UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

MERCK SHARP & DOHME CORP.
Petitioner

v.

WYETH LLC
Patent Owner

_____

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

_____

PETITION FOR *INTER PARTES* REVIEW

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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
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1006	US Provisional Application No. 60/669,605
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1031	Lin et al., "The efficacy of a *Salmonella typhi* Vi conjugate vaccine in two-to-five-year-old children," N. Engl. J. Med. 344(17):1263-1269 (2001)
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1074	Excerpts from 57 Physicians' Desk Reference® (2003)
1075	Excerpts from 58 Physicians' Desk Reference® (2004)
1076	U.S. Patent No. 9,492,559 to Emini *et al.*
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1081	Beall *et al*., "Pre- and Postvaccination Clonal Compositions of Invasive Pneumococcal Serotypes for Isolates Collected in the United States in 1999, 2001, and 2002," *J. Clin. Microbiol.* 44(3):999–1017 (2006)
1082	Declaration of Dennis L. Kasper, M.D.
1083	[Reserved]
1084	[Reserved]

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner" or "Merck") hereby requests *inter partes* review ("IPR") of claims 1-13 of U.S. Patent No. 9,399,060 ("the '060 Patent") (Ex. 1001), assigned to Wyeth LLC ("Patent Owner" or "Wyeth"). 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. 1082), there is a reasonable likelihood that Petitioner will prevail in establishing that (1) the effective filing date of claims 1 and 4-13 (and claims 2 and 3, depending on their construed scope) is no earlier than January 22, 2009, and (2) those claims are anticipated by the prior art under pre-AIA § 102(b).

Conjugates of polysaccharides (sugars) to proteins are commonly-used components of vaccines against disease-causing bacteria. The '060 Patent describes a single 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.

A patentee obtains "broad claim language 'at the peril of losing any claim that cannot be enabled across its full scope of coverage.'"[1] Here, independent claim 1 is not entitled to a priority date that would avoid anticipation by Patent Owner's own '380 Pub. (Ex. 1018), published October 12, 2006. The '380 Pub. is pre-AIA § 102(b) prior art against claim 1, unless the claim is supported under § 112 ¶ 1 (written description and enablement) by one of its parent applications with a filing date of October 12, 2007 or earlier - *i.e.*, an April 8, 2005 provisional application (the '605 Provisional) and a March 31, 2006 non-provisional application (the '593 App.) (together, "the '060 Parent Apps."). The next-filed application in the '060 Patent family was the '853 App., filed January 22, 2009. Because neither of the '060 Parent Apps. enables the full scope of claim 1, the effective filing date of claim 1 (for purposes of this IPR) is no earlier than January 22, 2009.

As an initial matter, 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

[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).

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 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 the filing dates of the '060 Parent Apps., the structures of at least 36 serotypes were 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** conjugates

added to 13vPnC would be immunogenic, potentially requiring the reworking of the conjugation strategy (or abandonment of the serotype).

The effective filing date of claim 1 for purposes of this IPR (*i.e.*, no earlier than January 22, 2009) likewise applies to at least dependent claims 4-13; those claims do not limit the number and/or identity of the serotypes of sole independent claim 1, and are not enabled by any of the '060 Parent Apps. for the same reasons as claim 1.

In turn, the '380 Pub. is § 102(b) prior art, and it anticipates claims 1-13; the '380 Pub. shares the same disclosure as the '060 Patent of (1) a 13-valent immunogenic pneumococcal conjugate composition within the scope of claims 1-3, (2) the adjuvant of dependent claims 4-7, (3) the additional antigens of dependent claims 8-12, and (4) the dosing parameters of claim 13.

II. MANDATORY NOTICES

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

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

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

Petitioner is concurrently filing two additional Petitions for *inter partes* review of the '060 Patent. Petitioner has also filed two Petitions for post grant review ("PGR") of the '060 Patent: PGR2017-00016 and PGR2017-00017. Petitioner has filed a Petition for *inter partes* review of Patent Owner's US Patent

No. 8,895,024: IPR2017-01194. Petitioner has filed three Petitions for *inter partes* review of Patent Owner's US Patent No. 8,562,999: IPR2017-00378, IPR2017-00380 and IPR2017-00390. Petitioner is unaware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding.

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

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

Petitioner consents to electronic service.

