UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME CORP.
Petitioner

v.

PFIZER INC.
Patent Owner

_____

Case IPR2017-_____
U.S. Patent No. 9,492,559

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PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner" or "Merck") hereby requests *inter partes* review ("IPR") of claims 11-15 and 20-37 of U.S. Patent No. 9,492,559 ("the '559 Patent") (Ex. 1001), a post-AIA patent assigned to Pfizer Inc. ("Patent Owner" or "Pfizer"). 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. 1087), there is a reasonable likelihood that Petitioner will prevail in establishing that claims 11-15 and 20-37 are unpatentable as obvious over the prior art.

Conjugates of polysaccharides (sugars) to carrier proteins are commonly-used components of vaccines against disease-causing bacteria. To create such "glycoconjugates" or "polysaccharide-protein conjugates," the polysaccharide is isolated from a particular "serotype" (*i.e.*, strain) of the disease-causing bacteria; that polysaccharide is then attached to a carrier protein (such as CRM_{197}) for enhanced immune response against the bacterial polysaccharide.

All challenged claims in this Petition depend from sole independent claim 1 of the '559 Patent, which recites an "immunogenic composition" that includes "a *Streptococcus pneumoniae* serotype 22F glycoconjugate." A co-pending Petition makes clear that there is nothing inventive to claim 1. Patent Owner had originally

sought claims that would have captured **any and all** immunogenic compositions featuring a pneumococcal serotype 22F conjugate. But, because serotype 22F conjugates were well-known and taught by prior art cited during prosecution, Patent Owner distinguished its immunogenic serotype 22F conjugate based on two features: (1) a polysaccharide to protein ratio "between 0.4 and 2," and (2) a molecular weight "between 1000 kDa and 12,500 kDa." And yet, as made abundantly clear by prior art authored by two of Patent Owner's major vaccine competitors, Merck and GlaxoSmithKline ("GSK"), there is no novelty to that claimed serotype 22F conjugate. The two recited features of claim 1 (ratio and molecular weight) are nothing more than typical attributes of immunogenic conjugates, constructed with routine conjugation chemistry disclosed in the '559 Patent. There is no merit to Patent Owner's assertions that (1) it "found that this combination" of ratio and molecular weight "produced" an immunogenic serotype 22F conjugate, or (2) its immunogenic serotype 22F conjugate is distinguishable over the prior art based on the "particular combination" of ratio and molecular weight recited in claim 1.

Merck 2011 (Ex. 1006) is the primary prior art reference of this Petition. It discloses serotype 22F conjugates that are immunogenic and with polysaccharide to protein ratios in the claimed range. The only claim limitation not specifically addressed in Merck 2011: the molecular weight of the serotype 22F conjugate. But

based on the prior art teachings of a pneumococcal conjugate vaccine manufacturer, namely GSK, it would have been obvious to achieve a serotype 22F conjugate satisfying that third, molecular weight requirement of sole independent claim 1.

The prior art combination of Merck 2011 and GSK 2008 (Ex. 1007) (hereinafter "Merck 2011/GSK 2008") renders obvious the vast majority of the challenged claims. Both Merck 2011 and GSK 2008 disclose immunogenic pneumococcal conjugate vaccines containing serotype 22F, and a POSITA would have considered both references - from two major vaccine companies - in combination for the development of such vaccines. Notably, both Merck 2011 and GSK 2008 disclose the claimed range of polysaccharide to protein ratios (0.4 to 2), consistent with a POSITA's general understanding that such ratios are typical for immunogenic conjugates.

Based on the disclosure of GSK 2008, it would have been obvious to construct the serotype 22F conjugates of Merck 2011/GSK 2008 with a molecular weight falling within claim 1's vast range (1,000 to 12,500 kDa). Although GSK 2008 does not expressly disclose the molecular weight of its immunogenic serotype 22F conjugates, it discloses the molecular weights of 10 other pneumococcal conjugates featured in a 10-valent conjugate vaccine composition; each of those disclosed molecular weights falls within the broad range of claim 1.

Since routine conjugation techniques and conditions readily achieved those disclosed molecular weights (as well as polysaccharide to protein ratios falling within the claimed range), a POSITA would have understood such molecular weights to be typical of immunogenic conjugates. And GSK 2008 expressly teaches adding a serotype 22F conjugate to that 10-valent pneumococcal conjugate vaccine. Given that disclosure by a leading vaccine company, a POSITA would have been motivated with a reasonable expectation of success to design an immunogenic serotype 22F conjugate in accordance with GSK 2008's disclosure.

Like sole independent claim 1, the challenged claims that depend from claim 1 do not reflect anything inventive over the prior art. Dependent claims 11-14, 23-33, and 35-37 recite a bevy of well-known features and applications of the immunogenic composition of claim 1, each of which is disclosed in Merck 2011 and/or GSK 2008. The remaining dependent claims are likewise directed to standard features and applications of the immunogenic composition of claim 1, which would have been obvious based on the teachings of the following prior art references: the '787 Patent (Ex. 1010) (claim 15, siliconized or glass syringe), Obaro 2002 (Ex. 1040) (claims 20-21, combination with certain non-pneumococcal antigens), Sigurdardottir 2008 (Ex. 1011) (claim 22, combination with a meningococcal conjugate), and MMWR 2012 (Ex. 1012) (claim 34, use in immunocompromised patients).

II. MANDATORY NOTICES

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

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

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

Petitioner is concurrently filing three additional Petitions for IPR of the '559 Patent on other grounds and/or addressing other patent claims.

Three IPRs, filed by Petitioner, have been instituted with respect to Patent Owner's US Patent No. 8,562,999: IPR2017-00378, IPR2017-00380 and IPR2017-00390.

Petitioner has filed two Petitions for post grant review ("PGR"), and three Petitions for IPR, of Patent Owner's US Patent No. 9,399,060: PGR2017-00016, PGR2017-00017, IPR2017-01211, IPR2017-01215 and IPR2017-01223. Petitioner has filed a Petition for IPR of Patent Owner's US Patent No. 8,895,024: IPR2017-01194.

Petitioner is unaware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding.

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

Lead counsel is Arlene L. Chow (Reg. No. 47,489), Hogan Lovells US LLP, 875 Third Avenue, New York, NY 10022, Phone: 212-918-3000, Fax: 212-918-

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

Petitioner consents to electronic service.

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

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

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

Petitioner certifies that the '559 Patent is available for IPR. The earliest possible effective filing date of the '559 Patent is January 21, 2014, after the March 16, 2013 effective date of the AIA first inventor to file provisions. AIA § 3(n)(1). This Petition is timely, as the '559 Patent issued November 15, 2016, and the present Petition is being filed more than nine months after the issuance of the patent. 37 C.F.R. § 42.102(a)(1). Finally, Petitioner certifies that it is not barred or estopped from requesting review on the grounds identified in this Petition.

