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 PGR2017-_____
U.S. Patent No. 9,399,060

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PETITION FOR POST GRANT REVIEW

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Other Authorities

LIST OF EXHIBITS

Exhibit No.	Document
1001	U.S. Patent No. 9,399,060 to Hausdorff *et al.* ("the '060 patent")
1002	Excerpts from the Prosecution History of the '060 patent
1003	Excerpts from the Prosecution History of US Patent Application No. 13/439,111
1004	Excerpts from the Prosecution History of US Patent Application No. 12/357,853
1005	Excerpts from the Prosecution History of US Patent Application No. 11/395,593
1006	US Provisional Application No. 60/669,605
1007	Declaration of Dennis L. Kasper, M.D.
1008	[RESERVED]
1009	[RESERVED]
1010	[RESERVED]
1011	Prevnar® entry from the 2001 (55th Edition) Physicians' Desk Reference ("Prevnar 2001")
1012	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")
1013	Overturf, "Pneumococcal Vaccination of Children," *Semin. Pediat. Infec. Dis.* 13(3):155-164 (2002) ("Overturf 2002")
1014	International Patent Publication No. WO 03/009869 A1 to Chiron SPA ("Chiron 2003")
1015	International Patent Publication No. WO 2002/083855 to American Cyanamid Company ("Wyeth 2002")
1016	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")
1017	Hausdorff *et al.*, "Multinational study of pneumococcal serotypes causing acute otitis media in children," *Pediatr. Infect. Dis. J.* 21(11):1008-1016 (2002) ("Hausdorff 2002")
1018	[RESERVED]

Exhibit No.	Document
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Exhibit No.	Document
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1033	Pena *et al.*, "Present and future of the pneumonia vaccination," *Pediatrika* 24(4):47-55 (2004) (Certified English Translation) ("Pena 2004")
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Exhibit No.	Document
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Exhibit No.	Document
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1063	Gatchalian *et al*., 17th Annual Meeting of the Eur. Soc. Paed. Inf. Dis. (ESPID), poster number 4, P1A Poster Session 1, Istanbul Turkey (Mar. 27, 2001)
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Exhibit No.	Document
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I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner" or "Merck") hereby requests post grant review ("PGR") 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"). 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. 1007), the '060 Patent is eligible for PGR, because its filing date is July 2, 2014 (after the PGR eligibility date of March 16, 2013) and at least one of its claims is not supported under 35 U.S.C. § 112(a) by any of its parent applications. In turn, claims 1-13 are unpatentable because: (1) at least claims 1 and 4-13 are not enabled, (2) claims 1-13 are obvious over the prior art, and (3) claim 3 is indefinite.

Conjugates of polysaccharides (sugars) to proteins are commonly-used components of vaccines against disease-causing bacteria. The '060 Patent describes a vaccine composition ("13vPnC") with 13 specific polysaccharides conjugated to CRM_{197} carrier proteins. Those polysaccharides are isolated from "serotypes" (*i.e.*, strains) of pneumococcus bacteria, with each claimed serotype (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) well-known as a top candidate for a pneumococcal conjugate vaccine.

To obtain the claims of the '060 Patent over the prior art, Patent Owner emphasized that the specific 13vPnC composition is "immunogenic" - a limitation recited in each claim of the '060 Patent - with respect to each serotype of the composition, especially serotype 3. Patent Owner expressly argued during prosecution that prior art multivalent vaccines had failed to elicit sufficient immunogenicity with respect to serotype 3. The '060 Patent devotes ~21 of its ~32 columns to detailing immunogenicity testing results for each conjugate of 13vPnC, as well as the specific conjugation conditions for constructing each 13vPnC conjugate. There is no description in the '060 Patent of conjugates made with any other pneumococcal serotypes.

Despite the limited disclosure of the '060 Patent, sole independent claim 1 recites a virtually unlimited number of combinations of pneumococcal serotypes. The only requirement: the claimed serotypes must include the 7 serotypes of Patent Owner's prior art Prevnar® vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), as well as serotype 3 (well-known as prevalent and associated with serious disease). Otherwise, any combination of nearly 100 pneumococcal serotypes falls within the scope of claim 1; based on the top 30 most prevalent serotypes alone, a vaccine with the 8 claimed serotypes and up to 15 additional serotypes covers over 4 million possible combinations.

By capturing countless combinations of pneumococcal serotypes that Patent Owner did not invent or disclose, claim 1 suffers from a critical defect – it is not enabled by any parent from which the '060 Patent claims priority ("the '060 Parent Apps."), including non-provisional applications sharing the same disclosure as the '060 Patent, and a April 8, 2005 provisional application with only a subset of the disclosure. A person of ordinary skill in the art ("POSITA") as of the filing date of each of the '060 Parent Apps. would have required undue experimentation to practice the full scope of open-ended claim 1.

A patentee obtains "broad claim language 'at the peril of losing any claim that cannot be enabled across its full scope of coverage.'"[1] There is no guidance in the '060 Parent Apps. as to the number and identity of serotypes that should or could be added to 13vPnC, while ensuring immunogenicity of all serotypes in the composition. Indeed, during prosecution and in other proceedings challenging the validity of foreign counterparts of the '060 Patent, Patent Owner has consistently argued that immunogenicity was unexpected for a CRM_{197}-conjugate composition with just the 13 disclosed serotypes. Taking Patent Owner's arguments at face value, it would have been unpredictable for higher-valency compositions to be immunogenic; a POSITA would have required undue experimentation to determine

[1] *Promega Corp. v. Life Techs. Corp*., 773 F.3d 1338, 1348 (Fed. Cir. 2014), *rev'd on other grounds,* 137 S. Ct. 734 (2017).

the full scope of additional serotypes that could be included in the composition of claim 1 while maintaining immunogenicity for all serotypes.

In addition, the disclosures of the '060 Parent Apps. do not teach a POSITA how to produce immunogenic conjugates from serotypes with unknown polysaccharide structures, despite such conjugates being captured by claim 1. Knowledge of a polysaccharide's structure is critical to producing immunogenic conjugates; and yet, of the nearly 100 pneumococcal serotypes identified as of April 8, 2005, the structures of at least 36 serotypes were unknown. (Even as of the actual filing date of the '060 Patent, July 2, 2014, at least 26 structures were still unknown.) Merely generating conjugates of such serotypes would have required months of undue experimentation **for each serotype**: approximately 7.5 to 8.5 months just to determine the polysaccharide structure, before undertaking ~3-6 weeks for conjugation and ~2 months to perform immunologic testing. In fact, Patent Owner has argued, in other proceedings challenging the validity of foreign counterparts of the '060 Patent, that determining the conjugation conditions for individual serotypes requires undue experimentation. Again taking Patent Owner's arguments at face value, it would have been unpredictable whether **any** new conjugate would be immunogenic, potentially requiring the reworking of the conjugation strategy (or abandonment of the serotype).