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

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

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

Petitioner respectfully submits that it has demonstrated, in co-pending Petitions for PGR of the '060 Patent (PGR2017-00016 and -00017), that the '060 Patent is a post-AIA patent containing at least one claim with an effective filing

date of July 2, 2014. However, to the extent the Board determines that the '060 Patent is a pre-AIA patent (based on a claim of priority to a pre-AIA application), Petitioner certifies that the '060 Patent is available for IPR. Petitioner further certifies that it is not barred or estopped from requesting review on the grounds identified.

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

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

Ground 1. Claims 1-13 are unpatentable as anticipated by the '380 Pub. (Ex. 1018) under pre-AIA § 102(b).

The above prior art reference (including publication information) is summarized in Section VI.E *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. 1082, ¶ 23. When the source of infection is encapsulated bacteria

(*i.e.*, bacteria covered in a shell of polysaccharides (which are polymers of sugars)), such as pneumococcus, the immune system often targets its response to the polysaccharides; this makes the polysaccharides attractive molecules for vaccines. *Id.*, ¶¶ 24-26.

Despite the successful use of bacterial polysaccharides to immunize adults and older children, polysaccharides were not very immunogenic in children under 2 years of age. *Id.*, ¶ 27 (citing Ex. 1020 at 18[2]). Successful immunization of that particularly susceptible age group took place with bacterial proteins, *e.g.*, tetanus and diphtheria toxoids (inactivated toxins). *Id.* (citing Ex. 1021 at 6-7). Through conjugation to carrier proteins, a robust antibody-mediated response against the polysaccharides can be achieved in very young children. *Id.*, ¶¶ 28-30 (citing Ex. 1022; Ex. 1023: Ex. 1024 at 17-19; Ex. 1025).

Polysaccharide-protein conjugate vaccines had been commercialized for nearly two decades before April 8, 2005. *Id.*, ¶ 31. Numerous conjugate vaccines had been approved, including a vaccine against pneumococcus (Prevnar®). *Id.*

[2] 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 __/__").

(citing Ex. 1026 at 2; Ex. 1070; Ex. 1072; Ex. 1074; Ex. 1075 at 28, 38, 42; Ex. 1027 at 5-6; Ex. 1028 at 6). CRM_{197} was commonly used as the carrier protein in many conjugate vaccines (*e.g.*, Vaxem HIB, HibTITER, Prevnar®, Meningitec, Menjugate®). *Id*. (citing Ex. 1028 at 6; Ex. 1072; Ex. 1075 at 38, 42).

2. Multivalent Polysaccharide-Protein Conjugate Vaccines

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

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

(citing Ex. 1052). That 14-valent Pneumovax® was replaced with a 23-valent version (Pneumovax® 23) in 1983. *Id*. (citing Ex. 1053).

Because the pneumococcal polysaccharide vaccines were not immunogenic in young children, Patent Owner introduced a polysaccharide-protein conjugate vaccine (Prevnar®) in 2000. *Id*. (citing Ex. 1033 at 3). Prevnar® was a 7-valent vaccine, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated to the CRM_{197} carrier protein. *Id*., ¶ 41 (citing Ex. 1011 at 2). Pneumococcal conjugate vaccines progressed to a 9-valent (adding serotypes 1 and 5), 11-valent (adding serotypes 3 and 7F), and the 13-valent (adding serotypes 6A and 19A) versions; a 13-valent iteration was approved and marketed as Prevnar 13® in 2010. *Id*., ¶¶ 37, 42 (citing Ex. 1033 at 7). As of April 8, 2005, the field had identified the most prevalent and/or virulent serotypes of extracellular bacteria affecting young children; with respect to pneumococcus, the serotypes of Prevnar 13® were well-known, top candidates for a multivalent conjugate vaccine. *Id*., ¶¶ 38, 42 (citing Ex. 1017 at 7; Ex. 1033 at 7; Ex. 1035 at 1; Ex. 1036 at 3).

3. Immunogenicity of Multivalent Polysaccharide-Protein Conjugate Vaccines

The characteristics of the immune response elicited by a vaccine reflect the likelihood that the vaccine will be successful at preventing disease. *Id*., ¶ 43 (citing Ex. 1037 at 6). For example, demonstration of immunologic memory, *e.g.*, that antibody responses can be quickly and robustly recalled *in vivo* after re-

exposure to the polysaccharide serotypes of the vaccine, is evidence that the immunity may persist for long periods of time and that antibody responses may be similarly fast and robust upon exposure to actual pathogens. *Id*. Likewise, if antibodies elicited by a vaccine are "functional" *in vitro*, *e.g.*, they are efficient mediators of bacterial death *in vitro*, one would expect such antibodies to prevent actual infection *in vivo*. *Id*. The degree to which the vaccine elicits desired immune responses is referred to as "immunogenicity"; in the context of a multivalent conjugate vaccine, immunogenicity is assessed on a serotype-by-serotype basis. *Id*. (citing Ex. 1037 at 3).

