

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.
Petitioner

v.

WYETH LLC
Patent Owner

Case IPR2017-_____
U.S. Patent No. 8,895,024

PETITION FOR *INTER PARTES* REVIEW

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LIST OF EXHIBITS

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1001	U.S. Patent No. 8,895,024 to Hausdorff <i>et al.</i> ("the '024 Patent")
1002	[Reserved]
1003	[Reserved]
1004	Excerpts from the Prosecution History of US Patent Application No. 12/357,853 (the '024 Patent)
1005	Excerpts from the Prosecution History of US Patent Application No. 11/395,593
1006	US Provisional Application No. 60/669,605
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1009	Declaration of Dennis L. Kasper, M.D.
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I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner" or "Merck") hereby requests *inter partes* review ("IPR") of claims 1-11 of U.S. Patent No. 8,895,024 ("the '024 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. 1009), there is a reasonable likelihood that Petitioner will prevail in establishing by a preponderance of the evidence that: (1) the effective filing date of claims 1-5 is the actual filing date of the '024 Patent, January 22, 2009, and claims 1-5 are therefore anticipated by the prior art under pre-AIA § 102(b); and (2) even if each of claims 1-11 is entitled to an effective filing date of April 8, 2005, the claims would have been obvious under pre-AIA § 103.

Conjugates of bacterial polysaccharides (sugars) to carrier proteins are commonly-used components of vaccines against disease-causing bacteria. The '024 Patent describes a single vaccine composition ("13vPnC"), in which the polysaccharides are from 13 specific "serotypes" (*i.e.*, strains) of pneumococcus bacteria, and each polysaccharide is conjugated to a CRM₁₉₇ carrier protein. The two independent claims of the '024 Patent (claims 1 and 6) each require the 13 conjugates of 13vPnC. In claim 6, the pneumococcal serotypes are limited to (*i.e.*,

"consist of") the 13 serotypes of 13vPnC, whereas the serotypes in claim 1 "consist essentially of" the 13 serotypes of 13vPnC.

To obtain the claims of the '024 Patent over the prior art, Patent Owner emphasized that the specific 13vPnC composition is "immunogenic" - a limitation recited in each claim of the '024 Patent - with respect to each serotype of the composition. The '024 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 '024 Patent of conjugates made with any other pneumococcal serotypes.

Despite the limited disclosure of the '024 Patent, the broadest reasonable interpretation of the "consist essentially of" language of claim 1 allows for unspecified additional pneumococcal serotypes conjugated to CRM₁₉₇ that are immunogenic and do not materially affect the immunogenicity of the underlying 13-valent composition. This potentially captures countless immunogenic compositions that Patent Owner did not invent, disclose, or enable in any of the parent applications of the '024 Patent ("the '024 Parent Apps."), including a non-provisional application sharing the same disclosure as the '024 Patent, and an April 8, 2005 provisional application with only a subset of the disclosure. Based on the top 30 most prevalent serotypes alone, a vaccine with the 13 claimed serotypes and

up to 10 additional serotypes covers over 100,000 possible combinations. A person of ordinary skill in the art ("POSITA") as of the filing date of each of the '024 Parent Apps. (April 8, 2005 and March 31, 2006) 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 '024 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 '024 Patent, Patent Owner has consistently argued that immunogenicity was unexpected for a CRM₁₉₇-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 '024 Parent Apps. do not teach a POSITA how to produce immunogenic conjugates from serotypes with unknown

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).

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 '024 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 '024 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** conjugate 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 of the '024 Patent (for purposes of this IPR) is therefore the actual filing date of the '024 Patent, January 22, 2009. That same effective filing date likewise applies to dependent claims 2-5, 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 '024 Parent Apps. And, given the January 22, 2009 effective filing date, another member of the '024 Patent family - the '380 Pub.

(Ex. 1018) (published years earlier, in 2006) - is prior art that anticipates claims 1-5. The '380 Pub. shares the same disclosure as the '024 Patent of (1) a 13-valent immunogenic pneumococcal conjugate composition within the scope of claim 1, and (2) the adjuvant of dependent claims 2-5.

Even if the Board determines that claims 1-5 are enabled by the '024 Parent Apps. and entitled to an effective filing date of April 8, 2005, the prior art renders those open-ended claims of the '024 Patent obvious - as well as claims 6-11, which are limited to exactly the 13 serotypes of 13vPnC. To the extent the full scope of claim 1 (with unidentified serotypes added to 13vPnC) is somehow deemed enabled, a POSITA necessarily would have had a reasonable expectation of success in relation to 13vPnC of all the claims, *i.e.*, expanding Patent Owner's strongly-immunogenic 9-valent pneumococcal CRM₁₉₇-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). (A POSITA would likewise have had a reasonable expectation of success with respect to dependent claim 11, which merely recites an immunogenic response with respect to all 13 serotypes.) To the extent 13vPnC of all the claims is deemed nonobvious given Patent Owner's emphasis on purported concerns of immunogenicity of multivalent vaccines, then even higher-valency compositions

captured by claim 1 must not be enabled (and must be anticipated by the '380 Pub.).

Dependent claims 2-5 and 7-10 recite only the well-known use of an adjuvant with the claimed compositions, and at their narrowest (claims 5 and 10) recite aluminum phosphate. It would have been obvious to further boost immunogenicity of the claimed composition with aluminum phosphate adjuvant, especially since Patent Owner's 7-valent Prevnar[®] vaccine (described in the Prevnar 2001 reference, Ex. 1011) was adjuvanted with aluminum phosphate, and was reported to be safe and immunogenic.