The effective filing date of claim 1 of the '060 Patent is therefore the actual filing date of the '060 Patent, July 2, 2014 (after the PGR eligibility date of March 16, 2013), and the '060 Patent is a post-AIA patent that is available for PGR in the nine month period following its issuance (July 26, 2016).[2] That same effective filing date (and rationale for PGR) likewise applies to dependent claims 4-13, which do not limit the number and/or identity of the serotypes of sole independent claim 1; they are also not enabled by any of the '060 Parent Apps. Additionally, the broad scopes of dependent claim 8 (further reciting "one or more antigens") and dependent claim 13 (reciting only a subset of dosage parameters of the disclosed compositions) provide an independent basis for PGR eligibility; they lack written description support in any of the '060 Parent Apps.

Petitioner further submits that the Board should find at least claims 1 and 4-13 invalid for lack of enablement, given that (1) the '060 Parent Apps. do not enable at least claims 1 and 4-13, (2) the '060 Patent does not contain any additional disclosure over the '060 Parent Apps., and (3) the state of the art as of

[2] *See, e.g., Arkema Inc. v. Honeywell Int'l Inc.*, PGR2016-00011, Paper 13 at 27 (PTAB Sept. 2, 2016); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 21 (PTAB Jan. 29, 2016); *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper 8 at 17-18 (PTAB Dec. 22, 2015).

the actual filing date of the '060 Patent (July 2, 2014) had not advanced to enable the full scope of the claims.

In any event, even if the Board determines that any claims of the '060 Patent are entitled to an effective filing date of April 8, 2005, the prior art renders those claims obvious. 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 7-valent CRM_{197}-conjugate Prevnar® vaccine. Sigurdardottir 2002 discloses immunogenic 8-valent conjugate vaccines (with the 7 serotypes of Prevnar® and serotype 3), in which each serotype is separately conjugated to the same carrier protein. 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}.

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.

In sharp contrast to the open-ended claims 1 and 4-13 of the '060 Patent, dependent claim 2 is limited to exactly the 13 serotypes of 13vPnC. But, Patent Owner cannot have it both ways: the open-ended claims of the '060 Patent and closed dependent claim 2 cannot both be patentable. To the extent the full scope of independent claim 1 (with unidentified serotypes, of which there are nearly 100, added to 13vPnC) is somehow deemed enabled, a POSITA would necessarily have had a reasonable expectation of success expanding Patent Owner's 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). To the extent 13vPnC of dependent claim 2 is deemed nonobvious given Patent Owner's emphasis on purported concerns of immunogenicity of multivalent vaccines, then even higher-valency compositions captured by claims 1 and 4-13 must not be enabled.

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 claims 1 and 4-13 (and possibly claims 2-3) that broadly cover virtually any multivalent immunogenic pneumococcal conjugate vaccine, which Patent Owner has not invented, disclosed or enabled, let alone practiced.

Finally, with respect to dependent claim 3, that claim is invalid as indefinite. The recitation of serotypes that "consist essentially of" the 13 recited serotypes is irreconcilable with the earlier limitation restricting the claimed composition to exactly (*i.e.*, "consist of") 13 distinct conjugates. Indeed, it is unclear how the recited 13 conjugates can be prepared from serotypes that "consist essentially of" (as opposed to "consist of") the 13 recited serotypes, especially since the specification of the '060 Patent only provides for a 1:1 serotype:conjugate ratio.

II. MANDATORY NOTICES

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

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

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

Petitioner has filed 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), 42.203)

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. § 42.204(a))

Petitioner certifies that the '060 Patent is available for PGR; as discussed herein, at least one claim of the '060 Patent has an effective filing date of July 2, 2014, after the PGR eligibility date of March 16, 2013, making the '060 Patent

available for PGR. AIA §§ 3(n)(1), 6(f)(2)(A). This Petition is timely, as the '060 Patent issued July 26, 2016, and the present Petition is being filed less than nine months after the issuance of the patent. 37 C.F.R. § 42.202. Finally, Petitioner certifies that it is not barred or estopped from requesting review on the grounds identified in this Petition.

V. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.204(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 and 4-13 are unpatentable under post-AIA §112(a) for lack of enablement.

Ground 2. Claims 1, 4-7 and 13 are unpatentable as obvious under post-AIA § 103 over Prevnar 2001 (Ex. 1011) in view of Sigurdardottir 2002 (Ex. 1012) and the general knowledge of a POSITA.

Ground 3. Claims 8-10 and 12 are unpatentable as obvious under post-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 4. Claim 11 is unpatentable as obvious under post-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 5. Claims 2-3 are unpatentable as obvious under post-AIA § 103 over Huebner 2004 (Ex. 1016) in view of Hausdorff 2002 (Ex. 1017) and the general knowledge of a POSITA.

Ground 6. Claim 3 is unpatentable as indefinite under post-AIA §112(b).

The above prior art references (including publication information) are summarized in Section VI.F *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. 1007, ¶ 27. 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*., ¶¶ 28-30.

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*., ¶ 31 (citing Ex. 1020 at 18[3]). Successful immunization of that particularly susceptible age group took place with bacterial proteins, *e.g.*, tetanus and diphtheria toxoids (inactivated toxins). *Id*. (citing Ex. 1021 at 6-7). Through conjugation to carrier proteins, a robust antibody-mediated response against the polysaccharides can be achieved in very young children. *Id*., ¶¶ 32-34 (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*., ¶ 35. 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).