4. Carrier Induced Epitopic Suppression in Multivalent Conjugate Vaccines

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

Those reports of CIES did not impact the natural progression of multivalent vaccine development. *Id*., ¶ 45. As of April 8, 2005, there were clear advantages to using a single carrier protein in a multivalent conjugate vaccine, *e.g.*, efficiency, cost, simplicity and minimization of the risk of adverse reactions. *Id*., ¶ 46. Institutionally, there is also typically a preference for particular carrier proteins for which there is prior successful experience and know-how. *Id*., ¶ 47. This is evidenced by Patent Owner's consistent usage of CRM_{197} as the single carrier protein in its own development efforts with respect to pneumococcal and other vaccines. *Id*. The prior art 7-valent Prevnar® (using CRM_{197} as the only carrier protein) was itself an expanded form of earlier lower-valency compositions using CRM_{197} as the only carrier protein. *Id*. (citing Ex. 1038 at 1). The next iteration was a prior art 9-valent vaccine, again using CRM_{197} as the sole carrier protein. *Id*. (citing Ex. 1016 at 1; Ex. 1039 at 2). The prior art literature further indicated that Patent Owner was expanding its 9-valent pneumococcal conjugate vaccine to an 11-valent iteration with CRM_{197} as the sole carrier protein. *Id*. (citing Ex. 1013 at 4; Ex. 1040 at 5).

Moreover, the literature as of April 8, 2005 indicated that CIES was not always observed when increasing the amount of a carrier protein; decreased antibody response due to CIES was not clinically relevant when other correlates of protection were still observed. *Id*., ¶ 48. With respect to CRM_{197}, at least one

study reported on the simultaneous administration of a 9-valent pneumococcal CRM_{197}-conjugate vaccine and a non-pneumococcal CRM_{197}-conjugate vaccine; the joint administration of a total of 45 μg of CRM_{197} (more than double the 20 μg in Prevnar®) did not result in suppression. *Id*. (citing Ex. 1039 at 6-7). Similarly, co-administration of the 7-valent pneumococcal CRM_{197}-conjugate vaccine and a non-pneumococcal CRM_{197}-conjugate vaccine "produced no meaningful increase or reduction in the concentration of pneumococcal or other vaccine antibodies." *Id*. (citing Ex. 1013 at 6; Ex. 1041 at 5). And, in a study (sponsored by Patent Owner) that did observe suppression of pneumococcal antibody responses in connection with increased amounts of carrier protein in a 7-valent pneumococcal CRM_{197}-conjugate vaccine, the authors concluded that "this may be clinically unimportant given that their [*i.e.*, the patients'] response to polysaccharide boosting suggested good priming [*i.e.*, memory]." *Id*. (citing Ex. 1042 at 8).

5. 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*., ¶ 49. 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*., ¶ 50. 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 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*., ¶ 52 (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*., ¶ 53. 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*., ¶ 54. 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*., ¶ 57. 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*., ¶ 58. 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*., ¶ 59 (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.*, ¶¶ 62-70.

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

B. State of the Art as of the Filing Date of the '593 App., March 31, 2006

As of March 31, 2006, it was still well known in the art that later iterations of multivalent vaccines may incorporate additional clinically relevant serotypes to broaden vaccine coverage. *Id.*, ¶ 72. Notably, the art had maintained its concerns regarding serotype replacement due to Prevnar®. *See, e.g., id.* (citing Ex. 1079; Ex. 1080). For example, in March 2006, it had been reported that, "[c]ompared to the proportion of cases in 1999, the proportion of cases due to non-PCV7 serotypes 3,

7F, 15BCF, 19A, 22F, 33F, and 38 significantly increased in 2002 . . ." *Id.* (quoting Ex. 1081 at 2). Yet, as of March 31, 2006, there were still at least 36 serotypes with unknown polysaccharide serotype. *Id.* (citing Ex. 1055; Ex. 1060 at 4-9). Such serotypes included serotype 38 (reported in 2006 to have increased significantly in prevalence, Ex. 1081), as well as serotypes 16, 21, 23B, 24F and 25 (which were known to be prevalent and/or emerging as of April 8, 2005). *Id.* 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. The '060 Patent

Sole independent claim 1 of the '060 Patent is generally directed to a multivalent immunogenic pneumococcal CRM_{197}-conjugate vaccine. The pneumococcal serotypes of the claim "comprise" the 7 polysaccharide serotypes (*i.e.*, 4, 6B, 9V, 14, 18C, 19F, 23F) in Patent Owner's prior art Prevnar® vaccine (also referred to in the '060 Patent specification as "7vPnC"), and "at least one additional serotype, wherein the additional serotype is serotype 3":

> 1. A multivalent immunogenic composition comprising polysaccharide-protein conjugates and a physiologically acceptable vehicle, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein, wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional

serotype, wherein the additional serotype is serotype 3, and wherein the carrier protein is CRM_{197}.