Finally, any secondary considerations that Patent Owner may allege will not overcome the strong evidence of obviousness based on prior art. There is no nexus between any alleged commercial success of Patent Owner's purported commercial embodiment (Prevnar 13[®]) and the claimed compositions; it was the prior art 7-valent Prevnar[®] that was a commercial success, and Prevnar 13[®] is its obvious next iteration. Moreover, in distinguishing the claimed compositions over the prior art during prosecution, Patent Owner relied on the purported immunogenicity against serotype 3; and yet, studies have demonstrated that Prevnar 13[®] does not provide significant protection against serotype 3. (In any event, the prior art taught the use of serotype 3 in a multivalent CRM₁₉₇-conjugate vaccine.) And, any alleged commercial success of Prevnar 13[®] is not commensurate with the scope of at least

claims 1-5, which broadly cover virtually any multivalent immunogenic pneumococcal conjugate vaccine, which Patent Owner has not invented, disclosed or enabled, let alone practiced.

II. MANDATORY NOTICES

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

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

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

Petitioner has filed two Petitions for post grant review of Patent Owner's US Patent No. 9,399,060: PGR2017-00016 and PGR2017-00017. 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

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ernest.yakob@hoganlovells.com.

Petitioner consents to electronic service.

III. PAYMENT OF FEES (37 C.F.R. §§ 42.15(a), 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 certifies that the '024 Patent is available for IPR, and that Petitioner 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 1-11 of the '024 Patent, and respectfully submits that the claims are unpatentable based on the following grounds:

Ground 1. Claims 1-5 are unpatentable as anticipated by the '380 Pub. (Ex. 1018) under pre-AIA § 102(b).

Ground 2. Claims 1, 6 and 11 are unpatentable as obvious under pre-AIA § 103 over Huebner 2004 (Ex. 1016) in view of Hausdorff 2002 (Ex. 1017) and the general knowledge of a POSITA.

Ground 3. Claims 2-5 and 7-10 are unpatentable as obvious under pre-AIA § 103 over Huebner 2004 (Ex. 1016) in view of Hausdorff 2002 (Ex. 1017), Plevnar 2001 (Ex. 1011) and the general knowledge of a POSITA.

The above prior art references (including publication information) are 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 '024 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. 1009, ¶ 21. 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.*, ¶¶ 22-24.

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.*, ¶ 25 (citing Ex. 1020 at 18²).

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

particularly susceptible age group took place with bacterial proteins, *e.g.*, tetanus and diphtheria toxoids (inactivated toxins). Ex. 1009, ¶ 25 (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.*, ¶¶ 26-28 (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.*, ¶ 29. Numerous conjugate vaccines had been approved, including a vaccine against pneumococcus (Prevnar[®]). *Id.* (citing Ex. 1026 at 2; Ex. 1070; Ex. 1072; Ex. 1074; Ex. 1075 at 28, 38, 42; Ex. 1027 at 5-6; Ex. 1028 at 6). CRM₁₉₇ was commonly used as the carrier protein in many conjugate vaccines (*e.g.*, Vaxem HIB, HibTITER, Prevnar[®], Meningitec, Menjugate[®]). *Id.* (citing Ex. 1028 at 6; Ex. 1072; Ex. 1075 at 38, 42).

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.*, ¶ 32. 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

added by Petitioners at the bottom of each Exhibit (and designated "PTAB PAGE ___/___").

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.*, ¶ 33. 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.*, ¶ 38 (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 (Pevnar[®]) in 2000. *Id.* (citing Ex. 1033 at 3). Pevnar[®] was a 7-valent vaccine, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated to the CRM₁₉₇ carrier protein. *Id.*, ¶ 39 (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 Pevnar 13[®] in 2010. *Id.*, ¶ 35 (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.*, ¶¶ 36, 40 (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.*, ¶ 41 (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.*, ¶ 42. 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.*, ¶ 43. 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.*, ¶ 44.

Institutionally, there is also typically a preference for particular carrier proteins for which there is prior successful experience and know-how. *Id.*, ¶ 45. This is evidenced by Patent Owner's consistent usage of CRM₁₉₇ as the single carrier protein in its own development efforts with respect to pneumococcal and other vaccines. *Id.* The prior art 7-valent Prevnar[®] (using CRM₁₉₇ as the only carrier protein) was itself an expanded form of earlier lower-valency compositions using

CRM₁₉₇ as the only carrier protein. *Id.* (citing Ex. 1038 at 1). The next iteration was a prior art 9-valent vaccine, again using CRM₁₉₇ as the sole carrier protein. *Id.* (citing Ex. 1016 at 1; Ex. 1039 at 2). The prior art literature further indicated that Patent Owner was expanding its 9-valent pneumococcal conjugate vaccine to an 11-valent iteration with CRM₁₉₇ as the sole carrier protein. *Id.* (citing Ex. 1013 at 4; Ex. 1040 at 5).

Moreover, the literature as of April 8, 2005 indicated that CIES was not always observed when increasing the amount of a carrier protein; decreased antibody response due to CIES was not clinically relevant when other correlates of protection were still observed. *Id.*, ¶ 46. With respect to CRM₁₉₇, at least one study reported on the simultaneous administration of a 9-valent pneumococcal CRM₁₉₇-conjugate vaccine and a non-pneumococcal CRM₁₉₇-conjugate vaccine; the joint administration of a total of 45 µg of CRM₁₉₇ (more than double the 20 µg in Prevnar[®]) did not result in suppression. *Id.* (citing Ex. 1039 at 6-7). Similarly, co-administration of the 7-valent pneumococcal CRM₁₉₇-conjugate vaccine and a non-pneumococcal CRM₁₉₇-conjugate vaccine "produced no meaningful increase or reduction in the concentration of pneumococcal or other vaccine antibodies." *Id.* (citing Ex. 1013 at 6; Ex. 1041 at 5). And, in a study (sponsored by Patent Owner) that did observe suppression of pneumococcal antibody responses in connection with increased amounts of carrier protein in a 7-valent pneumococcal

CRM₁₉₇-conjugate vaccine, the authors concluded that "this may be clinically unimportant given that their [*i.e.*, the patients'] response to polysaccharide boosting suggested good priming [*i.e.*, memory]." *Id.* (citing Ex. 1042 at 8).