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

2. Multivalent Polysaccharide-Protein Conjugate Vaccines

Strains of a species of extracellular bacteria, called "serotypes" or "serogroups," are characterized by the particular polysaccharides displayed on their surface. *Id.*, ¶ 38. 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*., ¶ 39. 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*., ¶ 44 (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*., ¶ 45 (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*., ¶ 41 (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*., ¶¶ 42, 46 (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*., ¶ 47 (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*., ¶ 48. 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*., ¶ 49. 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*., ¶ 50. Institutionally, there is also typically a preference for particular carrier proteins for which there is prior successful experience and know-how. *Id*., ¶ 51. 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*., ¶ 52. 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 ug of CRM_{197} (more than double the 20 ug 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. Progression of Multivalent Pneumococcal Conjugate Vaccines to Include Prevalent/Emerging Serotypes

As indicated above, the 13 serotypes of Prevnar 13® had been previously identified, prior to the earliest possible priority date of the '060 Patent (April 8, 2005), as top candidates for a multivalent pneumococcal conjugate vaccine. *Id*., ¶ 53. But, it also was well understood in the art that later iterations of multivalent vaccines may incorporate additional clinically relevant serotypes. *Id*. In doing so, such later vaccine iterations broaden coverage in either current markets or new markets (where serotype prevalence may also vary). *Id*.

The universe of clinically relevant serotypes does not remain static over time. *Id*., ¶ 54. Wide-scale immunization against particular serotypes (for example, the serotypes of Patent Owner's Prevnar® or Prevnar 13®) can lead to "serotype replacement," *i.e.*, replacement of vaccine serotypes with serotypes not present in vaccines. *Id*. (citing Ex. 1043; Ex. 1040 at 7; Ex. 1044 at 4-5).

Antibiotic resistance by certain serotypes can similarly lead to their increased prevalence. *Id*. (citing Ex. 1045 at 1-2). Indeed, after the introduction of 7-valent Prevnar® in 2000 (which did not include pneumococcal serotype 19A), serotype 19A emerged as the predominant replacement serotype; this was attributed to one or both of the serotype replacement/shift and antibiotic resistance phenomena. *Id*. (citing Ex. 1046 at 1; Ex. 1047). (Serotype 19A was then included in the 13-valent iteration, Prevnar 13®.)

At least the following non-Prevnar® and non-Prevnar 13® serotypes had been reported in the literature as of April 8, 2005 to be prevalent and/or emerging, depending on patient demographics: 2, 8, 9V, 9N, 10A, 11A, 12F, 13, 15B, 15C, 16, 17F, 20, 21, 22F, 23B, 24F, 25, 31 and 33F. *Id*., ¶ 56 (citing Ex. 1050 at 1; Ex. 1045 at 1; Ex. 1051 at 2). In that regard, Patent Owner has recently obtained a patent (US Patent No. 9,492,559, which is not in the '060 Patent family) claiming up to a 20-valent immunogenic pneumococcal conjugate composition, including serotypes 8, 10A, 11A, 12F, 15B, 22F and/or 33F (Ex. 1076 at claims 1, 3, 4 and 9); as of 1998, those serotypes were among the 28 most prevalent in invasive disease worldwide, and were already included in the Pneumovax® 23 polysaccharide-only vaccine. *Id*. (citing Ex. 1051 at 2; Ex. 1053).

6. Conjugation of Polysaccharides of Unknown Structure to Carrier Proteins

As of April 8, 2005, in order to develop immunogenic conjugates of new candidate vaccine serotypes, a POSITA needed to know the polysaccharide structure of such serotypes. *Id*., ¶ 57. And yet, that knowledge was not available for at least 36 serotypes: 7C, 10B, 10C, 11D, 12B, 16F, 16A, 21, 22A, 23A, 23B, 24F, 24A, 24B, 25F, 25A, 28F, 28A, 33A, 33C, 33D, 35F, 35C, 36, 38, 39, 40, 41F, 41A, 42, 43, 44, 46, 47F, 47A and 48. *Id*. (citing Ex. 1055). In turn, at least serotypes 16, 21, 23B, 24F and 25 were prevalent and/or emerging, but had unknown polysaccharide structures. *Id*.

As of April 8, 2005, a POSITA would have understood that knowledge of the actual polysaccharide structure is critical for tailoring conjugation reaction conditions to the particular polysaccharide. *Id*., ¶ 58. A POSITA would have expected that, for any given set of conjugation reaction conditions, conjugation of various polysaccharides would yield highly variable results, depending on the particular polysaccharide structure. *Id*., ¶ 61. Although most (if not all) polysaccharide serotypes contain at least some functional groups susceptible to reductive amination, they vary widely in the number of groups and susceptibility. *Id*. And, susceptibility to conjugation can be dramatically affected by even small structural changes in a polysaccharide. *Id*.

Polysaccharide structure also impacts the immunogenicity of the conjugate. *Id*., ¶ 62. As acknowledged by Patent Owner in other proceedings, "[v]arious factors affect[] immunogenicity of [conjugate] vaccines," such as the "[s]ize and structure of polysaccharide . . . ." *Id*. (citing Ex. 1056 at 19). For example, certain polysaccharides are wholly incapable of eliciting any antibody response in an immunized animal or human, because of the resemblance of the constituent polysaccharide sugars to sugars naturally present in the animal or human. *Id*. (citing Ex. 1057).

Moreover, conjugation details affect immunogenicity, *e.g.*, the following factors were identified by Patent Owner in other proceedings: "number and types of functional groups," the "[n]ature and number of covalent bonds linking polysaccharides to carrier proteins," and the "[r]atio of polysaccharides to carrier proteins." *Id*., ¶ 63 (citing Ex. 1056 at 19). Conjugation reaction conditions must strike a delicate balance; the conditions must be robust enough to ensure that a sufficient number of the polysaccharide sugars are conjugated, but mild enough to maintain a sufficient number of native (unconjugated sugars) and to minimize alteration of the polysaccharide structure (and consequently, its immunogenicity) at the site of conjugation. *Id*.

For any given serotype with unknown structure, purification and structural characterization would have taken a POSITA 7.5 to 8.5 months to complete, before conjugation (~3-6 weeks) and immunologic testing (~2 months). *Id*., ¶ 66.