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

Petitioner challenges claims 11-15 and 20-37 of the '559 Patent, and respectfully submits that the claims are unpatentable based on the following grounds:

Ground 1. Claims 11-14, 23-33, and 35-37 are unpatentable as obvious under post-AIA § 103 over Merck 2011 (Ex. 1006) in view of GSK 2008 (Ex. 1007) and the general knowledge of a POSITA.

Ground 2. Claim 15 is unpatentable as obvious under post-AIA § 103 over Merck 2011 (Ex. 1006) in view of GSK 2008 (Ex. 1007), the '787 Patent (Ex. 1010) and the general knowledge of a POSITA.

Ground 3. Claims 20-21 are unpatentable as obvious under post-AIA § 103 over Merck 2011 (Ex. 1006) in view of GSK 2008 (Ex. 1007), Obaro 2002 (Ex. 1040) and the general knowledge of a POSITA.

Ground 4. Claim 22 is unpatentable as obvious under post-AIA § 103 over Merck 2011 (Ex. 1006) in view of GSK 2008 (Ex. 1007), Sigurdardottir 2008 (Ex. 1011) and the general knowledge of a POSITA.

Ground 5. Claim 34 is unpatentable as obvious under post-AIA § 103 over Merck 2011 (Ex. 1006) in view of GSK 2008 (Ex. 1007), MMWR 2012 (Ex. 1012) and the general knowledge of a POSITA.

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

VI. BACKGROUND

A. State of the Art as of the Earliest Possible Priority Date of the '559 Patent, January 21, 2014

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. 1087, ¶ 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 (citing Ex. 1041 at 2).

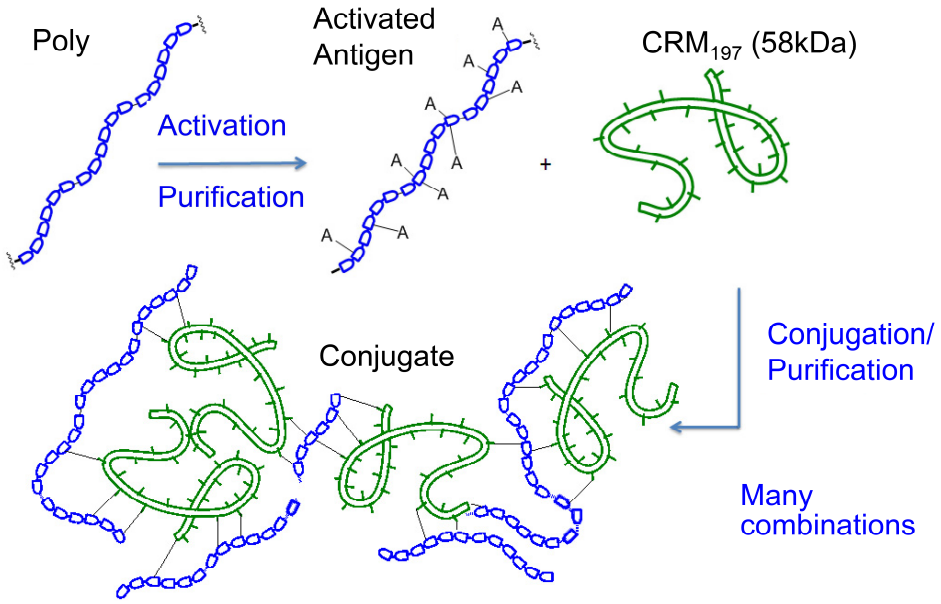
Despite the successful use of bacterial polysaccharides to immunize adults and older children, polysaccharides were not very immunogenic in children under 2 years of age. *Id*., ¶ 25 (citing Ex. 1042 at 18[1]). Successful immunization of that particularly susceptible age group took place with bacterial proteins, *e.g.*, tetanus and diphtheria toxoids (inactivated toxins). *Id*. (citing Ex. 1043 at 6-7). Through

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

conjugation to such proteins ("carrier proteins"), a robust antibody-mediated response against the polysaccharides can be achieved in very young children. *Id*., ¶¶ 26-28 (citing Ex. 1044; Ex. 1045; Ex. 1046 at 17-19; Ex. 1047). Polysaccharide-protein conjugate vaccines had been commercialized for nearly three decades before January 21, 2014. *Id*., ¶ 29 (citing Ex. 1048 at 2; Ex. 1054 at 2). Numerous conjugate vaccines had been approved, including three vaccines against pneumococcus (Prevnar®, Prevnar 13®, Synflorix®). *Id*. (citing Ex. 1049; Ex. 1050; Ex. 1051; Ex. 1052; Ex. 1055; Ex. 1056; Ex. 1057; Ex. 1058; Ex. 1059; Ex. 1061; Ex. 1062); *see also id*., ¶¶ 30-31 (citing Ex. 1063; Ex. 1064; Ex. 1065).

2. Cross-linking of Polysaccharide-Protein Conjugates

Common chemistries for preparing polysaccharide-protein conjugates are based on "reductive amination" or "CDAP." *Id*., ¶ 32. Either chemistry can be used to link multiple sites of the polysaccharide to multiple sites of the carrier protein; such cross-linking forms a high molecular weight "lattice" containing multiple polysaccharides and carrier proteins, as illustrated by the diagram below for a CRM_{197} conjugate:



Id., ¶¶ 33-35 (citing Ex. 1008 at 20; Ex. 1035 at 5-8; Ex. 1066 at 32). Both reductive amination and CDAP have been used to construct immunogenic conjugates, including in licensed pneumococcal vaccines. *Id.*, ¶ 36 (citing Ex. 1055 at 2 (Prevnar®); Ex. 1058 at 6 (Prevnar 13®); Ex. 1059 at 12 (Synflorix®)). As of January 21, 2014, it was well-known in the art that "[t]he degree of crosslinking and overall size of the network or lattice can be regulated by routine variation of the conditions of the conjugation reaction." *Id.*, ¶ 37 (citing Ex. 1030 at 4:56-59; Ex. 1032 at 11-12 ("The properties that may be controlled include . . . selecting the degree of crosslinking of the construct (to obtain variations of size) . . .")).

