier. Ex. 1016 at 1. Hausdorff 2002 discloses the further progression to an "11-valent pneumococcal conjugate vaccine formulation, containing [9-valent] PCV-9 serotypes plus 3 and 7F (PCV-11)." Ex. 1017 at 2. Hausdorff 2002 identifies serotypes 6A and 19A as the next group of "major serotypes"; in doing so, Hausdorff provides the motivation to develop a 13-valent conjugate vaccine with the serotypes of claim 2. *Id*. at 7 ("It appears that the serotypes represented in PCV-11, plus 6A and 19A, comprise all major serotypes

in each age group studied."); *see also* Ex. 1083, ¶ 195 and other references disclosing the 13 serotypes of 13vPnC: Ex. 1035 at 1; Ex. 1036 at 3.

Notably, a POSITA would not have ignored or discounted serotypes 6A and 19A as the next group of "major serotypes"(as reported in Hausdorff 2002); a POSITA would not have assumed that serotypes 6B and 19F of Prevnar® would provide sufficient cross-protection with respect to serotypes 6A and 19A. Ex. 1083, ¶ 196. In fact, the '060 Patent itself cites to numerous prior art publications showing that any such cross-protection is limited. Ex. 1001 at 4:60-5:29; Ex. 1035 at 1; Ex. 1061 at 5.

When expanding the 9-valent iteration of Prevnar® to a 13-valent version, it would have been obvious to continue the successful use of CRM_{197} carrier protein. Ex. 1083, ¶ 197. CRM_{197} was well-known to be safe and effective, as evidenced by its use in 7-valent Prevnar®, the 9-valent vaccine of Huebner 2004 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. In fact, the literature had already reported that Patent Owner was developing an 11-valent pneumococcal CRM-conjugate vaccine as well (adding serotypes 3 and 7F). Ex. 1013 at 4; Ex. 1040 at 5.

Given the strong immunogenicity exhibited for all 9 pneumococcal serotypes of the Huebner 2004 vaccine (Ex. 1016 at 3), a POSITA would have had

a reasonable expectation that the claimed 13-valent CRM_{197}-conjugate vaccine would be immunogenic as well. Ex. 1083, ¶ 198. Again, Patent Owner was already reported to have been developing an 11-valent pneumococcal CRM_{197}-conjugate vaccine. Ex. 1013 at 4; Ex. 1040 at 5. And, contrary to Patent Owner's argument during prosecution, a POSITA would not have been discouraged from pursuing a multivalent conjugate vaccine that included serotype 3; for example, Sigurdardottir 2002 discloses 8-valent immunogenic pneumococcal conjugate vaccines that include serotype 3 and only a single carrier protein (either diphtheria or tetanus toxoid). Ex. 1012 at 2, 4, 6; *see* Ex. 1083, ¶ 198.

Reports of CIES as of April 8, 2005 would not have deterred a POSITA from pursuing a 13-valent conjugate vaccine with CRM_{197} as the single carrier protein. Ex. 1083, ¶ 199. As discussed above at Section VI.A.4, there were clear advantages to using a single carrier protein. *Id*. Moreover, the literature as of April 8, 2005 indicated that CIES was not always observed when increasing the amount of a carrier protein, and that decreased antibody response due to CIES was not clinically relevant when other correlates of protection are still observed. *Id*.; Ex. 1039 at 6-7; Ex. 1013 at 6; Ex. 1041 at 5; Ex. 1042 at 8. (Importantly, the claim does not require any particular amount of carrier protein, and merely expanding from a 9-valent to a 13-valent composition does not require adding large amounts of carrier protein. Ex. 1083, ¶ 199.)

3. Claim 3

a. "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."

As explained above, claim 3 is indefinite, but to the extent it is definite, it is limited to exactly 13 conjugates prepared separately from the same 13 serotypes as claim 2. For the same reasons given with respect to claims 1 and 2, the composition of claim 3 would have been obvious. Ex. 1083, ¶ 200.

E. 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. *Id.*, ¶ 201.

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.*, ¶ 202. 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*., ¶ 203; *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. 1083, ¶ 204.

X. CONCLUSION

Petitioner respectfully submits that it has established a reasonable likelihood that it will prevail as to the obviousness of claims 1-13 of the '060 Patent. Petitioner respectfully requests that this Petition be granted, *inter partes* review be instituted, and claims 1-13 of the '060 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: March 30, 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 CRM_{197}.

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 influenza*, *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, 13,596 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: March 30, 2017

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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 30, 2017, by FedEx overnight delivery at the following address:

Pfizer Inc.
Attn: Legal Patent Department, Chief IP Counsel
235 East 42nd Street
New York, NY 10017

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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