Ex. 1001. Since "comprise" is an open-ended term, the broadest reasonable interpretation of claim 1 is that it is directed to any pneumococcal CRM_{197}-conjugate vaccine with any combination of pneumococcal serotypes (of which nearly 100 are presently known), so long as the composition includes the 8 serotypes recited in the claim and is immunogenic.

Despite the open-ended (*i.e.*, "comprise") scope of claim 1, the '060 Patent discloses only a vaccine with the 13 serotypes of 13vPnC. *See, e.g., id*. at 2:20-24. The '060 Patent provides no guidance with respect to an immunogenic vaccine with any other specific polysaccharide serotypes. Dependent claims 4-13 retain the open-endedness of claim 1 with respect to the number and identity of the "additional serotype[s]," and instead recite limitations regarding adjuvant (claims 4-7), additional antigens other than pneumococcal conjugates (claims 8-12), and dosage (claim 13). *Id*. at claims 4-13.

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

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

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

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

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

Id. (emphasis added).

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

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

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

Id. The Summary of the Invention is the same:

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

Id. at 2:13-24. Of the ~32 columns in the '060 Patent disclosure (excluding references and claims), ~16 columns provide details for preparing conjugates of each of the 13 serotypes of 13vPnC (*id*. at 11:21-27:35), and ~5 columns are devoted to immunologic testing of 13vPnC (*id*. at 28:1-32:64). There is no corresponding disclosure for any other pneumococcal serotype. The only "additional serotypes" (of claim 1) disclosed in the specification are the 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A) of 13vPnC (*see, e.g., id.* at 2:63-65).

2. The 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. 1082, ¶¶ 85-86.

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 1:43-46. The specification makes clear that the addition of 6 specific serotypes (1, 3, 5, 6A, 7F and 19A) to 7vPnC "would increase coverage for invasive disease to >90% in the US and Europe, and as high as 70%-80% in Asia and Latin America." *Id*. at 2:1-6.

The '060 Patent acknowledges Patent Owner's prior development of a 9-valent vaccine, which was "7vPnC plus serotypes 1 and 5" (*id*. at 6:23-25), and cites to a 2002 publication (*id*. at 4:15-18), which discloses an "11-valent pneumococcal conjugate vaccine formulation, containing [9-valent] PCV-9 serotypes plus 3 and 7F (PCV-11)." Ex. 1017 ("Hausdorff 2002") at 2. That same Hausdorff 2002 publication identifies 6A and 19A as the next group of "major serotypes": "It appears that the serotypes represented in PCV-11, plus 6A and 19A, comprise all major serotypes in each age group studied." *Id*. at 7. Similarly, a 1999 paper, discussed in the '060 Patent, expressly discloses that future vaccines may include the 13 serotypes of 13vPnC: "The current experimental conjugate vaccines contain 7 (e.g., serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) or more serotypes. To increase the coverage for protection, additional serotypes (e.g., serotypes 1, 3, 5, 6A, 7F, and 19A) may be added to the conjugate vaccines in the future." Ex. 1035 at 1.

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

even after vaccination with Prevnar® (which contains serotype 6B). Ex. 1061 at 5; *see* Ex. 1001 at 1:46-49.

D. 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"). The '060 Patent is also the last issued patent in a chain of non-provisional applications, all claiming priority back to the '605 Provisional. The first non-provisional application, US Patent Application No. 11/395,593 ("the '593 App."), was filed on March 31, 2006, and is now abandoned. Ex. 1005. The second non-provisional application, US Patent Application No. 12/357,853 ("the '853 App."), is listed as a continuation of the '593 App., was filed on Jan. 22, 2009, and issued as US Patent No. 8,895,024. Ex. 1004. The third non-provisional application, US Patent Application No. 13/439,111 ("the '111 App."), is listed as a continuation of the '853 App., was filed on April 4, 2012, and issued as US Patent No. 8,808,708. Ex. 1003. Finally, the application issuing as the '060 Patent (US Patent Application No. 14/322057), is listed as a continuation of the '111 App. Ex. 1002.