3. Multivalent Polysaccharide-Protein Conjugate Vaccines

Strains of a species of extracellular bacteria, called "serotypes" or "serogroups," are characterized by the particular polysaccharides displayed on their surface. *Id.*, ¶ 38. In general, antibodies are serotype-specific, recognizing the specific structure of a polysaccharide; antibodies against a polysaccharide from one serotype are generally not cross-protective against structurally-unrelated serotypes. *Id.* Because of this lack of cross-protection, vaccines are frequently multivalent, *i.e.*, they include polysaccharides from more than one serotype. *Id.* (citing Ex. 1067 at 1).

There is a natural progression in the development of multivalent vaccines. *Id.*, ¶ 39. The earliest version utilizes the most prevalent polysaccharide serotypes. *Id.* Over time, later vaccine versions incorporate additional clinically-relevant serotypes for broader protection. *Id.* ¶¶ 39-41 (citing, *e.g.*, replacement of 14-valent Pneumovax® with 23-valent Pneumovax® 23 (Ex. 1053; Ex. 1054)). With respect to pneumococcal conjugate vaccines, Prevnar® was a 7-valent vaccine, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated to the CRM_{197} carrier protein. *Id.*, ¶ 42. The next licensed iteration of Prevnar® was a 13-valent CRM_{197} conjugate vaccine (Prevnar 13®), adding serotypes 1, 3, 5, 6A, 7F and 19A to the 7 serotypes of Prevnar®. *Id.* (citing Ex. 1068 (English translation of Ex. 1069) at 8; Ex. 1058).

4. Progression of Multivalent Pneumococcal Conjugate Vaccines to Include Prevalent/Emerging Serotypes

Multivalent pneumococcal conjugate vaccines (Patent Owner's Prevnar® and Prevnar 13®, and GSK's Synflorix®) had been licensed for years before the earliest possible priority date of the '559 Patent (January 21, 2014). *Id*., ¶ 43 (citing Ex. 1055; Ex. 1058; Ex. 1059 at 5). 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*., ¶¶ 43-45 (citing Ex. 1070; Ex. 1071; Ex. 1072; Ex. 1073; Ex. 1074; Ex. 1075; Ex. 1076; Ex. 1077). At least the following non-Prevnar®, non-Prevnar 13®, and non-Synflorix® serotypes had been reported in the literature as of January 21, 2014 to be prevalent and/or emerging, depending on patient demographics: 2, 8, 9A, 9V, 9N, 10A, 11A, 12A, 12F, 13, 15A, 15B, 15C, 16, 17F, 20, 21, 22F, 23B, 24F, 25, 31, 33F, 45 and 46. *Id*., ¶ 46 (citing Ex. 1078 at 11; Ex. 1079 at 1; Ex. 1074 at 1; Ex. 1080 at 1; Ex. 1081 at 1; Ex. 1073 at 1; Ex. 1031 at 2). Such serotypes were natural candidates for later iterations of multivalent vaccines. *Id*.

5. Immunogenicity of Multivalent Polysaccharide-Protein Conjugate Vaccines

The characteristics of the immune response elicited by a vaccine reflect the likelihood that the vaccine will be successful at preventing disease. *Id*., ¶ 47. For

example, 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.* (citing Ex. 1033 at 1-2). A common assay for evaluating whether and to what degree functional antibody is elicited after immunization is an opsonophagocytic activity ("OPA") assay. *Id.*

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.*, ¶ 48 (citing Ex. 1033 at 1).

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.*, ¶ 49 (citing Ex. 1033 at 3-5).

B. The '559 Patent

The '559 Patent is generally directed to immunogenic compositions that include "at least one glycoconjugate from a *S. pneumoniae* serotype not found in PREVNAR®, SYNFLORIX® and/or PREVNAR 13®." Ex. 1001 at Abstract. The rationale is to broaden coverage of the conjugate vaccines and to account for disease by emerging pneumococcal serotypes:

> [T]here is a need to address remaining unmet medical need for coverage of pneumococcal disease due to serotypes not found in PREVNAR 13® and potential for serotype replacement over time. The specific serotypes causing disease beyond the 13 in PREVNAR 13® vary by region, population, and may change over time due to acquisition of antibiotic resistance, pneumococcal vaccine introduction and secular trends of unknown origin.

Id. at 2:3-10.

Sole independent claim 1 broadly covers any immunogenic composition that includes a pneumococcal serotype 22F conjugate, as long as the conjugate has a molecular weight and polysaccharide to protein ratio within a wide range of possible values:

> 1. An immunogenic composition comprising a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2.

Id. at 141:27-33.

Example 13 of the '559 Patent recites standard reductive amination chemistry for the "Preparation of Serotype 22F Polysaccharide-CRM_{197} Conjugate." *Id*. at 114:21-116:11. The disclosed reductive amination chemistry is routine in the art, and the '559 Patent does not purport to employ anything other

than routine chemistry to obtain the disclosed conjugates. Ex. 1087, ¶ 52. Table 16 reports the properties of various serotype 22F conjugates, including wide-ranging molecular weights and polysaccharide to protein ratios. Ex. 1001 at 116:22-49. Tables 17 and 18 report the results of immunogenicity testing in OPA assays; every tested serotype 22F conjugate was immunogenic, *i.e.*, each conjugate "elicited OPA titers [*i.e.*, functional antibody] in a murine immunogenicity model." *Id*. at 117:26-58.

Dependent claims 11-15, and 20-29 of the '559 Patent recite the following additional features of the immunogenic composition of claim 1:

- common formulation ingredients, including buffer and adjuvant (claims 11-13 and 23-26);
- a container, including a standard syringe that is siliconized and/or made of glass (claims 14-15 and 29);
- inclusion of additional well-known bacterial and viral antigens (claims 20-22);
- formulating the composition as a liquid or in lyophilized form (claims 27-28);

Dependent claims 30-37 recite well-known methods of using the immunogenic composition of claim 1, *e.g.*, immunizing children, the elderly and/or

immunocompromised patients with single or multiple dose schedules. Ex. 1087, ¶¶ 57-58.

C. Prosecution History of the '559 Patent

The '559 Patent issued on November 15, 2016 from US Patent Application No. 14/597,488 ("the '488 App."), filed on January 15, 2015, claiming priority from US Provisional Application No. 61/929,547 (Ex. 1003), filed on January 21, 2014.

In the originally-filed claims of the '488 App., Patent Owner sought claims that would have covered, *inter alia*, any immunogenic composition featuring at least one conjugate of an emerging pneumococcal serotype (*i.e.*, 15B, 22F, 33F, 12F, 10A, 11A, 8) "not found in PREVNAR®, SYNFLORIX® and/or PREVNAR 13®," three known and approved conjugate vaccines. Ex. 1002 at 200. Original claim 1, thus, captured any pneumococcal serotype 22F conjugate as one emerging serotype option, with dependent claim 3 more narrowly-tailored to just that emerging serotype:

> 1. An immunogenic composition **comprising at least one glycoconjugate selected from the group consisting of** a glycoconjugate from *S. pneumoniae* serotype 15B, **a glycoconjugate from *S. pneumoniae* serotype 22F**, a glycoconjugate from *S. pneumoniae* serotype 33F, a glycoconjugate from *S. pneumoniae* serotype 12F, a glycoconjugate from *S. pneumoniae* serotype 10A, a

glycoconjugate from *S. pneumoniae* serotype 11A and a glycoconjugate from *S. pneumoniae* serotype 8.