5. 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 '024 Patent (April 8, 2005), as top candidates for a multivalent pneumococcal conjugate vaccine. *Id.*, ¶ 47. 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.*, ¶ 48. 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.*, ¶ 50 (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 '024 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. Ex. 1009, ¶ 50 (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.*, ¶ 51. 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.*, ¶ 52. 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.*, ¶ 55. 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.*, ¶ 56. 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.*, ¶ 57 (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.*, ¶ 60.

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.*, ¶ 69. 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 '024 Parent 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.*, ¶ 70. 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.* (citing Ex. 1081). 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). Ex. 1009, ¶ 70. 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 '024 Patent

The '024 Patent contains two independent claims (1 and 6), both of which are generally directed to 13-valent immunogenic pneumococcal CRM₁₉₇-conjugate vaccines against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Although the serotypes of claim 6 are limited to (*i.e.*, "consist of") the above serotypes, the serotypes of claim 1 "consist essentially of" the above serotypes. Ex. 1001. Dependent claims 2-5 and 7-10 recite only the addition of adjuvant, with aluminum phosphate as the narrowest claim limitation. *Id.* Finally, dependent claim 11 recites that the 13-valent composition of claim 6 "elicits an opsonophagocytic antibody response to all 13 serotype capsular polysaccharides when administered to a subject." *Id.*

As discussed below, although the serotypes of independent claim 1 "consist essentially of," but are not necessarily limited to, serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, the '024 Patent specification discloses only a composition with those 13 serotypes (referred to in the specification as "13vPnC"). The '024 Patent provides no guidance with respect to a multivalent immunogenic composition with specific additional pneumococcal polysaccharide serotypes.

1. The '024 Patent Only Discloses Immunogenic Vaccines with the 13 Serotypes of 13vPnC

In contrast to the broad scope of claim 1, the specification of the '024 Patent discloses only an immunogenic composition with the 13 serotypes of 13vPnC. The

Abstract of the '024 Patent summarizes the narrowly-tailored disclosure of the '024 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 2:8-19. Of the ~32 columns in the '024 Patent disclosure (excluding references and claims), ~16 columns provide details for preparing conjugates of each of the 13 serotypes of 13vPnC (*id.* at 11:25-27:39), and ~5 columns are devoted to immunologic testing of 13vPnC (*id.* at 28:4-32:56). There is no corresponding disclosure for any other pneumococcal serotype.

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

Although each of the 13 disclosed CRM₁₉₇-conjugates are linked by reductive amination (*see, e.g., id.* at 8:7-10), the '024 Patent discloses activation and conjugation conditions that vary depending on the particular serotype's polysaccharide structure (*id.* at 11:25-27:39). By way of example, for any given serotype requiring hydrolysis, a different combination of reagent, reaction temperature and reaction time is required. *Id.* at 13:54-56, 16:41-44, 18:65-19:3, 24:9-12, 24:21-23, 24:27-29. And the '024 Patent further describes a variety of conjugation reaction conditions that likewise vary depending on a serotype's polysaccharide structure. *See* Ex. 1009, ¶¶ 78-80.

3. The Immunogenicity Studies of the '024 Patent Are Serotype-Specific and Limited to the 13 Disclosed Serotypes

The '024 Patent reports only 2 immunogenicity studies, both of which relate to 13vPnC; such results are serotype-specific. Ex. 1001 at 28:4-32:56. 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 AlPO₄ adjuvant to elicit vaccine serotype-specific immune responses." *Id.* at 28:19-21. 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 29:1-62.

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 CRM₁₉₇ protein." *Id.* at 29:65-30:34. 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 CRM₁₉₇." *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 31:1-32:56.

4. The Inventors of the '024 Patent Chose the 13 Serotypes of 13vPnC Based on Publicly Available Data

For the selection of the 13 serotypes of 13vPnC, the '024 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 '024 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 1:38-41. 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 1:63-2:1.

The '024 Patent acknowledges Patent Owner's prior development of a 9-valent vaccine, which was "7vPnC plus serotypes 1 and 5" (*id.* at 6:18-20), and cites to a 2002 publication (*id.* at 4:10-13), 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 '024 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 '024 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 4:55-5:24. For example, the data of Figure 1 of the '024 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 1:41-44.

D. Prosecution History of the '024 Patent

The '024 Patent was filed on January 22, 2009, 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 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 '024 Patent is listed as a continuation of the '593 App. Ex. 1004.

During prosecution of the '024 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 '024 Patent, as well as

CRM₁₉₇ as a carrier protein; according to the Examiner, there was nothing inventive about Patent Owner's choice of serotypes, nor the choice of CRM₁₉₇. Ex. 1004 at 440-443. To overcome the prior art, Patent Owner argued that it would not have been obvious to use CRM₁₉₇ as the single carrier for the claimed conjugates because: (1) unlike the claims of the '024 Patent, the particular GSK prior art that was cited by the Examiner did not disclose "commonly used carriers such as CRM₁₉₇" as 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 11 of the serotypes of claim 1) failed to "elicit an immunogenic response specific to serotype 3 polysaccharides." *Id.* at 462-467.