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.

E. Prior Art

1. The '380 Pub.

This Petition relies on US Patent Application Publication No. US 2006/0228380 ("the '380 Pub."). Ex. 1018. Because Petitioner submits that the effective filing date of claims 1 and 4-13 (and claims 2 and 3, depending on their construed scope) is no earlier than January 22, 2009, and because the '380 Pub. was published more than one year prior to that date (on October 12, 2006), it is prior art

under pre-AIA § 102(b) with respect to those claims. The '380 Pub. is the publication of the '593 App. (Ex. 1005), and shares the same specification and disclosure as the '060 Patent.

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. 1082, ¶ 102. Therefore, a POSITA would have been an individual or team with Ph.D. degrees in the biological and chemical sciences and at least 3 years of work experience, or an M.D. degree and at least 6 years of work experience, developing conjugate vaccines, including specifically growing sufficient quantities of bacteria, extracting, purifying and analyzing bacterial polysaccharides, conjugating polysaccharides to a carrier protein (and analyzing the conjugates), and performing immunologic testing. *Id.*

VIII. CLAIM CONSTRUCTION

Petitioner submits that the term "immunogenic" (recited in every claim) requires construction. Likewise, the limitation in sole independent claim 1 regarding the number and identity of the claimed serotypes - "wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional serotype, wherein the additional serotype is serotype 3" - should be construed, as should the scope of dependent claims 2 and 3 with respect to the number and

identity of the claimed serotypes. Because the '060 Patent has not expired and will not expire before a final written decision is entered in this proceeding, each claim term is construed based on "its broadest reasonable construction [a/k/a broadest reasonable interpretation] in light of the specification of the patent in which it appears."[3] 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). In AIA post-grant proceedings, the broadest reasonable interpretation standard also takes into account Patent Owner's statements and arguments during prosecution history. *See, e.g., Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015).

A. "immunogenic"

Every claim of the '060 Patent recites an "immunogenic" composition. Ex. 1001. The broadest reasonable interpretation of that term is "elicits immunologic memory and/or functional antibody with respect to each serotype of the vaccine, including serotype 3." Ex. 1082, ¶ 107.

As detailed below, although the term "immunogenic" appears in the claim preambles, Patent Owner repeatedly emphasized immunogenicity in the specification, and relied on it during prosecution history to gain allowance of the claims over a prior art vaccine that purportedly failed to elicit immunologic

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

memory or functional antibody with respect to serotype 3. Ex. 1082, ¶ 108; *see, e.g., Rotatable Techs. LLC v. Motorola Mobility LLC*, 567 F. App'x 941, 943 (Fed. Cir. 2014) ("The specification is replete with references to [the preamble language] 'selectively rotating,' underscoring the importance of the feature to the claimed invention. . . . Further the prosecution history shows 'clear reliance on the preamble' to distinguish the claimed invention from the prior art") (internal citations omitted); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1347 (Fed. Cir. 2002) ("[B]oth the specification and prosecution history indicate that the phrase 'rich in glucosinolates' helps to define the claimed invention and is, therefore, a limitation of claim 1"). The fact that the preamble of every claim recites an "immunogenic" composition underscores the intended limiting nature of the term. Ex. 1082, ¶ 108; *see, e.g., Poly-Am., L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) (emphasizing that "the entire preamble 'blown-film textured liner' is restated in each of the patent's seven claims").

In the specification of the '060 Patent and during prosecution, Patent Owner conceded that GSK had disclosed a prior art 11-valent pneumococcal conjugate vaccine ("11-Pn-PD") with (1) the 8 polysaccharide serotypes recited in claim 1 (including serotype 3), and (2) each of the 11 total polysaccharide serotypes conjugated to protein D carrier proteins. Ex. 1001 at 4:26-42; Ex. 1002 at 180. Patent Owner stressed the importance of immunogenicity. Ex. 1001 at 4:43-47;

Ex. 1002 at 180-181. More specifically, Patent Owner argued that 11-Pn-PD suffered from a deficiency with respect to the immune response against serotype 3 - the failure to elicit immunologic memory or functional antibody (both important correlates of protection) - which the purported invention of the '060 Patent allegedly overcame.[4] Ex. 1082, ¶¶ 109-115.