3. The immunogenic composition of any one of claims 1-2 **comprising at least one glycoconjugate from *S. pneumoniae* serotype 22F**.

Id. at 172 (emphasis added); *see also id*. at 297 (claims 1 and 3 after Preliminary Amendment). In relation to the serotype 22F conjugate, Patent Owner also originally filed dependent claims that recited ranges of molecular weight and polysaccharide to protein ratio; those ranges were either much broader or much narrower than the ranges of the ultimately-issued claims:

50. The immunogenic composition of any one of claims 3, 9, 10, 12-49 wherein, said serotype 22F glycoconjugate has **a molecular weight of between 400 kDa and 15,000 kDa**.

51 . The immunogenic composition of any one of claims 3, 9, 10, 12-49 wherein, said serotype 22F glycoconjugate has **a molecular weight of between 1,000 kDa and 8,000 KDa**.

52. The immunogenic composition of any one of claims 3, 9, 10, 12-51 wherein, **the ratio (w/w) of serotype 22F capsular polysaccharide to carrier protein in serotype 22F glycoconjugate is between 0.5 and 3**.

53. The immunogenic composition of any one of claims 3, 9, 10, 12-52 wherein, **the ratio (w/w) of serotype 22F capsular polysaccharide to carrier protein in serotype 22F glycoconjugate is between 0.9 and 1.1**.

Id. at 176 (emphasis added). Patent Owner canceled those claims prior to examination. *Id*. at 298.

An unidentified third party subsequently filed a pre-issuance submission under 37 CFR § 1.290, identifying 4 prior art references relevant to the then-pending claims; the pre-issuance submission did not address molecular weight or polysaccharide to protein ratio, because the claims reciting those limitations had already been canceled by Patent Owner. *Id*. at 386-403. The Examiner rejected all pending claims as independently anticipated by two references of the third party submission: US Patent Application Publication No. 2004/0202668 ("Boutriau"); and US Patent Application Publication No. 2012/0052088 ("Davis"). *Id*. at 419-420. Both references disclosed serotype 22F conjugates. *Id*.

Patent Owner amended claim 1 by restricting it to serotype 22F conjugates with previously-unclaimed ranges of molecular weight and polysaccharide to protein ratios: "[C]laim 1, from which all other claims depend, has been amended to specify that the [serotype 22F] glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and that the ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2." *Id*. at 457-458; *see also id*. at 451. Patent Owner referred to serotype 22F conjugates disclosed in the pending application, which elicited functional antibody in the immunogenicity testing: "As shown in Example 13, Applicant found that this combination of glycoconjugate

molecular weight and saccharide-to-protein ratio produced sera having opsonophagocytic activity." *Id.* at 458. Example 13 of the '559 Patent, in turn, recites standard reductive amination chemistry for the preparation of serotype 22F conjugates. Ex. 1001 at 114:21-116:11. Patent Owner did not contend that non-standard techniques or conditions were necessary to obtain the claimed molecular weight and polysaccharide to protein ratio; to the contrary, the disclosed conjugation chemistry was routine in the art. Ex. 1087, ¶ 52.

Notably, Patent Owner did not disclose that the claimed molecular weight and polysaccharide to protein ratio, independently and in combination, were typical values for immunogenic pneumococcal conjugates. *See e.g.*, Ex. 1006 at 17:24-25, 19:3-8 (Table 1); Ex. 1007 at 20:24-26, 54:27-55:1; Ex. 1008 at 6. For example, Patent Owner did not compare the immunogenicity of conjugates in the claimed ranges against conjugates outside the claimed ranges, nor does the '559 Patent disclose any such data. Patent Owner instead made the bare assertion that the cited prior art "does not disclose, nor suggest, an immunogenic composition comprising *S. pneumoniae* serotype 22F glycoconjugates having this particular combination of characteristics or that such glycoconjugates produce functional antibodies." Ex. 1002 at 458.

In response to Patent Owner's arguments, the claims of the '559 Patent were allowed. *Id*. at 467. And, no further third party pre-issuance submissions are permitted after the notice of allowance has issued. 37 CFR § 1.290(b).

D. Prior Art

1. Merck 2011

Grounds 1-5 of this Petition rely on Merck's International Patent Publication No. WO 2011/100151 A1 ("Merck 2011"). Ex. 1006. Because Merck 2011 was published on August 18, 2011, before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under post-AIA § 102(a)(1).

Merck 2011 is directed to immunogenic multivalent pneumococcal conjugate compositions that include a serotype 22F conjugate. *See, e.g., id*. at Abstract. The disclosed compositions include 15 pneumococcal conjugates from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F. *See, e.g., id*. at 3:19-24. And, the preferred carrier protein is CRM_{197}. *See, e.g., id*. at 1:8-11. The disclosed pneumococcal conjugate compositions can be used "to protect or treat a human susceptible to pneumococcal infection." *Id*. at 10:27-11:3.

To construct the conjugates of the disclosed compositions, "purified polysaccharides are chemically activated to make the saccharides capable of reacting with the carrier protein. Once activated, each capsular polysaccharide is separately conjugated to a carrier protein to form a glycoconjugate." *Id*. at 6:11-

13. For example, the individual conjugates can be generated using chemistry based on reductive amination, *i.e.*, "activation of pneumococcal polysaccharide by reaction with any oxidizing agent which oxidizes a terminal hydroxyl group to an aldehyde, such as periodate " and "conjugation is carried out by reacting a mixture of the activated polysaccharide and carrier protein with a reducing agent such as sodium cyanoborohydride." *Id*. at 6:15-26. Alternatively, the conjugates can be generated using CDAP-based chemistry. *Id*. at 6:27-7:6; Ex. 1087, ¶ 76.

Example 2 of Merck 2011 describes a "common process flow" for generating the 15 disclosed conjugates:

> The different serotype saccharides are individually conjugated to the purified CRM_{197} carrier protein using a common process flow. In this process the saccharide is dissolved, sized to a target molecular mass, chemically activated and buffer-exchanged by ultrafiltration. The purified CRM_{197} is then conjugated with the activated saccharide and the resulting conjugate is purified by ultrafiltration prior to a final 0.2 μm membrane filtration.