Patent Owner argued that the data of the '024 Patent demonstrates that "multivalent compositions of the present invention, which include serotype 3-CRM₁₉₇ conjugates, elicit substantial opsonophagocytic antibody responses to all polysaccharides present in the compositions, including serotype 3 polysaccharides, when present in specific combinations such as those recited in the instant claims." *Id.* at 465-466. In further support of the allegedly unexpected "robust immune response," Patent Owner cited more recent immunogenicity data with respect to the purported commercial embodiment, Prevnar 13[®]. *Id.* at 464. When the Examiner ultimately allowed the claims of the '024 Patent, she explained the following as her Reasons for Allowance:

The instant claims are specifically drawn to a 13 valent polysaccharide protein conjugate composition comprising polysaccharide from different *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. The language "consisting essentially of" in claim 1 requires the specific serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. However, the claim allows for adding other ingredients that do not materially affect the 13 valent polysaccharide-protein conjugate novel characteristics of the claimed invention.

Id. at 526.

E. Prior Art

1. The '380 Pub.

Ground 1 of 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 1-5 is 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 '024 Patent.

2. Huebner 2004

Grounds 2 and 3 rely on Huebner *et al.*, "Long-term antibody levels and booster responses in South African children immunized with nonavalent pneumococcal conjugate vaccine," *Vaccine* 22:2696-2700 (2004) ("Huebner

2004"). Ex. 1016. Because Huebner 2004 was published on February 19, 2004, more than one year prior to the earliest possible priority date of the '024 Patent (April 8, 2005), it is prior art under pre-AIA § 102(b).

Huebner 2004 presents immunogenicity data with respect to Patent Owner's next iteration of Prevnar[®], a 9-valent pneumococcal CRM₁₉₇-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.

3. Hausdorff 2002

Grounds 2 and 3 further rely on Hausdorff *et al.*, "Multinational study of pneumococcal serotypes causing acute otitis media in children," *Pediatr. Infect. Dis. J.* 21:1008-1016 (2002) ("Hausdorff 2002). Ex. 1017. Because Hausdorff 2002 was published in 2002, more than one year prior to the earliest possible priority date of the '024 Patent (April 8, 2005), it is prior art under pre-AIA § 102(b).

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

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

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

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

Id. at 2.

Two of the most frequently isolated pneumococcal serotypes were serotypes 6A and 19A, representing 7.3% and 6.6% of all datasets, respectively. *Id.* at 5.

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

4. Pevnar 2001

Ground 3 of this Petition further relies on the Pevnar[®] entry from the 2001 (55th Edition) Physicians' Desk Reference ("Pevnar 2001"). Ex. 1011. Because Pevnar 2001 was published on or before January 4, 2001 (*id.* at 9), more than one year prior to the earliest possible priority date of the '024 Patent (April 8, 2005), it is prior art under pre-AIA § 102(b).

"Pprevnar™, Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein), is a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM₁₉₇ protein." *Id.* at 2. With respect to dosing, "[e]ach 0.5 mL dose is formulated to contain: 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of serotype 6B per dose (16 µg total saccharide); approximately 20 µg of CRM₁₉₇ carrier protein; and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant." *Id.*

Pprevnar 2001 expressly discloses that "Pprevnar™ 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 Pprevnar® elicits immunologic memory and is protective with respect to each of its serotypes. *See, e.g.*, Ex. 1042 at 8; Ex. 1061 at 4.

VII. LEVEL OF ORDINARY SKILL IN THE ART

The claims of the '024 Patent are generally directed to multivalent immunogenic pneumococcal conjugate vaccines with 13 specific serotypes (the 7 serotypes of Pprevnar® and serotypes 1, 3, 5, 6A, 7F and 19A). Ex. 1009, ¶ 97.

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 scope of conjugates and serotypes captured by claim 1 requires construction. Because the '024 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).

³ 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 '024 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. 1009, ¶ 102.

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. *Id.* at ¶ 103; *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. 1009, ¶ 103; *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 '024 Patent and during prosecution, Patent Owner conceded that GSK had disclosed a prior art 11-valent pneumococcal conjugate vaccine ("11-Pn-PD"), in which 11 of the polysaccharide serotypes recited in claim 1 - including serotype 3 - were each conjugated to protein D carrier proteins. Ex. 1001 at 4:21-37; Ex. 1004 at 200, 465. Patent Owner repeatedly stressed the importance of immunogenicity. Ex. 1001 at 4:38-42; Ex. 1004 at 147-148, 200-201, 465-466. 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 '024 Patent allegedly overcame.⁴ Ex. 1009, ¶¶ 104-110.

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

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 4:21-27; Ex. 1004 at 147, 200-201, 465; *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 4:27-33; Ex. 1004 at 147, 201, 465; *see also* Ex. 1063 ("Except for serotype 3, opsonophagocytic anti-Pn GMTs were 4 to 50-fold higher in subjects who received 11-Pn-PD than in controls").

In purported contrast to the prior art, Patent Owner cited the data of the '024 Patent and stressed that "multivalent compositions of the present invention, which include serotype 3-CRM₁₉₇ conjugates, elicit substantial opsonophagocytic antibody responses to all polysaccharides present in the compositions, including serotype 3 polysaccharides, when present in specific combinations such as those

immunologic memory and functional antibody, as the baseline of acceptable immunogenicity. Ex. 1009, ¶ 105.

recited in the instant claims." Ex. 1004 at 465-466. In further support (*id.* at 464), 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).

Patent Owner also repeatedly emphasized that its "multivalent immunogenic composition" is immunogenic with respect to **each** of the polysaccharide serotypes of the composition. *See, e.g.*, Ex. 1004 at 201, 466 ("Importantly, applicants' multivalent immunogenic composition elicits antibody responses to serotype 3 polysaccharides while also eliciting antibody responses to the polysaccharides of the other twelve serotypes present in the multivalent composition . . ."); *id.* at 199 ("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.").