7. 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*., ¶ 75. 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. State of the Art as of the Filing Date of the Last-Filed '060 Parent App., April 4, 2012

Prevnar 13® was licensed in 2010, but there was a concern in the art, as of April 4, 2012, that pneumococcal serotypes could emerge even after vaccination with the expanded Prevnar 13® vaccination. *Id.*, ¶ 76. Indeed, only three months later (in July 2012), a member of Patent Owner's pneumococcal vaccine advisory board publicly recommended "serotype reformulation or expansion of protein conjugate vaccines on a scheduled basis every 5 to 10 years until the development of protein-based vaccines that provide immunity to all pneumococcal serotypes that cause disease in humans or of vaccines that prevent nasopharyngeal

colonization." *Id.* (citing Ex. 1059 at 8). Notably, as of April 4, 2012, there were still at least 34 serotypes with unknown polysaccharide serotype; only the structures for serotypes 10B and 10C had been reported in the interim. *Id.*, ¶ 77 (citing Ex. 1060 at 4-9). As was the case as of April 8, 2005, a POSITA still would have required undue experimentation to determine the polysaccharide structure of such serotypes, before even undertaking conjugation and immunologic testing. *Id.*

C. State of the Art as of the Actual Filing Date of the '060 Patent, July 2, 2014

As of July 2, 2014, there were still at least the following 26 serotypes with unknown polysaccharide structures: 7C, 12B, 16F, 16A, 21, 22A, 23A, 23B, 24F, 24A, 24B, 25F, 25A, 28F, 28A, 35F, 35C, 36, 38, 40, 41F, 41A, 43, 44, 46, 48. *Id.*, ¶ 78. As was the case as of April 8, 2005 through April 4, 2012, a POSITA still would have required undue experimentation to determine the polysaccharide structure of such serotypes, before even undertaking conjugation and immunologic testing. *Id.*

D. 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.

Claim 8 broadly recites that "the composition [of claim 1] further comprises one or more antigens," without reciting a pathogen (*e.g.*, virus, fungus, bacteria, parasite) or disease, or even whether the antigen is from a pathogen (rather than a cancer or autoimmunity disorder antigen, for example). *Id.*

Dependent claim 13 recites volume, saccharide dose and amount of adjuvant:

> 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.

Id.

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 Disclosed Conjugation Conditions Are Tailored to the Well-Known Structures of the 13vPnC Polysaccharides

Although each of the 13 disclosed CRM_{197}-conjugates are linked by reductive amination (*see, e.g., id*. at 8:5-8), the '060 Patent discloses activation and conjugation conditions that vary depending on the particular serotype's polysaccharide structure (*id*. at 11:21-27:35). By way of example, for any given serotype requiring hydrolysis, a different combination of reagent, reaction

temperature and reaction time is required. *Id*. at 13:51-53, 16:40-44, 18:64-19:2, 4:9-12, 24:21-23, 24:27-29. And the '060 Patent further describes a variety of conjugation reaction conditions that likewise vary depending on a serotype's polysaccharide structure. *See* Ex. 1007, ¶¶ 91-92.

3. The Immunogenicity Studies of the '060 Patent Are Serotype-Specific and Limited to the 13 Disclosed Serotypes

The '060 Patent reports only 2 immunogenicity studies, both of which relate to 13vPnC; such results are serotype-specific. Ex. 1001 at 28:1-32:64. There is no suggestion that the results can be extrapolated to serotypes beyond those of the 13vPnC vaccine, nor would a POSITA so extrapolate. The first study (#HT01-0021) "examined the ability of the 13vPnC vaccine with $AlPO_4$ adjuvant to elicit vaccine serotype-specific immune responses." *Id*. at 28:17-19. Based on the results, the inventors concluded that adjuvanted 13vPnC was "immunogenic in rabbits, eliciting substantial antibody responses to the pneumococcal capsular polysaccharides contained in the vaccine and these responses are associated with functional activity." *Id*. at 28:60-64. Tables 3 and 4 report the "[s]erotype specific" study data, and demonstrate that the immune responses vary widely by serotype. *Id*. at 29:1-58.

The second study (#HT01-0036) similarly reports serotype-specific immunogenicity results, "compar[ing] rabbit immune responses to the polysaccharides (PSs) contained in the vaccine, after immunization with the

13vPnC vaccine with or without conjugation to the CRM_{197} protein." *Id*. at 29:60-63. The inventors concluded that "conjugation of the 13-valent pneumococcal vaccine polysaccharides produces higher serum IgG titers and overall greater functional antibody activity than seen with free polysaccharide alone or mixed with unconjugated CRM_{197}." *Id*. at 30:63-67. Tables 5 and 6 report the "[s]erotype specific" study data, and - as with the first study - demonstrate that immune responses vary widely by serotype. *Id*. at 31:1-32:64.

4. 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 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.

E. 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.

F. Prior Art

1. Prevnar 2001

Grounds 2-4 of this Petition rely on the Prevnar® entry from the 2001 (55th Edition) Physicians' Desk Reference ("Prevnar 2001"). Ex. 1011. Because Prevnar 2001 was published on or before January 4, 2001 (*id*. at 9), prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under post-AIA § 102(a)(1). 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 ug 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 2-4 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, prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under post-AIA § 102(a)(1).

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 3 (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, prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under post-AIA § 102(a)(1).

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 4 (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, prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under post-AIA § 102(a)(1).

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 5 (concerning dependent claims 2 and 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, prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under post-AIA § 102(a)(1).

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 5 further relies on Hausdorff 2002 (Hausdorff *et al*., "Multinational study of pneumococcal serotypes causing acute otitis media in children," *Pediatr. Infect. Dis. J*. 21:1008-1016 (2002)). Ex. 1017. Because Hausdorff 2002 was published in 2002, prior to the earliest possible priority date of the '060 Patent (April 8, 2005), it is prior art under post-AIA § 102(a)(1).

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. 1007, ¶ 108. 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."[4] 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).

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

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. 1007, at ¶ 113.

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. 1007, ¶ 114; *see, e.g., Rotatable Techs. LLC v. Motorola Mobility LLC,* 567 F. App'x 941, 943 (Fed. Cir. 2014) ("The specification is replete with references to [the preamble language] 'selectively rotating,' underscoring the importance of the feature to the claimed invention. . . . Further the prosecution history shows 'clear reliance on the preamble' to distinguish the claimed invention from the prior art") (internal citations omitted); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1347 (Fed. Cir. 2002) ("[B]oth the specification and prosecution history indicate that the phrase 'rich in glucosinolates' helps to define the claimed invention and is, therefore, a limitation of claim 1"). The fact that the preamble of every claim recites an "immunogenic" composition underscores the intended limiting nature of the term.

Ex. 1007, ¶ 114; *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 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.[5] Ex. 1007, ¶¶ 115-121.

[5] 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

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 ("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

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immunologic memory and functional antibody, as the baseline of acceptable immunogenicity. Ex. 1007, ¶ 116.

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. 1007, ¶ 122. 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. 1007, ¶ 123.

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. 1007, ¶ 124. 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. 1007, ¶ 125.