Ex. 1006 at 16:27-31.

In Example 2, the polysaccharides are oxidized using sodium periodate, and the activated polysaccharides are "mixed with CRM_{197} carrier protein in a 0.2 - 2 to 1 charge ratio," *i.e.*, a 0.2-2:1 w/w polysaccharide to protein ratio. *Id.* at 17:11-25. Conjugation is effected by reductive amination with sodium cyanoborohydride solution, and the resulting conjugates are sterile-filtered through a 0.2 μm filter

prior to formulation. *Id*. at 17:26-29, 18:14-15. In Example 3, the 15 conjugates from Example 2 exhibit, on average, a polysaccharide to protein ratio (w/w) of ~1:1. *Id*. at 19:3-8 (Table 1 discloses formulations with "32 μg of total polysaccharide" and "~32 μg" of "Carrier protein CRM_{197}"). Ex. 1087, ¶ 78.

In Example 4, Merck 2011 discloses immunogenicity studies in infant rhesus monkeys ("IRMs") to assess serotype-specific antibody responses to the 15-valent pneumococcal conjugate compositions (a/k/a "PCV-15"). Ex. 1006 at 22:16-18. The results are presented in Figures 1 and 2, and "indicate that antibody responses to PCV-15 and [7-valent] Prevnar were comparable for the 7 common serotypes and that post-vaccination responses to PCV-15 were >10-fold higher than baseline for the 8 added serotypes." *Id*. at 22:18-28, Figures 1 and 2. Merck 2011 also performed OPA assays "to determine whether PCV-15 induced functional antibody responses." *Id*. at 22:30-31. The results are provided in Table 2 (*id*. at 23:8-13) and show that, "[a]fter 3 vaccine doses, PCV-15 induced high OPA GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine." *Id*. at 23:2-4; Ex. 1087, ¶ 81.

The immunogenicity of PCV-15 was also assessed "in 4 studies in adult New Zealand White Rabbits (NZWRs)," benchmarked against Prevnar®. Ex. 1006 at 23:14-25:1. Merck discloses that PCV-15 is "highly immunogenic" in both IRMs and rabbits. *Id*. at 30:2-14. Merck 2011 discloses that the "robust antibody

responses" with respect to PCV-15 "demonstrate[] the feasibility of expanding coverage of pneumococcal serotypes not covered by existing pneumococcal vaccines." *Id*. at 3:32- 4:4; Ex. 1087, ¶ 82.

2. GSK 2008

Grounds 1-5 of this Petition further rely on GSK's International Patent Publication No. WO 09/000825 ("GSK 2008"). Ex. 1007. Because GSK 2008 was published on December 31, 2008, before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under post-AIA § 102(a)(1).

GSK 2008 is directed to multivalent pneumococcal conjugate compositions that include a serotype 22F conjugate. *Id*. at Abstract. Such vaccines are typically 10- to 23-valent, with capsular polysaccharides selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15, 17F, 18C, 19A, 19F, 20, **22F**, 23F and 33F. *Id*. at 8:17-21, 8:29-31. GSK 2008 also discloses that "one or two other serotypes could be substituted depending on the age of the recipient receiving the vaccine and the geographical location where the vaccine will be administered." *Id*. at 8:31-33; Ex. 1087, ¶ 84.

The carrier protein is "selected from the group consisting of TT, DT, CRM197, fragment C of TT, PhtD, PhtDE fusions (particularly those described in WO 01/98334 and WO 03/54007), detoxified pneumolysin [(Ply)] and protein D [(PD)]." Ex. 1007 at 10:12-16. The molecular weights of the above carrier

proteins were well-known to be in the range of ~40 kDa (PD) to ~150 kDa (TT). Ex. 1043 at 7, 8, 13; Ex. 1082 at 2; Ex. 1008 at 20; Ex. 1083 at 3. Conjugation of each polysaccharide to a carrier protein may be performed "by any known coupling technique," including conjugation chemistries based on CDAP and/or reductive amination. Ex. 1007 at 17:1-30; Ex. 1087, ¶ 85.

Preparation of multivalent pneumococcal vaccines containing serotype 22F conjugates is exemplified in Example 2. For instance, GSK 2008 discloses a 13-valent conjugate vaccine that includes a serotype 22F conjugate. Ex. 1007 at 55:2-8.

Table 2 discloses the "characteristics of the conjugates," including the molecular weights of the polysaccharide ("PS size ($Dax10^3$)") and the conjugate ("Conj. Size (kDa)"), as well as "Carrier/PS Ratio," and "Free PS." Ex. 1007 at 54:27-55:1. The molecular weight of the serotype 22F polysaccharide is "159-167" kDa (*id*.), which is consistent with GSK 2008's broader disclosure that "the average size (e.g. M_w) of the 22F saccharide is between 50 and 800 kDa . . ." *Id*. at 93 (claim 56). For the PS22F-PhtD conjugate, the carrier protein to polysaccharide ratio is 2.17 (which translates to a polysaccharide to carrier protein ratio of 1/2.17 or 0.46), with only 5.8% free (unconjugated) polysaccharide. *Id*. at 54:27-55:1. The molecular weight of the PS22F-PhtD conjugate was "not determined," but the

conjugate molecular weights that were determined (for every conjugate of the underlying 10-valent composition) ranged from 1,303-9,572 kDa. *Id*.

The immunogenicity of the above 13-valent composition was assessed in several animal models. Ex. 1007 at 68:39-72:9 (elderly C57Bl mice), 72:11- 76:5 (young Balb/c mice), 77:1-78:3 (young OF1 mice), 79:1-81:3 (guinea pigs). In each case, the composition elicited functional antibody against serotype 22F. *See id*. at Figures 14, 16, 18, 20 and 22; *id* at 75:6-8 ("19A-dPly and 22F-PhtD administered within the 13-valent conjugate vaccine formulation were shown immunogenic and induced opsono-phagocytic titers in young Balb/c mice (Table 17 and figures 19-20)."), 77:21-23 (same, for young OF1 mice). Ex. 1087, ¶ 88.

GSK 2008 claims both directly- and indirectly-linked immunogenic serotype 22F conjugates. Ex. 1007 at 92 (claim 43) ("The immunogenic composition according to any preceding claim comprising a 22F capsular saccharide directly conjugated to the carrier protein."); *id*. (claim 44) ("The immunogenic composition of any one of claims 1-42 comprising 22F capsular saccharide conjugated to the carrier protein via a linker."). Both types of conjugates were demonstrated to be immunogenic. *See, e.g., id*. at Figures 6, 14, 16, 18, 20 and 22; Ex. 1087, ¶ 89.