Given the disclosure in the '024 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. 1009, ¶ 112.

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

Independent claim 1 of the '024 Patent recites the following "multivalent immunogenic composition" (including the highlighted terms that require construction):

1. A multivalent immunogenic composition **comprising 13 distinct 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 consist essentially of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F**, and wherein the carrier protein is CRM₁₉₇.

Ex. 1001 (emphasis added). Petitioner submits that the broadest reasonable interpretation of the highlighted terms is "comprises 13 different pneumococcal polysaccharide-CRM₁₉₇ conjugates; wherein the polysaccharide serotypes comprise serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F; wherein

all conjugates (for both recited and unrecited serotypes) are immunogenic; and wherein conjugates featuring unrecited serotypes do not materially affect the immunogenicity with respect to the recited serotypes." Ex. 1009, ¶ 113.

The core composition that is claimed is the only one that is described in the specification of the '024 Patent, *i.e.*, a 13-valent pneumococcal CRM₁₉₇-conjugate vaccine with the 13 recited serotypes. *Id.*, ¶ 114. However, in reciting that the serotypes "consist essentially of" the recited serotypes, the claim is open to "other ingredients that do not materially affect the 13 valent polysaccharide-protein conjugate novel characteristics of the claimed invention." *See, e.g.*, Ex. 1004 at 526; *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998). In this case, the purportedly novel feature of the claimed 13-valent vaccine is that it is immunogenic, *i.e.*, it elicits immunologic memory and/or functional antibody with respect to each serotype of the vaccine, including serotype 3. Ex. 1009, ¶ 114.

Although (as discussed below) Petitioner submits that the "consist essentially of" language is not enabled, the broadest reasonable interpretation (for purposes of this proceeding only) allows for unspecified additional serotypes, so long as they do not materially affect the immunologic memory and/or functional antibody elicited by the 13-valent vaccine with respect to each serotype of that 13-valent vaccine, including serotype 3. *Id.*, ¶ 115.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. The Effective Filing Date of Claims 1-5 Is January 22, 2009

As detailed below, due to lack of enablement, claims 1-5 are not entitled to the benefit of the filing date of either of the '024 Parent Apps.; instead, the effective filing date of those claims is the actual filing date of the '024 Patent, 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:

⁵ The "effective filing date" of a patent claim 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 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).

(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).

2. Claim 1 of the '024 Patent is open-ended with respect to the number and identity of serotypes added to 13vPnC

Although nearly 100 pneumococcal serotypes had been identified as of the filing dates of the '024 Parent Apps., the broadest reasonable interpretation of open-ended claim 1 covers multivalent immunogenic compositions with any combination of serotypes added to 13vPnC, so long as each of the conjugates is immunogenic and the immunogenicity of 13vPnC is not materially affected. Ex. 1009, ¶ 120. Assuming a vaccine with the 13 claimed serotypes and up to 10 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 **1.7 x10¹²** possible combinations. *Id.* Even when choosing from the top 30 most prevalent serotypes, a vaccine with the 13 claimed serotypes and up to 10 additional serotypes covers over **100,000** possible combinations. *Id.*

3. The '024 Parent Apps. do not enable a POSITA to practice the full scope of independent claim 1 without undue experimentation

The '024 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 maintaining the immunogenicity against every serotype of the vaccine. *Id.*, ¶ 121. The '024 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 '024 Parent Apps. do not enable immunogenic compositions other than 13vPnC

The only immunogenic conjugates disclosed in the '024 Parent Apps. are those of 13vPnC. *Id.*, ¶ 122. 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 the '024 Patent itself - 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 '024

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 '024 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'8081, 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, 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 . . .") (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 CRM₁₉₇-conjugate vaccines; and the full scope of claim 1 (capturing approximately 100 serotypes) is not enabled by the disclosure of the '024 Parent Apps. Ex. 1009, ¶ 125.

b. Without knowledge of polysaccharide structure, undue experimentation is necessary to develop conjugation conditions for an immunogenic pneumococcal polysaccharide-CRM₁₉₇ conjugate

Knowledge of polysaccharide structure is critical for the development of an immunogenic polysaccharide-CRM₁₉₇ conjugate. *Id.*, ¶ 126. 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 CRM₁₉₇ depends on the number of

functional groups on the polysaccharide, as well as such groups' degree of susceptibility to conjugation. Ex. 1009, ¶ 126. 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 '024 Parent Apps.

Since claim 1 is open-ended and potentially covers any pneumococcal conjugate vaccine with **at least** the 13 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 '024 Parent Apps. (April 8, 2005 and March 31, 2006). *Id.*, ¶ 127. At that time, nearly 100 distinct pneumococcal serotypes had been identified, but the structures of at least 36 serotypes had not yet been reported: 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. Ex. 1055; Ex. 1060 at 4-9.

Many of the structurally uncharacterized serotypes were clinically relevant candidates for vaccines. Ex. 1009, ¶ 128. 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 '024 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. 1009, ¶ 128. 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 '024 Parent Apps., a POSITA would have understood that the universe of clinically relevant serotypes does not remain static. Ex. 1009, ¶ 129. 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. 1009, ¶ 129.