In alleging that the 11-Pn-PD vaccine did not generate immunologic memory, Patent Owner cited to a 2004 GSK-sponsored study (Ex. 1037), arguing that "no priming effect [*i.e.*, immunologic memory] was observed for serotype 3 . . ." Ex. 1001 at 4:26-32; Ex. 1002 at 180; *see also* Ex. 1056 at 38 ("failed to induce significant immunogenic memory"); Ex. 1062 at 2 ("failed to exhibit sufficient immune response, in particular with regard to immunologic memory"). Patent Owner also stressed that GSK's prior art 11-Pn-PD vaccine did not elicit functional antibody, citing to a 2001 meeting abstract (Ex. 1063), and arguing that

[4] Importantly, Patent Owner did not (and could not) argue that 11-Pn-PD failed to elicit significant antibody production for all serotypes, including serotype 3. *See, e.g.*, Ex. 1037 at 3 ("significantly higher antipneumococcal PS IgG concentrations for all vaccine serotypes after 3 doses of Pn-PD at 7 months"). Patent Owner's argument instead focused on more direct correlates of protection, generation of immunologic memory and functional antibody, as the baseline of acceptable immunogenicity. Ex. 1082, ¶ 110.

"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 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. 1082, ¶ 116. For example, Patent Owner argued for the patentability of a claim (Ex. 1005 at 63 (claim 18)), which was similar to (if not broader than) the claims of the '060 Patent. Patent Owner argued that an unexpected feature of the claimed composition was "the ability of a multivalent conjugate composition comprising more than seven individual polysaccharide conjugates to elicit immunogenic responses to **each** of its component polysaccharide serotypes (claims 18-24)." Ex. 1005 at 144 (emphasis added).

Given the disclosure in the '060 Patent specification, as well as Patent Owner's clear and unambiguous representations to the Patent Office, the broadest reasonable interpretation limits the claimed "immunogenic" composition to one that "elicits immunologic memory and/or functional antibody with respect to each serotype of the vaccine, including serotype 3." Ex. 1082, ¶ 117.

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

Petitioner submits that, although the disclosure of the '060 Patent does not support an immunogenic composition with more than the 13 disclosed pneumococcal polysaccharide serotypes, the broadest reasonable interpretation of sole independent claim 1 is that it is open-ended with respect to the number "additional serotypes" that can be included. Ex. 1082, ¶ 118. The broadest reasonable interpretation of "wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional serotype, wherein the additional serotype is serotype 3" - which uses the open-ended phrases "comprise" and "at least" - is: "the serotypes must include at least serotypes 3, 4, 6B, 9V, 14, 18C, 19F and 23F." *Id*.

C. Claim 2

Petitioner submits that the broadest reasonable interpretation of claim 2 is "the immunogenic composition of claim 1, wherein the claimed polysaccharide-protein conjugates consist of 13 different pneumococcal polysaccharide-CRM_{197} conjugates, wherein the polysaccharide serotypes consist of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F." Ex. 1082, ¶ 119.

The above construction follows the plain and ordinary meaning of the claim language (which was present in the claims as filed in the '060 Patent and was not discussed during prosecution history). *Id*., ¶ 120. Claim 1 requires at least 8

pneumococcal polysaccharide-CRM_{197} conjugates with "different" serotypes - the 7 serotypes of Prevnar® and "at least one additional serotype" (that must include serotype 3). *Id*. Claim 2 specifies that the "additional serotypes consist of serotypes 1, 3, 5, 6A, 7F and 19A"; thus, Claim 2 is restricted to a 13-valent immunogenic CRM_{197}-conjugate vaccine with the 7 serotypes of Prevnar® and additional serotypes 1, 3, 5, 6A, 7F, and 19A. *Id*. The above construction is consistent with the 13vPnC composition, the only disclosed immunogenic composition (other than the prior art 7vPnC) in the '060 Patent. *Id*.

D. Claim 3

In co-pending PGR proceedings (PGR2017-00016 and -00017), Petitioner has asserted that claim 3 is invalid as indefinite. *See also* Ex. 1082, ¶ 121. However, to the extent the Board deems the claim amenable to construction, Petitioner submits that the claim must be limited to 13 conjugates prepared separately from the 13 recited serotypes. *Id.*

In claim 3, the recitation of serotypes that "consist essentially of" the 13 recited serotypes is irreconcilable with the earlier limitation that the claimed composition is exactly 13 conjugates. *Id*., ¶ 122. The claim plainly recites that "said polysaccharide-protein conjugates **consist of** 13 distinct polysaccharide-protein conjugates" (emphasis added), unequivocally limiting the number of conjugates to exactly 13. *Id*. Furthermore, each conjugate contains "a capsular

polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein," and the claim identifies the 13 specific serotypes of Patent Owner's 13vPnC composition. *Id*. The specification of the '060 Patent explains in no uncertain terms that the individual polysaccharide serotypes are conjugated to a carrier protein in separate processes:

> In the present invention, capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F of *Streptococcus pneumoniae*. **These pneumococcal conjugates are prepared by separate processes** and formulated into a single dosage formulation. . . . Once activated, **each capsular polysaccharide is separately conjugated to a carrier protein** to form a glycoconjugate.