3. The '787 Patent

Ground 2 of the Petition relies on Patent Owner's US Patent No. 7,935,787 ("the '787 Patent"). Ex. 1010. Because the '787 Patent issued on May 3, 2011,

before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under § 102(a)(1).

The '787 Patent discloses polysaccharide-protein conjugate formulations in siliconized containers, including glass syringes; the formulations inhibit protein aggregation caused by the silicone oil. *See, e.g.*, *id*. at 13:34-14:23. The purpose of the silicone oil in a syringe is "to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel (i.e., silicone oil improves the syringeability of the formulation)." *Id*. at 2:25-29; Ex. 1087, ¶ 91.

In Example 1 of the '787 Patent, the inventors demonstrate the effect of surfactant on aggregation of a 13-valent polysaccharide-protein conjugate composition ("13vPnC") in "3 mL BD HYPAK™ SCF™ glass syringe with w4432 grey stoppers." Ex. 1010 at 20:9-12. The '787 Patent explains that the BD Hypak syringes were siliconized. *See, e.g.*, *id*. at 23:34-38 (referencing "ready to use (single-dose) Becton Dickinson® (BD) Hypak Type 1 borosilicate glass syringes treated with Dow Corning® medical grade DC 360 silicone"), 29:48-56 ("syringes with higher silicone levels" include "BD Hypak syringe (control 1)"). Ex. 1087, ¶ 92.

4. Obaro 2002

Ground 3 further relies on Obaro *et al.*, "Safety and immunogenicity of pneumococcal conjugate vaccine in combination with diphtheria, tetanus toxoid,

pertussis and *Haemophilus influenzae* type b conjugate vaccine," *Pediatr. Infect. Dis. J.* 21:940-946 (2002) ("Obaro 2002"). Because Obaro 2002 was published in 2002, before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under post-AIA § 102(a)(1).

Obaro 2002 reported the safety and immunogenicity of Patent Owner's 9-valent pneumococcal CRM_{197}-conjugate vaccine ("PnCV") when given in combination with a vaccine ("TETRAMUNE") containing diphtheria toxoid, tetanus toxoid, whole cell pertussis, and CRM197-conjugated *Haemophilus influenzae* type B oligosaccharide. *Id.* at 2. The authors conclude that "[t]he combination of TETRAMUNE and PnCV is safe and immunogenic." *Id.* at 1; Ex. 1087, ¶ 94.

5. Sigurdardottir 2008

Ground 4 of this Petition relies on Sigurdardottir *et al.*, "Safety and immunogenicity of CRM_{197}-conjugated pneumococcal–meningococcal C combination vaccine (9vPnC–MnCC) whether given in two or three primary doses," *Vaccine* 26:4178–4186 (2008) ("Sigurdardottir 2008"). Ex. 1011. Because Sigurdardottir 2008 was published in 2008, before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under post-AIA § 102(a)(1).

Sigurdardottir 2008 "evaluated safety and immunogenicity of a combined 9-valent pneumococcal and meningococcal C conjugate vaccine ["9vPnC-MnCC"], administered according to either a two- or a three-dose primary immunization schedule, followed by a booster dose." *Id*. at 2. The authors conclude that, for both immunization schedules, 9vPnC-MnCC is safe and immunogenic:

> The data from this study suggest a pneumococcal–meningococcal conjugate combination vaccine (9vPnC–MnCC) administered either as a two-dose primary infant schedule (3 and 5 months of age) or as a three dose primary infant schedule (3, 4, and 5 months of age) followed by a toddler dose at 12 months of age, is safe and induces a significant primary immune responses to both vaccination schedules, priming for similar memory responses at 12 months of age.

Id. at 8; Ex. 1087, ¶ 96.

6. MMWR 2012

Ground 5 of this Petition relies on "Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *MMWR* 61:40 (2012) ("MMWR 2012"). Ex. 1012. Because MMWR 2012 was published on October 12, 2012, before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under post-AIA § 102(a)(1).

Authored by the Centers for Disease Control and Prevention ("CDC"), "the MMWR series is the agency's primary vehicle for scientific publication of timely, reliable, authoritative, accurate, objective, and useful public health information and recommendations." Ex. 1025 at 1. MMWR 2012 discloses the "recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ≥19 years with immunocompromising conditions . . ." Ex. 1012 at 12; Ex. 1087, ¶ 98.

VII. LEVEL OF ORDINARY SKILL IN THE ART

The claims of the '559 Patent are generally directed to immunogenic compositions that include at least one glycoconjugate from pneumococcal serotype 22F. Ex. 1087, ¶ 62. 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" in sole independent claim 1 (and repeated in nearly every dependent claim) requires construction. Because the

'559 Patent has not expired and will not expire before a final written decision is entered in this proceeding, each claim term is construed based on "its broadest reasonable construction [a/k/a broadest reasonable interpretation] in light of the specification of the patent in which it appears."[2] 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). In AIA post-grant proceedings, the broadest reasonable interpretation standard also takes into account Patent Owner's statements and arguments during prosecution history. *See, e.g., Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015).

1. "immunogenic"

Sole independent claim 1 recites an "immunogenic" composition. Ex. 1001. Petitioner respectfully submits that the broadest reasonable interpretation of the term "immunogenic" is "elicits functional antibody against at least pneumococcus serotype 22F." Ex. 1087, ¶ 67.

A POSITA would understand that, even though "immunogenic" is recited in the preamble of claim 1 of the '559 Patent, it is a claim limitation. *Id.*, ¶ 68. Initially, the claims repeatedly characterize the claimed composition as "immunogenic." *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

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

textured liner' is restated in each of the patent's seven claims"). Apart from usage of the term "immunogenic" in sole independent claim 1, 40 of 44 dependent claims expressly reiterate that the claimed composition is "immunogenic"; only dependent claims 15 (directed to a particular syringe) and 32-34 (specifying patient demographics) do not expressly reiterate the term "immunogenic." Ex. 1001. Several dependent claims (9, 11, 18-20, 22-23, and 27-28) refer to the claimed composition as "immunogenic" more than once, including in the body of the claim. *Id*. For example, claim 18 recites "[t]he **immunogenic** composition of claim 1, wherein each dose of said **immunogenic** composition comprises 0.1 μg to 100 μg of the polysaccharide." *Id*. (emphasis added).

Patent Owner relied on the immunogenicity of claim 1's composition and, in particular, the generation of functional antibody against pneumococcal serotype 22F - to overcome the prior art during prosecution. Ex. 1087, ¶ 71; *see, e.g.*, *Rotatable Techs. LLC v. Motorola Mobility LLC*, 567 F. App'x 941, 943 (Fed. Cir. 2014) ("[T]he prosecution history shows 'clear reliance on the preamble' to distinguish the claimed invention from the prior art").