It was also understood in the art that wide immunization against particular serotypes could lead to "serotype replacement," *i.e.*, replacement of serotypes with serotypes not in the vaccine. *Id.*, ¶ 130; 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 (16F, 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. 1009, ¶ 130; Ex. 1055; Ex. 1060 at 4-9.

d. The '024 Parent Apps. have no enabling disclosure of reaction conditions necessary to construct immunogenic polysaccharide-CRM₁₉₇ conjugates for all additional serotypes covered by claim 1

Although a POSITA would have understood as of the filing dates of the '024 Parent Apps. that serotype candidates for a pneumococcal conjugate vaccine include serotypes with unknown polysaccharide structure, the '024 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. 1005 at 17 ("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. 1009, ¶ 131. 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 '024 Parent Apps. (which only describe 13vPnC) have no enabling disclosure of reaction conditions necessary to construct immunogenic polysaccharide-CRM₁₉₇ conjugates for all additional serotypes covered by claim 1. Ex. 1009, ¶ 132. Patent Owner has argued, in other proceedings challenging the validity of foreign counterparts of the '024 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. 1009, ¶ 132. 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 '024 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); *see 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 '024 Parent Apps. also do not enable claims 2-5, because those claims depend from claim 1, but do not restrict its open-endedness

For the same reasons given with respect to independent claim 1 above, the effective filing date of dependent claims 2-5 is also January 22, 2009, the actual filing date of the '024 Patent. Ex. 1009, ¶ 133. Claims 2-5 merely recite composition limitations with respect to adjuvant, but they do not narrow the scope of claim 1 to an embodiment(s) enabled by the disclosures of the '024 Parent Apps. *Id.*

B. Claims 1-5 Are Invalid as Anticipated by the '380 Pub.

Years before the January 22, 2009 effective filing date of claims 1-5 of the '024 Patent, Patent Owner published on October 12, 2006 a parent application of the '024 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 '024 Patent, claims 1-5 are anticipated by the identical disclosure of that composition in the '380 Pub. Ex. 1009, ¶¶ 154-164.

1. Claim 1

a. "A multivalent immunogenic composition comprising"

The '380 Pub. discloses a 13-valent pneumococcal composition. The disclosed composition is reported to be immunogenic, *i.e.*, it elicits functional antibody against each serotype of the vaccine. 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. Ex. 1018 at [0228].

b. "13 distinct 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 consist essentially of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and"**

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

- f. **"wherein the carrier protein is CRM₁₉₇."**

The '380 Pub. discloses that, for the disclosed 13-valent pneumococcal conjugate vaccine, "the carrier protein is CRM₁₉₇." *Id.* at [0006].

2. Claim 2

- 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].

3. Claim 3

- a. **"The immunogenic composition claim 2, wherein the adjuvant is an aluminum-based adjuvant."**

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

4. Claim 4

- a. **"The immunogenic composition of claim 3, 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.*

5. Claim 5

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

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

C. Claims 1, 6 and 11 Are Invalid as Obvious over Huebner 2004 in View of Hausdorff 2002 and the General Knowledge of a POSITA

Even if the Board determines that claims 1-5 are enabled by the '024 Parent Apps. and entitled to an effective filing date of April 8, 2005, the prior art renders those open-ended claims of the '024 Patent obvious - as well as claims 6-11, which are limited to exactly the 13 serotypes of 13vPnC. Ex. 1009, ¶ 165. To the extent the full scope of claim 1 (with unidentified serotypes added to 13vPnC) is somehow deemed enabled, a POSITA necessarily would have had a reasonable expectation of success in relation to 13vPnC of all the claims, *i.e.*, expanding Patent Owner's strongly-immunogenic 9-valent pneumococcal CRM₁₉₇-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). Ex. 1009, ¶ 166. A POSITA would likewise have had a reasonable expectation of success with respect to dependent claim 11, which merely recites an immunogenic response to all 13 serotype capsular polysaccharides. *Id.* To the extent 13vPnC of all the claims is deemed nonobvious

given Patent Owner's emphasis on purported concerns of immunogenicity of multivalent vaccines, then even higher-valency compositions captured by claim 1 must not be enabled (and must be anticipated by the '380 Pub.). *Id.*, ¶ 167.

1. Claim 1

a. "A multivalent immunogenic composition comprising"

Huebner 2004 (Ex. 1016) describes Patent Owner's prior art 9-valent pneumococcal CRM₁₉₇-conjugate vaccine that adds serotypes 1 and 5 to the 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) of Prevnar[®], and demonstrates that the vaccine is immunogenic, as it elicits immunologic memory. Ex. 1009, ¶ 168; Ex. 1016 at 4 ("In conclusion, the nonavalent pneumococcal conjugate vaccine given at 6, 10, and 14 weeks of age elicits significant and long-lasting antibody responses [*i.e.*, memory] which can be boosted with either the conjugate or polysaccharide vaccine.").

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

7-valent pneumococcal conjugate vaccine formulation, containing serotypes 4, 6B, 9V, 14, 18C, 19F, 23F (PCV-7); 9-valent

pneumococcal conjugate vaccine formulation, containing PCV-7 serotypes plus 1 and 5 (PCV-9); 11-valent pneumococcal conjugate vaccine formulation, containing PCV-9 serotypes plus 3 and 7F (PCV-11).

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

b. "13 distinct polysaccharide-protein conjugates"

A POSITA would have been motivated (with a reasonable expectation of success) to expand the well-known immunogenic 9-valent pneumococcal CRM₁₉₇-conjugate composition of Huebner 2004 (with serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F) to the claimed 13 distinct conjugates, in view of Hausdorff 2002; Hausdorff 2002 discloses an 11-valent pneumococcal conjugate vaccine (adding serotypes 3 and 7F) and identifies serotypes 6A and 19A as the only other "major serotypes" in terms of prevalence. Ex. 1009, ¶ 170.