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*., ¶ 126. 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

Claim 3 is indefinite. Ex. 1007, ¶ 127. However, to the extent the Board deems the claim definite, 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*., ¶ 128. 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. 1007, ¶ 128.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. The '060 Patent Is a Post-AIA Patent Eligible for PGR

The '060 Patent is eligible for PGR because it has at least one claim with an "effective filing date" (as defined in 35 U.S.C. § 100(i)) that is on or after March 16, 2013 (the earliest date for PGR eligibility).[6] AIA §§ 3(n)(1), 6(f)(2)(A). As detailed below, due to lack of enablement (at least claims 1 and 4-13) and written description (claims 8 and 13), at least one claim of the '060 Patent is not entitled to the benefit of the filing date of any parent application; instead, the effective filing date is the actual filing date of the '060 Patent, July 2, 2014.[7]

[6] The patent must also have issued within 9 months of the filing of the PGR Petition, and the Petitioner cannot have previously filed a civil action challenging the validity of a claim of the patent. 35 U.S.C. §§ 321(c), 325(a)(1).

[7] The "effective filing date" of a patent claim under 35 U.S.C. § 100(i) is the patent's actual filing date, unless the patent properly claims priority (or the benefit of an earlier filing date) from a parent application that discloses the claimed invention in compliance with the written description and enablement requirements of post-AIA § 112(a). *See, e.g., Arkema*, PGR2016-00011, Paper 13 at 27; *US*

1. Legal Standard for Enablement and Written Description

To satisfy the enablement requirement of § 112(a), the specification must enable a POSITA, as of the filing date, to practice the full scope of the claims without "undue experimentation." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). Relevant factors in assessing whether undue experimentation would be necessary include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). However, the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts . . . ." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

To comply with the written description requirement of § 112(a), the specification must reasonably convey to a POSITA that the inventor had possession of the claimed subject matter as of the filing date. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). A description that merely renders the invention obvious does not satisfy the requirement. *Id.* at 1352.

Endodontics, PGR2015-00019, Paper 17 at 21; *Inguran*, PGR2015-00017, Paper 8 at 17-18.

In cases where a claim discloses a broad genus, but the specification describes only one or more species, the relevant question is whether a POSITA would "readily discern that other [species] of the genus would perform similarly to the disclosed members"; if not, "disclosure of more species is necessary to adequately show possession of the entire genus." *Synthes USA, LLC v. Spinal Kinetics, Inc*., 734 F.3d 1332, 1344 (Fed. Cir. 2013) (citation omitted).

2. The Effective Filing Date of Claims 1 and 4-13 Is the Actual Filing Date of the '060 Patent, Because the '060 Parent Apps. Do Not Enable the Full Scope of the Claims

Due to lack of enablement, claims 1 and 4-13 are not entitled to the benefit of the filing date of any of the '060 Parent Apps.; instead, the effective filing date of those claims is the actual filing date of the '060 Patent, July 2, 2014.

a. Claim 1 of the '060 Patent is open-ended with respect to the number and identity of "additional serotypes" in the claimed "multivalent immunogenic composition"

Although nearly 100 pneumococcal serotypes had been identified as of the filing dates of the '060 Parent Apps., the broadest reasonable interpretation of open-ended claim 1 covers multivalent immunogenic compositions with **any number of "additional serotypes**," so long as the composition includes the eight serotypes recited in the claim. Assuming a vaccine with the 8 claimed serotypes and up to 15 "additional serotypes" (a total of 23 serotypes, as in the Pneumovax® 23 polysaccharide vaccine that was licensed in 1983) selected from 90 possible

serotypes, claim 1 would cover over **1x10^16** possible combinations. Ex. 1007, ¶ 135. Even when choosing from the top 30 most prevalent serotypes, a vaccine with the 8 claimed serotypes and up to 15 "additional serotypes" covers over **4 million** possible combinations. *Id*.

b. The '060 Parent Apps. do not enable a POSITA to practice the full scope of independent claim 1 without undue experimentation

The '060 Parent Apps. provide no guidance as to the number and identity of serotypes that could be added to 13vPnC (the only disclosed embodiment of claim 1), while ensuring immunogenicity against every serotype of the vaccine. *Id*., ¶ 136. The '060 Parent Apps. also do not teach a POSITA how to construct a large fraction of the immunogenic pneumococcal conjugates captured by claim 1. *Id*.

i. The '060 Parent Apps. do not enable immunogenic compositions other than 13vPnC

The only immunogenic conjugates disclosed in the '060 Parent Apps. are those of 13vPnC. *Id*., ¶ 137. A POSITA would have required undue experimentation to determine the number and identity of additional immunogenic conjugates (if any) that could be added to 13vPnC, while at the same time maintaining the immunogenicity of other serotypes, especially serotype 3. *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. *Id*. But, Patent Owner cannot have it both ways. Taking Patent Owner's argument at face value, the limited disclosure in the '060 Parent Apps. of 13vPnC would not (and could not) have enabled the countless higher-valency immunogenic compositions within the full scope of claim 1. *Id*.

In recent proceedings against a foreign counterpart of the '060 Patent family, Patent Owner contended the immunogenicity of any multivalent candidate pneumococcal conjugate vaccine is wholly unpredictable:

> The technical field to which the present invention relates, IN'808 l, even as of today is highly unpredictable and complicated. 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. 1066 at 7 (emphasis added). Patent Owner similarly argued in other foreign proceedings that "[e]ven today, it is not predictable whether conjugate of certain serotype(s) and certain carrier protein(s) would properly elicit immunogenicity against each serotype." Ex. 1056 at 30.

And, during prosecution of the '024 Patent (a parent of the '060 Patent), Patent Owner insisted that it was unexpected for even its 13-valent composition to be successful:

> While it may have been obvious to add as many polysaccharide components as possible to a multivalent vaccine, it is **unexpected** and **surprising** that applicants' multivalent immunogenic composition generates a robust immune response against each of the 13 distinct polysaccharide components.

Ex. 1004 at 199 (emphasis added). *See also id*. at 128 ("It would be **unpredictable** to extrapolate immunogenicity from other serotypes to serotype 3 in view of the failure of others to produce a successful 11 valent pneumococcal polysaccharide conjugate vaccine with respect to serotype 3.") (emphasis added). In fact, according to Patent Owner, "[p]rior to the filing date of the instant application, all attempts to produce a multivalent pneumococcal conjugate vaccine comprising additional pneumococcal serotype polysaccharides combined with those in the approved heptavalent [Prevnar®] vaccine had been unsuccessful." *Id*. at 200.