The Examiner rejected the originally-filed claims of the '559 Patent as anticipated by each of two prior art references - Boutriau and Davis. Ex. 1002 at 419-420. Patent Owner amended claim 1 "to specify that the [serotype 22F] glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and

that the ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2." *Id*. at 451. Patent Owner argued that, in contrast to the claimed invention, the prior art did not specifically disclose an immunogenic composition with a serotype 22F glycoconjugate that elicits functional antibody. *Id*. at 458.

In particular, Patent Owner relied on Example 13 of the '559 Patent, which is directed to the preparation and characterization of pneumococcal serotype 22F conjugates. *Id*. at 457-458. The immunogenicity of the disclosed serotype 22F conjugates was assessed by measuring functional antibody by OPA assay. Ex. 1001 at 116:50-52 ("The immunogenicity of the [serotype 22F] conjugates obtained above have been assessed using the opsonophagocytic assay (OPA) described below."), 116:59-61 ("Opsonophagocytic activity (OPA) assays are used to measure functional antibodies . . ."). Based on the data in Tables 17 and 18, the inventors concluded that "the serotype 22F conjugate . . . elicited OPA titers [*i.e.*, functional antibody] in a murine immunogenicity model." *Id*. at 117:28-34. Patent Owner relied on the OPA data of Example 13 to distinguish over each of the cited prior art references:

> As shown in Example 13, Applicant found that this combination of glycoconjugate molecular weight and saccharide-to-protein ratio produced sera **having opsonophagocytic activity**. Boutriau does not disclose, nor suggest, **an immunogenic composition comprising *S. pneumoniae* serotype 22F glycoconjugates** having this particular

combination of characteristics **or that such glycoconjugates produce functional antibodies**.

Ex. 1002 at 458 (emphasis added); *see also id* (same argument with respect to the Davis prior art reference). In response to Patent Owner's arguments, the claims of the '559 Patent were allowed. *Id.* at 467.

Given Patent Owner's clear and unambiguous representations - which are consistent with the claim language and the specification - to the Patent Office to obtain the claims of the '559 Patent over the prior art, the broadest reasonable interpretation limits the claimed "immunogenic" composition to one that "elicits functional antibody against at least pneumococcus serotype 22F."[3] Ex. 1087, ¶ 73.

[3] In pending proceedings that implicate Patent Owner's patents from a distinct patent family, US. Patent Nos. 8,895,024 and 9,399,060, Petitioner has advanced a claim construction of immunogenic directed to immunologic memory and/or functional antibody. IPR2017-01194, IPR2017-01211, IPR2017-01215, IPR2017-01223, PGR2017-00016, and PGR2017-00017. As required by law, Petitioner's proposed constructions in those proceedings are informed by Patent Owner's specific usage of that term in the specification and prosecution history of the '060 and '024 patents. Here, in relation to the '559 patent, based on Patent Owner's specific usage of the term "immunogenic" in the specification and the prosecution

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Claims 11-14, 23-33, and 35-37 Are Invalid as Obvious over Merck 2011 In View of GSK 2008 and the General Knowledge of a POSITA

It would have been obvious for a POSITA to arrive at the immunogenic pneumococcal conjugate composition of sole independent claim 1 based on the combination of Merck 2011 (Ex. 1006) and GSK 2008 (Ex. 1007). Ex. 1087, ¶ 105. Both Merck 2011 and GSK 2008 disclose immunogenic pneumococcal conjugate compositions containing serotype 22F conjugates; a POSITA would have considered both references - from two major vaccine companies - in combination when developing a pneumococcal conjugate vaccine featuring

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history of the '559 Patent, the proposed claim construction focuses on functional antibody. Petitioner notes, however, that it does not object to a construction of "immunogenic" consistent with the broadest reasonable interpretation standard and that proposed in relation to the '060 and '024 proceedings. As explained *supra* at §VI.A.7, as of January 21, 2014, "immunogenicity" generally referred to characteristics of an immune response that reflect a likelihood of preventing disease; in addition to functional antibody, immunologic memory is a correlate of protection against disease that may demonstrate immunogenicity of a composition. *See* Ex. 1033 at 1.

serotype 22F. *Id*. Merck 2011 discloses every limitation of sole independent claim 1 except for the molecular weight of the immunogenic serotype 22F conjugate. *Id*.

Based on the disclosure of conjugate molecular weights of 1,303-9,572 kDa in GSK 2008, it would have been obvious to construct the serotype 22F conjugates of Merck 2011/GSK 2008 with a molecular weight falling within claim 1's vast range (1,000 to 12,500 kDa). *Id*., ¶ 106. Although GSK 2008 does not expressly disclose the molecular weight of its immunogenic serotype 22F conjugates, it reports the molecular weights of 10 other pneumococcal conjugates featured in a 10-valent conjugate composition; each of those molecular weights falls within the broad range of claim 1. *Id*. Given that routine conjugation techniques and conditions readily achieved GSK's molecular weights (as well as polysaccharide to protein ratios falling within claim 1's range), a POSITA would have understood such molecular weights to be typical of immunogenic conjugates. *Id*. And GSK 2008 expressly teaches adding a serotype 22F conjugate to that 10-valent pneumococcal conjugate composition. *Id*. Given that disclosure by a leading vaccine company, a POSITA would been motivated with a reasonable expectation of success to design an immunogenic serotype 22F conjugate in accordance with GSK 2008's disclosure. *Id*.

Dependent claims 11-14, 23-33, and 35-37 recite only (1) additional features of the immunogenic composition of claim 1, and (2) methods of using the

immunogenic composition of claim 1; every limitation of those dependent claims would have been obvious to a POSITA based on Merck 2011 and/or GSK 2008. *Id*., ¶ 107.

1. Claim 1

a. "An immunogenic composition comprising a *Streptococcus pneumoniae* serotype 22F glycoconjugate,"

Both Merck 2011 and GSK 2011 disclose immunogenic compositions that include a conjugate of pneumococcal serotype 22F. Ex. 1087, ¶ 108. Merck 2011 is directed to immunogenic multivalent pneumococcal conjugate compositions that include a serotype 22F conjugate. *Id*. at ¶ 109; *see*, *e.g.*, Ex. 1006 at Abstract. The disclosed compositions include 15 pneumococcal conjugates from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F. *See*, *e.g.*, *id*. at 3:19-24. Merck 2011 demonstrates immunogenicity against serotype 22F by the generation of functional antibody against that serotype: "After 3 vaccine doses, PCV-15 induced high OPA GMTs to each serotype [including serotype 22F] and a 100% OPA response rate for all 15 serotypes contained in the vaccine." *Id*. at 23:2-4; *see also id*. at 30:13-14 ("Functional (OPA) antibody responses were elicited by PCV-15 to all 15 serotypes in the vaccine . . .").