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 CRM₁₉₇ as the single carrier. *Id.*, ¶ 171 (citing 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 claimed serotypes. *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. 1009, ¶ 171 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. 1009, ¶ 172. In fact, the '024 Patent itself cites to numerous prior art publications showing that any such cross-protection is limited. Ex. 1001 at 4:55-5:24; Ex. 1035 at 1; Ex. 1061 at 5.

c. "and a physiologically acceptable vehicle,"

The disclosed vaccine in both Huebner 2004 and Hausdorff 2002 include a physiologically acceptable vehicle. Ex. 1009, ¶ 173. As an initial matter, the '024 Patent discloses that "[e]xamples of [physiologically acceptable] vehicles include, but are not limited to, water, buffered saline, polyols (e.g., glycerol, propylene glycol, liquid polyethylene glycol) and dextrose solutions." Ex. 1001 at 8:59-62.

A POSITA would have understood that the vaccines of Huebner 2004 and Hausdorff 2002 are injected intramuscularly, and so, they were provided in a physiologically acceptable vehicle such as water or buffered saline. Ex. 1009, ¶ 173.

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

The conjugates of both Huebner 2004 and Hausdorff 2002 are prepared individually, each with a capsular polysaccharide from a different serotype of *Streptococcus pneumoniae*. *Id.*, ¶ 174. It was well-known that conjugates of distinct serotypes are prepared individually to ensure inclusion of accurate amounts of each polysaccharide and more reproducible polysaccharide to protein ratios in each conjugate. *Id.* Indeed, the underlying 7-valent Prevnar[®] vaccine was "a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F **individually conjugated** to diphtheria CRM₁₉₇ protein." Ex. 1011 at 2 (emphasis added); *see also id.* ("The individual glycoconjugates are compounded to formulate the vaccine, Prevnar[™].").

e. "wherein the serotypes consist essentially of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and"

As discussed above with respect to the 13 claimed conjugates, a POSITA would have been motivated (with a reasonable expectation of success) to expand the well-known immunogenic 9-valent pneumococcal CRM₁₉₇-conjugate composition of Huebner 2004 (with serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F) to the 13 claimed serotypes, in view of Hausdorff 2002. Hausdorff 2002 discloses an 11-valent pneumococcal conjugate vaccine (adding serotypes 3 and 7F) and identifies serotypes 6A and 9A as the only other "major serotypes" in terms of prevalence; in doing so, Hausdorff provides the motivation to develop a 13-valent conjugate vaccine with the claimed serotypes. Ex. 1017 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. 1009, ¶ 175 and other references disclosing the 13 serotypes of 13vPnC: Ex. 1035 at 1; Ex. 1036 at 3.

f. "wherein the carrier protein is CRM₁₉₇."

When expanding the 9-valent iteration of Prevnar[®] to a 13-valent version, it would have been obvious to continue the successful use of CRM₁₉₇ carrier protein. Ex. 1009, ¶ 176. CRM₁₉₇ 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 CRM₁₉₇-conjugate vaccine would be immunogenic as well. Ex. 1009, ¶ 177. Again, Patent Owner was already reported to have been developing an 11-valent pneumococcal CRM₁₉₇-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, at least one study discloses 8-valent immunogenic pneumococcal conjugate vaccines that include serotype 3 and only a single carrier protein (either diphtheria or tetanus toxoid). Ex. 1012 at 2, 4, 6; *see* Ex. 1009, ¶ 177.

Reports of CIES as of April 8, 2005 would not have deterred a POSITA from pursuing a 13-valent conjugate vaccine with CRM₁₉₇ as the single carrier protein. Ex. 1009, ¶ 178. 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. 1009, ¶ 178.)

2. Claim 6

- a. **"A 13-valent immunogenic composition comprising 13 distinct 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 consist of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and wherein the carrier protein is CRM₁₉₇."**

Claim 6 is limited to only a 13-valent CRM₁₉₇-conjugate vaccine; otherwise, the language of claims 1 and 6 are identical. For the same reasons provided above with respect to claim 1, a POSITA would have been motivated (with a reasonable expectation of success) to expand the well-known immunogenic 9-valent pneumococcal CRM₁₉₇-conjugate composition of Huebner 2004 to the 13 claimed serotypes, in view of Hausdorff 2002. *Id.*, ¶ 179. And, it would have been obvious to use the same safe and effective CRM₁₉₇ carrier protein used in Huebner 2004 and the previous lower-valency iterations (including the licensed 7-valent Prevnar[®]). *Id.*

3. Claim 11

- a. **"The immunogenic composition of claim 6, whereby the immunogenic composition elicits an opsonophagocytic antibody response to all 13 serotype capsular polysaccharides when administered to a subject."**

As explained with respect to claim 1, 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 CRM₁₉₇-conjugate vaccine would be immunogenic as well. Ex. 1009, ¶ 180. This would include an expectation that the claimed 13-valent CRM₁₉₇-conjugate vaccine would elicit "an opsonophagocytic antibody response to all 13 serotype capsular polysaccharides," *i.e.*, functional antibody. *Id.*

D. Claims 2-5 and 7-10 Are Invalid as Obvious over Huebner 2004 in View of Hausdorff 2002, Prevnar 2001 and the General Knowledge of a POSITA

As discussed above, the immunogenic composition of independent claims 1 and 6 would have been obvious over Patent Owner's 9-valent pneumococcal CRM₁₉₇-conjugate vaccine of Huebner 2004 in view of Hausdorff 2004 and the general knowledge of a POSITA. *Id.*, ¶ 181. Dependent claims 2-5 and 7-10 recite only the well-known use of an adjuvant with the claimed compositions, and at their narrowest (claims 5 and 10) recite aluminum phosphate. It would have been obvious to further boost immunogenicity with aluminum phosphate adjuvant,

especially since the underlying 7-valent Prevnar[®] vaccine was adjuvanted with aluminum phosphate and was reported to be safe and immunogenic. *Id.*

1. Claim 2

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

A POSITA would have had a reasonable expectation of success in using adjuvants, such as aluminum phosphate, in the claimed 13-valent composition to boost immunogenicity. *Id.*, ¶ 182. There is nothing inventive about the use of adjuvants to boost the immunogenicity of conjugate vaccines, and aluminum phosphate is one of the most-commonly used adjuvants in conjugate vaccines. *Id.* Indeed, Prevnar 2001 discloses the use of aluminum phosphate as an adjuvant for the underlying 7-valent pneumococcal CRM₁₉₇-conjugate vaccine. Ex. 1011 at 2 ("0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant").