Taking Patent Owner's contention at face value that the immunogenicity of even its 13-valent vaccine was surprising and unexpected, such unpredictability necessarily applies to the immunogenicity of higher-valency CRM_{197}-conjugate vaccines; and the full scope of claim 1 (capturing approximately 100 serotypes) is not enabled by the disclosure of the '060 Parent Apps. Ex. 1007, ¶ 140.

ii. Without knowledge of polysaccharide structure, undue experimentation is necessary to develop conjugation conditions for an immunogenic pneumococcal polysaccharide-CRM_{197} conjugate

Knowledge of polysaccharide structure is critical for the development of an immunogenic polysaccharide-CRM_{197} conjugate. Ex. 1007, ¶ 141. Indeed, Patent Owner has conceded in other proceedings that "[v]arious factors affect[] immunogenicity of [conjugate] vaccines," such as the "[s]ize and structure of polysaccharide, number and types of functional groups." Ex. 1056 at 19. For example, the extent of conjugation of a given polysaccharide to CRM_{197} depends on the number of functional groups on the polysaccharide, as well as such groups' degree of susceptibility to conjugation. Ex. 1007, ¶ 141. Conjugation reaction conditions must strike a delicate balance; the conditions must be robust enough to ensure that a sufficient number of the polysaccharide sugars are conjugated, but mild enough to maintain a sufficient number of native (unconjugated sugars) and to minimize alteration of the polysaccharide structure (and consequently, its immunogenicity) at the site of conjugation. *Id*.

iii. Claim 1 captures conjugates of clinically relevant pneumococcal polysaccharide serotypes that had not been structurally characterized as of the filing dates of the '060 Parent Apps.

Since claim 1 is open-ended and covers all pneumococcal conjugate vaccines with **at least** the 8 recited conjugates, it includes a large number of prevalent and clinically relevant pneumococcal serotypes that had not been structurally characterized as of the filing dates of the '060 Parent Apps. (April 8, 2005 through April 4, 2012). Ex. 1007, ¶ 142. At that time, nearly 100 distinct pneumococcal serotypes had been identified, but the structures of at least 34 serotypes had not yet been reported: 7C, 11D, 12B, 16F, 16A, 21, 22A, 23A, 23B, 24F, 24A, 24B, 25F, 25A, 28F, 28A, 33A, 33C, 33D, 35F, 35C, 36, 38, 39, 40, 41F, 41A, 42, 43, 44, 46, 47F, 47A and 48. Ex. 1055; Ex. 1060 at 4-9.

Many of the structurally uncharacterized serotypes were clinically relevant candidates for vaccines. Ex. 1007, ¶ 143. For example, even though it has been known since 1983 that serotypes 25, 16, 24F (listed in order of prevalence) were among the top 28 most prevalent serotypes (Ex. 1051 at 2), their structures were not known as of the filing dates of the '060 Parent Apps. Ex. 1055; Ex. 1060 at 4-9. Based on their prevalence, serotypes 25, 16, 24F were candidates for a pneumococcal vaccine in order to broaden coverage. Ex. 1007, ¶ 143. Indeed, all 23 serotypes of Pneumovax 23 vaccine (licensed in 1983), and all 13 serotypes of

Patent Owner's Prevnar 13®, were also among the 28 most prevalent serotypes. Ex. 1053; Ex. 1051 at 2.

Importantly, as of the filing dates of the '060 Parent Apps., a POSITA would have understood that the universe of clinically relevant serotypes does not remain static. Ex. 1007, ¶ 144. For example, epidemiological factors can lead to an increase in prevalence for one or more serotypes, as was the case with Type V group B *Streptococcus*. Ex. 1048; Ex. 1049. Additionally, serotypes that are only prevalent in certain geographic locations may not have been covered by earlier vaccines, but could be candidates for later versions. Ex. 1007, ¶ 144.

It was also understood in the art that wide immunization against particular serotypes could lead to "serotype replacement," *i.e.*, replacement of vaccine serotypes with serotypes not in the vaccine. *Id*., ¶ 145; Ex. 1043; Ex. 1040 at 7; Ex. 1044 at 4-5. And, antibiotic resistance can likewise lead to an increase in prevalence of certain serotypes. Ex. 1045 at 1-2. Yet, the polysaccharide structure of at least 5 prevalent and/or emerging serotypes as of April 8, 2005 (16, 21, 23B, 24F and 25) remain unknown to this day (let alone by April 8, 2005), with no conjugates of those serotypes (or their conjugation reaction conditions) having been described. Ex. 1007, ¶ 145; Ex. 1055; Ex. 1060 at 4-9.

iv. The '060 Parent Apps. have no enabling disclosure of reaction conditions necessary to construct immunogenic polysaccharide-CRM_{197} conjugates for all "additional serotypes" covered by claim 1

Although a POSITA would have understood as of the filing dates of the '060 Parent Apps. that serotype candidates for a pneumococcal conjugate vaccine include serotypes with unknown polysaccharide structure, the '060 Parent Apps. fail to disclose such serotypes (or their structure); nor do they provide an enabling disclosure as to the preparation of immunogenic conjugates with serotypes other than the 13 serotypes of 13vPnC. *See, e.g.,* Ex. 1003 at 35 ("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*."). Merely generating conjugates of serotypes of unknown polysaccharide structure would have required months of undue experimentation **for each serotype**: approximately 7.5 to 8.5 months just to determine the polysaccharide structure, before undertaking ~3-6 weeks to set up and carry out the conjugation reaction and ~2 months to perform immunologic testing. Ex. 1007, ¶ 146. For a POSITA, generating immunogenic conjugates of the many serotypes of unknown structure would have taken years. *Id.* The Federal Circuit has characterized similarly extensive amounts of research and development as undue experimentation. *See, e.g., White Consol. Indus., Inc. v. Vega Servo–Control, Inc.*, 713 F.2d 788, 790–92

(Fed. Cir. 1983) ("1 ½ to 2 man years of effort" is "a clearly unreasonable requirement").