Ex. 1001 at 7:59-8:5 (emphasis added). It follows that the claim must be limited to 13 conjugates with the recited 13 serotypes. Ex. 1082, ¶ 122.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. The Effective Filing Date of at Least Claims 1and 4-13 Is No Earlier than January 22, 2009

As detailed below, due to lack of enablement, claims 1 and 4-13 (and claims 2 and 3, depending on their construed scope) are not entitled to the benefit of the

filing date of either of the '060 Parent Apps.; instead, the effective filing date of those claims is no earlier than January 22, 2009.[5]

1. Legal Standard for Enablement

To satisfy the enablement requirement of pre-AIA § 112 ¶ 1, 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.

[5] A patent claim is entitled to the benefit of the filing date of an earlier filed application only if 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 pre-AIA 35 U.S.C. § 112 ¶ 1. *See, e.g.*, *Rackspace US, Inc. v. PersonalWeb Techs., LLC*, IPR2014-00058, Paper 10 at 18 (PTAB Apr. 15, 2014); *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008).

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).

2. 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. 1082, ¶ 128. 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*.

3. 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*., ¶ 129. 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*.

a. 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*., ¶ 130. 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. 1082, ¶ 133.

b. 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. *Id.*, ¶ 134. 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. 1082, ¶ 134. 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*.

c. 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 March 31, 2006). Ex. 1082, ¶ 135. 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. 1082, ¶ 136. 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. 1082, ¶ 136. 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. 1082, ¶ 137. 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. 1082, ¶ 137.

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*., ¶ 138; 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. 1082, ¶ 138; Ex. 1055; Ex. 1060 at 4-9.

d. 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. 1082, ¶ 139. 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. 1082, ¶ 140. 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** conjugate added to 13vPnC would be immunogenic. Ex. 1082, ¶ 140. 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.*

e. 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").

4. 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 no earlier than January 22, 2009. Ex. 1082, ¶ 141. 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*.

5. 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. *Id.*, ¶ 142. 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 no earlier than January 22, 2009 for the same reasons as set forth above with respect to claim 1. *Id*.

A. Claims 1-13 Are Invalid as Anticipated by the '380 Pub.

Years before the January 22, 2009 (or later) effective filing date of claims 1 and 4-13 (and claims 2 and 3, depending on their construed scope), Patent Owner published on October 12, 2006 a parent application of the '060 Patent, the '380 Pub., which discloses a 13-valent composition within the scope of those claims. Ex. 1018. Since the 13-valent composition (and only that composition) is enabled by the specification of the '060 Patent, the above claims are anticipated by the identical disclosure of that composition in the '380 Pub. Ex. 1082, ¶¶ 146-166.

1. Claim 1

a. "A multivalent immunogenic composition comprising"

The '380 Pub. discloses a 13-valent pneumococcal composition. *Id.*, ¶ 147. The disclosed composition is reported to be immunogenic, *i.e.*, it elicits functional antibody against each serotype of the vaccine. *Id.* Table 4 reports that immunization of rabbits with the 13-valent composition generated functional antibody, as assessed in an OPA assay, against each serotype of the vaccine:

> **Functional antibody** responses were also assessed in rabbits following immunization with the two 13vPnC formulations (Table 4). When comparing vaccine formulations with or without adjuvant, higher OPA GMTs were observed in the 13vPnC+$AlPO_4$ vaccine treatment group. OPA titers were detected in week 4 serum pools to **all vaccine serotypes** in both groups.

Ex. 1018 at [0228] (emphasis added).

b. "polysaccharide-protein conjugates"

The '380 Pub. discloses a 13-valent pneumococcal conjugate vaccine. *Id*. at [0005].

c. "and a physiologically acceptable vehicle,"

The '380 Pub. discloses that the 13-valent pneumococcal conjugate vaccine contains a physiologically acceptable vehicle. *Id*.

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

The '380 Pub. discloses that, for the disclosed 13-valent pneumococcal conjugate vaccine, "each of the conjugates contains a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein." *Id*.; *see also id*. at [0033].