2. Claim 3

a. "The immunogenic composition of claim 2, wherein the adjuvant is an aluminum-based adjuvant."

For the same reasons given above with respect to claim 2, it would have been obvious to include the claimed adjuvant in the claimed 13-valent pneumococcal conjugate vaccine. Ex. 1009, ¶ 183.

3. Claim 4

- a. "The immunogenic composition of claim 3, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide."**

For the same reasons given above with respect to claim 2, it would have been obvious to include the claimed adjuvant in the claimed 13-valent pneumococcal conjugate vaccine. *Id.*, ¶ 184.

4. Claim 5

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

For the same reasons given above with respect to claim 2, it would have been obvious to include the claimed adjuvant in the claimed 13-valent pneumococcal conjugate vaccine. *Id.*, ¶ 185.

5. Claim 7

- a. "The immunogenic composition of claim 6, further comprising an adjuvant."**

For the same reasons given above with respect to claim 2, it would have been obvious to include the claimed adjuvant in the claimed 13-valent pneumococcal conjugate vaccine. *Id.*, ¶ 186.

6. Claim 8

- a. "The immunogenic composition of claim 7, wherein the adjuvant is an aluminum-based adjuvant."**

For the same reasons given above with respect to claim 2, it would have been obvious to include the claimed adjuvant in the claimed 13-valent pneumococcal conjugate vaccine. *Id.*, ¶ 187.

7. Claim 9

- a. "The immunogenic composition of claim 8, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide."**

For the same reasons given above with respect to claim 2, it would have been obvious to include the claimed adjuvant in the claimed 13-valent pneumococcal conjugate vaccine. *Id.*, ¶ 188.

8. Claim 10

- a. "The immunogenic composition of claim 9, wherein the adjuvant is aluminum phosphate."**

For the same reasons given above with respect to claim 2, it would have been obvious to include the claimed adjuvant in the claimed 13-valent pneumococcal conjugate vaccine. *Id.*, ¶ 189.

E. Secondary Considerations

To the extent Patent Owner argues that secondary considerations support a finding of non-obviousness with respect to the challenged claims, Petitioner reserves the right to address any such arguments in Petitioner's Reply. However,

any secondary considerations that Patent Owner may allege will not overcome the strong evidence of obviousness based on prior art. *Id.*, ¶ 190.

There is no nexus between any alleged commercial success of Patent Owner's purported commercial embodiment (Pevnar 13[®]) and the claimed compositions; it was the prior art 7-valent Pevnar[®] that was a commercial success, and Pevnar 13[®] is its obvious next iteration. *Id.*, ¶ 191. 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 Pevnar 13[®] does not provide significant protection against serotype 3. *Id.*, ¶ 192; *see, e.g.*, Ex. 1077 at 1; Ex. 1078 at 1. (In any event, the prior art taught the use of serotype 3 in a multivalent CRM₁₉₇-conjugate vaccine. Ex. 1009, ¶ 192; *see, e.g.*, Ex. 1013 at 4.) Finally, any alleged commercial success of Pevnar 13[®] is not commensurate with the scope of at least claims 1-5, which broadly cover virtually any multivalent immunogenic pneumococcal conjugate vaccine, which Patent Owner has not invented, disclosed or enabled, let alone practiced. Ex. 1009, ¶ 193.

X. CONCLUSION

Petitioner respectfully submits that it has established a reasonable likelihood that it will prevail as to the obviousness of claims 1-11 of the '024 Patent.

Petitioner respectfully requests that this Petition be granted, *inter partes* review be instituted, and claims 1-11 of the '024 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: March 29, 2017

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CLAIM LISTING APPENDIX

1. A multivalent immunogenic composition comprising 13 distinct 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 consist essentially of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and wherein the carrier protein is CRM₁₉₇.

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

3. The immunogenic composition of claim 2, wherein the adjuvant is an aluminum-based adjuvant.

4. The immunogenic composition of claim 3, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide.

5. The immunogenic composition of claim 4, wherein the adjuvant is aluminum phosphate.

6. A 13-valent immunogenic composition comprising 13 distinct 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 consist of 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and wherein the carrier protein is CRM₁₉₇.
7. The immunogenic composition of claim 6, further comprising an adjuvant.
8. The immunogenic composition of claim 7, wherein the adjuvant is an aluminum-based adjuvant.
9. The immunogenic composition of claim 8, wherein the adjuvant is selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide.
10. The immunogenic composition of claim 9, wherein the adjuvant is aluminum phosphate.

11. The immunogenic composition of claim 6, whereby the immunogenic composition elicits an opsonophagocytic antibody response to all 13 serotype capsular polysaccharides when administered to a subject.

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. 8,895,024 contains, as measured by the word processing system used to prepare this paper, 13,969 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: March 29, 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. 8,895,024, along with all exhibits and other supporting documents, was served on March 29, 2017, by FedEx overnight delivery at the following address:

Pfizer Inc.
Attn: Legal Patent Department, Chief IP Counsel
235 East 42nd Street
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which is the correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,895,024.

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