Taking at face value Patent Owner's own arguments in support of the purported non-obviousness of 13vPnC, the '060 Parent Apps. (which only describe 13vPnC) have no enabling disclosure of reaction conditions necessary to construct immunogenic polysaccharide-CRM_{197} conjugates for all "additional serotypes" covered by claim 1. Ex. 1007, ¶ 147. Patent Owner has argued, in other proceedings challenging the validity of foreign counterparts of the '060 Patent, that "[a]lthough conjugation chemistry (e.g., reductive amination) is generally known, preparation method/condition should be tailored for each specific serotype. Not easy to find such preparation method/condition for some serotypes." Ex. 1056 at 19; *see also* Ex. 1067 at 16 ("[I]t is unavoidable to conduct undue experiments to apply the conditions [of other bacterial polysaccharides or carrier proteins] to each serotype-carrier combination and to confirm immunogenicity."). According to Patent Owner, it would have been unpredictable whether **any** new conjugate would be immunogenic. Ex. 1007, ¶ 147. And, for non-immunogenic conjugates, a POSITA would have had to redesign the conjugation strategy and repeat conjugation and immunologic testing until obtaining an immunogenic conjugate, or abandon the serotype. *Id*.

v. Federal Circuit case law is clear that the facts of this case warrant a finding of nonenablement with respect to the disclosures of the '060 Parent Apps.

Petitioner respectfully submits that the Federal Circuit's holding in *Promega* is controlling in this case. 773 F.3d 1338. Like the present case, in *Promega*, the claim at issue was an open-ended claim directed to simultaneous co-amplification of **at least** three particular loci by PCR. *Id*. at 1343. The Federal Circuit noted that the claim "encompasses not only the 3–plex co-amplification recited in the claims, but it also encompasses **any other** larger, more complex multiplex reaction, so long as it includes the three recited loci." *Id*. at 1346 (emphasis added). Just as in the present case, the open-ended claim language in *Promega* "expands the claims at a key limitation in order to cover what are indisputably advances in this unpredictable art." *Id*. at 1350. "[U]ndue experimentation would have been required in order to enable the full scope of coverage sought by Promega - the successful co-amplification of potentially thousands of unrecited STR loci combinations." *Id*. at 1349. The Federal Circuit held that the claim was not enabled, explaining that "Promega has chosen broad claim language 'at the peril of losing any claim that cannot be enabled across its full scope of coverage.'" *Id*. at 1348, 1350 (citation omitted)); s*ee also MagSil*, 687 F.3d at 1383-1384 (finding nonenablement where "[t]he asserted claims . . . cover resistive changes

from 10% up to infinity, while the . . . patent specification only discloses enough information to achieve an 11.8% resistive change").

c. The '060 Parent Apps. also do not enable claims 4-13, because those claims depend from claim 1, but do not restrict its open-endedness

For the same reasons given with respect to sole independent claim 1 above, the effective filing date of dependent claims 4-13 is also July 2, 2014, the actual filing date of the '060 Patent. Ex. 1007, ¶ 148. Claims 4-13 recite composition limitations with respect to adjuvant (claims 4-7), the presence of additional antigens other than pneumococcal conjugates (claims 8-12), and dosage (claim 13). *Id*. But they do not narrow the scope of claim 1 to an embodiment(s) enabled by the disclosures of the '060 Parent Apps. *Id*.

3. To the Extent Claims 2 and/or 3 Are Not Limited to the Recited 13-Valent Composition, the '060 Parent Apps. Do Not Enable Those Open-Ended Claims for the Same Reasons as with Claim 1

Claim 2 is limited 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. 1007, ¶ 149. Claim 3 is indefinite, and in any event must be limited to 13 conjugates with the same 13 serotypes as in claim 2. *Id*. However, to the extent claims 2 and/or 3 are somehow construed to be open-ended, those claims are also not enabled by the '060 Parent Apps., and their effective filing date is July 2, 2014 for the same reasons as set forth above with respect to claim 1. *Id*.

4. The Effective Filing Date of Claims 8 and 13 Is the Actual Filing Date of the '060 Patent, Because the '060 Parent Apps. Lack Written Description of the Broadly-Claimed Subject Matter

Dependent claims 8 and 13 (both included for the first time in the '060 Patent application as filed) lack written description support in the '060 Parent Apps.; their effective filing date is the actual filing date of the '060 Patent, July 2, 2014. Ex. 1007, ¶ 150.

Claim 8 broadly recites that "the composition [of claim 1] further comprises one or more antigens," without reciting a pathogen (*e.g.*, virus, fungus, bacteria, parasite) or disease, or even whether the antigen is from a pathogen (rather than a cancer or autoimmunity disorder antigen, for example). In contrast, the non-provisional '060 Parent Apps. provide no written description support for the broad scope of claim 8, and only describe a much narrower universe of additional antigens, *i.e.*, "one or more additional antigens for use against otitis media caused by infection with other bacteria," "one or more proteins from *Streptococcus pneumoniae*," and "one or more proteins from *Neisseria meningitidis type B*." *See, e.g.*, Ex. 1003 at 40-41. (The '605 Provisional does not even include the above disclosure; it was added in the first non-provisional application, Ex. 1005 at 22.)

Similarly, claim 13 recites a formulation that is much broader than the description in the '060 Parent Apps.:

> 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.

Claim 13 specifies only the volume, saccharide dose and amount of adjuvant, and broadly includes any possible value for other dosing parameters (such as amount of protein) and any formulation ingredients (such as salt and buffer). Ex. 1007, ¶ 152. Yet, the '060 Parent Apps. describe only a 0.5 ml dose formulation that is further limited to 29 ug of CRM_{197}, as well as sodium chloride and sodium succinate buffer as excipients. *See, e.g.*, Ex. 1003 at 28, 39.

B. Claims 1 and 4-13 (and Claims 2 and 3, Depending on their Construed Scope) Are Invalid for Nonenablement

Claims 1 and 4-13 are invalid under post-AIA § 112(a). Ex. 1007, ¶ 153. As detailed above, at least claims 1 and 4-13 were not enabled as of the filing dates of the '060 Parent Apps. Those claims were likewise not enabled by the specification of the '060 Patent as of its filing date (July 2, 2014). *Id*. Indeed, the '060 Patent does not teach anything more than the '060 Parent Apps. *Id*., ¶ 154. The non-provisional '060 Parent Apps. (Exs. 1003-1005) share the same disclosure as the '060 Patent (Ex. 1001), and the only provisional application (the '605 Provisional, Ex. 1006) contains a subset of the disclosure in the '060 Parent Apps. Ex. 1007, ¶ 154.

For the same reasons provided above, a POSITA would have required undue experimentation to determine the number and identity of additional serotypes that could be included in the immunogenic composition of sole independent claim 1, and to construct immunogenic CRM_{197}-conjugates that fall within the overly broad scope of that claim. *Id*. As of July 2, 2014, there were still at least 26 pneumococcal polysaccharide serotypes of unknown structure. Ex. 1060 at 4-9.