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,"

The 13-valent pneumococcal conjugate vaccine disclosed in the '380 Pub. includes the polysaccharide serotypes recited in the claim. *Id*. at [0005].

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

The '380 Pub. discloses that, for the disclosed 13-valent pneumococcal conjugate vaccine, "the carrier protein is CRM_{197}." *Id*. at [0006].

2. Claim 2

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

The 13-valent pneumococcal conjugate vaccine disclosed in the '380 Pub. consists of the polysaccharide serotypes recited in the claim. *Id*.

3. Claim 3

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

The 13-valent pneumococcal conjugate vaccine disclosed in the '380 Pub. consists of the polysaccharide serotypes recited in the claim. *Id*. at [0005].

4. Claim 4

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

The 13-valent pneumococcal conjugate vaccine of the '380 Pub. is adjuvanted with aluminum phosphate. *Id*. at [0013].

5. Claim 5

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

The 13-valent pneumococcal conjugate vaccine of the '380 Pub. is adjuvanted with aluminum phosphate. *Id.*

6. 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 13-valent pneumococcal conjugate vaccine of the '380 Pub. is adjuvanted with aluminum phosphate. *Id.*

7. Claim 7

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

The 13-valent pneumococcal conjugate vaccine of the '380 Pub. is adjuvanted with aluminum phosphate. *Id.*

8. Claim 8

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

The '380 Pub. discloses that "[t]he compositions of this invention may further include one or more additional antigens for use against otitis media caused by infection with other bacteria. Such bacteria include nontypable *Haemophilus*

influenza, *Moraxella catarrhalis* (formerly known as *Branhamella catarrhalis*) and *Alloiococcus otitidis*." *Id*. at [0059].

9. Claim 9

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

The '380 Pub. discloses that "[t]he compositions of this invention may further include one or more additional antigens for use against otitis media caused by infection with other bacteria. Such bacteria include nontypable *Haemophilus influenza*, *Moraxella catarrhalis* (formerly known as *Branhamella catarrhalis*) and *Alloiococcus otitidis*." *Id*.

10. 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*."

The '380 Pub. discloses that "[t]he compositions of this invention may further include one or more additional antigens for use against otitis media caused by infection with other bacteria. Such bacteria include nontypable *Haemophilus influenza*, *Moraxella catarrhalis* (formerly known as *Branhamella catarrhalis*) and *Alloiococcus otitidis*." *Id*.

11. Claim 11

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

The '380 Pub. discloses that "[t]he compositions of this invention may also include one or more proteins from *Streptococcus pneumoniae*." *Id*. at [0063].

12. Claim 12

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

The '380 Pub. discloses that "[t]he compositions of this invention may further include one or more proteins from *Neisseria meningitidis* type B." *Id*. at [0064].

13. Claim 13

a. "The immunogenic composition of claim 1, wherein the composition is formulated as a single 0.5 ml dose comprising"

The '380 Pub. discloses that "[t]he present invention further provides that any of the immunogenic compositions administered is a single 0.5 mL dose." *Id*. at [0013].

b. "2.2 µg of each polysaccharide, except for 6B at 4.4 µg, and"

Example 16 of the '380 Pub. discloses "a dose of 2.2 µg of each PS [polysaccharide] (except 4.4 µg of 6B)." *Id*. at [0232].

c. "125 µg aluminum phosphate adjuvant."

Example 16 of the '380 Pub. discloses "$AlPO_4$ as the adjuvant at 125 µg/dose." *Id*.

X. CONCLUSION

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

Respectfully submitted,

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CLAIM LISTING APPENDIX

1. A multivalent immunogenic composition comprising polysaccharide-protein conjugates and a physiologically acceptable vehicle, wherein each of the conjugates comprises a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae* conjugated to a carrier protein, wherein the serotypes comprise 4, 6B, 9V, 14, 18C, 19F, 23F and at least one additional serotype, wherein the additional serotype is serotype 3, and wherein the carrier protein is CRM_{197}.

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

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

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

5. The immunogenic composition claim 4, wherein the adjuvant is an aluminum-based adjuvant.

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

7. The immunogenic composition of claim 6, wherein the adjuvant is aluminum phosphate.

8. The immunogenic composition of claim 1, wherein the composition further comprises one or more antigens.

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

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

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

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

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

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §42.24(d), the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,399,060 contains, as measured by the word processing system used to prepare this paper, 11,419 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: March 30, 2017

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,399,060, along with all exhibits and other supporting documents, was served on March 30, 2017, by FedEx overnight delivery at the following address:

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

which is the correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 9,399,060.

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