Given that claims 4-13 do not further limit the serotypes covered by claim 1, a POSITA would have required undue experimentation to practice those claims as well. Ex. 1007, ¶ 155. (With respect to claims 2 and 3, to the extent those claims are construed to be open-ended with respect to the number and/or identity of polysaccharide serotypes, they are invalid for the same reasons. *Id*.)

C. 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. 1007, ¶ 197. 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. 1007, ¶ 199. 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. 1007, ¶ 200. 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. 1007, ¶ 201. 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. 1007, ¶ 201.

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.*, ¶ 202. 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. 1007, ¶ 203. A previous report confirms this:

> The PncD vaccine . . . was an octavalent pneumococcal conjugate vaccine containing 3ug 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 ug 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. 1007, ¶ 203.

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. 1007, ¶ 204. As conceded by Patent Owner during the prosecution of the '024 Patent, there was a "high motivation in the vaccine art" to create "a complex, multivalent conjugate vaccine that provides effective protection against all *S. pneumoniae* serotype polysaccharides incorporated in the vaccine (including serotype 3)". Ex. 1004 at 198. In that regard, it was well-known in the art that serotype 3 was prevalent and a cause of serious disease. *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*.

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. 1007, ¶ 205. 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. 1007, ¶ 206. 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. 1007, ¶ 207. 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, 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. 1007, ¶ 207.

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. 1007, ¶ 208.

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. 1007, ¶ 209.

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. 1007, ¶ 210.

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. 1007, ¶ 211.

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.[8]

Ex. 1011 at 2; *see* Ex. 1007, ¶ 212. 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. 1007, ¶ 213.

[8] 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.

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." *Id*. at 10:32-38. There is no significance in the slight difference between 2.2 ug of the claims and 2 ug in Prevnar® (as well as 4.4 ug in the claims vs. 4 ug in Prevnar®); the '060 Patent itself uses the two dosages interchangeably for the disclosed 13-valent composition. *See, e.g., id.* at 3:9-15; 10:24-28; 29:63-65; *see* Ex. 1007, ¶ 215.

D. 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. 1007, ¶ 216. 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. 1007, ¶ 217.

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. 1007, ¶ 218.

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. 1007, ¶ 219. 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.

E. 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. 1007, ¶ 220. 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." *Id*. at 96:17-22.

F. Claims 2-3 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. With respect to claim 3, as

discussed below, 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. But, Patent Owner cannot have it both ways: the open-ended claims of the '060 Patent and closed dependent claim 2 cannot both be patentable. To the extent the full scope of independent claim 1 (with unidentified serotypes, of which there are nearly 100, added to 13vPnC) is somehow deemed enabled, a POSITA would necessarily have had a reasonable expectation of success expanding Patent Owner's strongly-immunogenic 9-valent immunogenic 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 Hausdorff 2002, Ex. 1017). Ex. 1007, ¶ 221. To the extent 13vPnC of dependent claim 2 is deemed nonobvious given Patent Owner's emphasis on purported concerns of immunogenicity of multivalent vaccines, then even higher-valency compositions captured by claims 1 and 4-13 must not be enabled.

1. 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. 1007, ¶ 222. It would have been

obvious, based on Hausdorff 2002 (in a study sponsored by Patent Owner) (Ex. 1017), to further expand the 9-valent vaccine of Huebner 2004 to a 13-valent vaccine with the claimed serotypes. Ex. 1007, ¶ 222.

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. 1007, ¶ 223 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. 1007, ¶ 224. 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. 1007, ¶ 225. 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. 1007, ¶ 226. Indeed, 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 2 distinct 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. 1007, ¶ 226.

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. 1007, ¶ 227. As discussed above, 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. 1007, ¶ 227.)

2. 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 below, 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 claim 2, the composition of claim 3 would have been obvious. Ex. 1007, ¶ 228.

G. 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.*, ¶ 229.

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.*, ¶ 230. 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*., ¶ 231; *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 claims 1 and 4-13 (and possibly claims 2-3) that broadly cover virtually any multivalent immunogenic pneumococcal conjugate vaccine, which Patent Owner has not invented, disclosed or enabled, let alone practiced. Ex. 1007, ¶ 232.

H. Claim 3 Is Invalid for Indefiniteness

Petitioner submits that claim 3 is invalid as indefinite under post-AIA § 112(b); it is unclear how the transitional phrase "consist essentially of" applies to the claimed serotypes, given that the claim is unequivocally limited to 13 conjugates separately prepared from the 13 recited conjugates. Ex. 1007, ¶ 158; *see Telebrands Corp. v. Tinnus Enterprises, LLC*, PGR2015-00018, Paper 75 at 16-19 (PTAB Dec. 30, 2016) ("In this post-grant review AIA proceeding, we apply the test for indefiniteness approved by the Federal Circuit in *Packard*, i.e., 'a claim is indefinite when it contains words or phrases whose meaning is unclear.'") (quoting *In re Packard*, 751 F.3d 1307, 1313 (Fed. Cir. 2014)).

Claim 3 initially recites that the "polysaccharide-protein conjugates **consist of** 13 distinct polysaccharide-protein conjugates" (emphasis added), namely that the composition must contain exactly 13 conjugates. 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 (Ex. 1001 at 7:59-8:5), and it follows that the claim must be limited to 13 conjugates with the recited 13 serotypes. Ex. 1007, ¶ 159. And yet, the claim later recites that "the serotypes **consist essentially of** 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F."

The scope of the claim is entirely unclear, and therefore indefinite under *Packard*. *Id.*, ¶ 160. Because the claim's contradiction cannot be reconciled, it also fails to inform those of skill in the art of the scope of the claims with reasonable certainty, as required under the *Nautilus* indefiniteness standard that is applied in the courts. *Id.*, ¶ 161; *Nautilus, Inc., v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

X. CONCLUSION

Petitioner respectfully submits that it has established that it is more likely than not that it will prevail as to the unpatentability of claims 1-13 of the '060 Patent. Petitioner respectfully requests that this Petition be granted, post grant review be instituted, and claims 1-13 of the '060 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: March 22, 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 Post Grant Review of U.S. Patent No. 9,399,060 contains, as measured by the word processing system used to prepare this paper, 18,559 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), a copy of the foregoing Petition for Post Grant Review of U.S. Patent No. 9,399,060, along with all exhibits and other supporting documents, was served on March 22, 2017, by FedEx overnight delivery at the following address:

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

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