GSK 2008 likewise discloses immunogenic compositions "wherein the composition comprises a serotype 22F saccharide conjugate." Ex. 1007 at

Abstract; Ex. 1087, ¶ 110. For example, GSK 2008 discloses a 13-valent pneumococcal conjugate composition with polysaccharides from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F** and 23F. Ex. 1007 at 54:23-55:8. The serotype 22F conjugate is immunogenic (*i.e.*, it elicits functional antibody) in several animal models, including various mice (Figures 14, 16, 20 and 22), and guinea pigs (Figure 18). *See also id.* at 75:6-8 ("19A-dPly and 22F-PhtD administered within the 13-valent conjugate vaccine formulation were shown immunogenic and induced opsono-phagocytic titers in young Balb/c mice (Table 17 and figures 19-20)."), 77:21-23 (same, for young OF1 mice).

b. "wherein the glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa"

Based on the GSK 2008 disclosure of pneumococcal conjugates between 1,303-9,572 kDa, a POSITA would have been motivated with a reasonable expectation of success to construct the serotype 22F conjugate of Merck 2011/GSK 2008 in that approximate molecular weight range. Ex. 1087, ¶ 111. In GSK 2008, Table 2 discloses the "characteristics of the conjugates," including the molecular weights of the conjugate ("Conj. Size (kDa)"). Ex. 1007 at 54:27-55:1. Although the molecular weight of the PS22F-PhtD conjugate was "not determined," every disclosed conjugate molecular weight (for every conjugate in the 10-valent composition) ranged from 1,303-9,572 kDa, squarely within claim 1's molecular weight range. *Id*. A POSITA would have found the conjugate molecular weight

range disclosed by GSK (a major vaccine manufacturer) to be desirable and would have been motivated to construct a serotype 22F conjugate in that approximate molecular weight range. Ex. 1087, ¶ 111. A POSITA also would have understood that, given the molecular weights of the polysaccharides (all of which were several-fold smaller than the corresponding conjugate molecular weights), the disclosed conjugates of 1,303-9,572 kDa had been cross-linked into lattice structures containing multiple polysaccharide and carrier proteins. *Id*. (citing Ex. 1007 at 54:27-55:1; Ex. 1035 at 7 ("Since the CDAP activation process creates a multiplicity of reactive sites and the protein has a large number of amines, a lattice is formed . . .")). Notably, a POSITA would have understood that the commonly-used carrier proteins (including CRM_{197}) can be cross-linked with pneumococcal polysaccharides to form lattice structures falling within the disclosed molecular weight range; the 10 conjugates with reported molecular weights in the claimed range feature 3 different carrier proteins (PD, TT and DT). *Id*. (citing Ex. 1007 at 54:27-55:1).

In view of the known molecular weights of serotype 22F capsular polysaccharide and suitable carrier proteins, a POSITA also would have had a reasonable expectation of success in constructing a serotype 22F conjugate in GSK's range of about 1,303-9,572 kDa, using the standard conjugation chemistries disclosed in Merck 2011 and GSK 2008. *Id*., ¶ 112. GSK 2008 discloses that the

serotype 22F polysaccharide in its immunogenic conjugates can be, *e.g.*, "between 50 and 800 kDa." Ex. 1007 at 93 (claim 56). Similarly, Merck 2011 references (Ex. 1006 at 4:12-15) European Patent Application Publication No. 0497525, which discloses that pneumococcal polysaccharides in conjugates have "an average molecular weight between about $1x10^5$ and $1x10^6$ daltons," *i.e.*, 100 to 1,000 kDa. Ex. 1084 at 4:2-3. And, both Merck 2011 and GSK 2008 disclose several suitable carrier proteins of known molecular weight, *e.g.*, CRM_{197} (~58 kDa), diphtheria toxoid (~58 kDa), tetanus toxoid (~150 kDa), Protein D (~42 kDa), and PhtD (~94 kDa). Ex. 1006 at 4:23-6:10; Ex. 1007 at 10:12-16; Ex. 1043 at 7, 8, 13; Ex. 1082 at 2; Ex. 1008 at 20; Ex. 1083 at 3. A POSITA easily could have constructed a cross-linked serotype 22F conjugate in GSK 2008's molecular weight range, using the well-known reductive amination or CDAP conjugation chemistries disclosed in both Merck 2011 and GSK 2008. Ex. 1087, ¶ 112. In fact, the '559 Patent employs only standard reductive amination chemistry to obtain the serotype 22F conjugates in the claimed molecular weight range. *Id.* (citing Ex. 1001 at 114:21-116:49). Similarly, it was well-known that conjugates (formed with CDAP-based chemistry, as in GSK 2008) "can have a molecular weight in the multimillions [Daltons]." Ex. 1035 at 7.

There was motivation for a POSITA to stay roughly within the upper limit of molecular weights disclosed in GSK 2008, because "excessive modifications to the

PS or protein molecules can have an adverse impact on immunogenicity." Ex. 1087, ¶ 113 (citing Ex. 1035 at 8-9 and Ex. 1060 at 6). Additionally, "care must be taken to avoid forming conjugates so large as to precipitate, form a gel, or become too large to be sterile filtered." *Id*. (citing Ex. 1035 at 7-8). Notably, both Merck 2011 and GSK 2008 disclose a sterile filtration step through a 0.2 μm filter, which sets an upper limit on conjugate molecular weight. *Id*. (citing Ex. 1006 at 16:30-31, 18:14-15; Ex. 1007 at 14:13-15, 14:33-15:2, 52:11-12).

Patent Owner's disclosure in a 2012 scientific meeting that the "Typical Mass (kDa)" for a glycoconjugate is "500-5000 [kDa]," largely overlapping with the range recited in GSK 2008 (and claim 1), further reflects a POSITA's reasonable expectation of success. Ex. 1087, ¶ 114 (citing Ex. 1008 at 6). For example, cross-linked conjugates of 5,000 kDa were well-known: "As there are multiple activation points within each polysaccharide and multiple linkage points on each carrier protein, the resulting conjugate is a crosslinked network of polysaccharide and protein with a molecular weight of, on average, 5×10^6 Da." Ex. 1026 at 7 (conjugate vaccine against *Haemophilus influenzae* type b). Patent Owner even disclosed in a 2007 scientific meeting that its own pneumococcal conjugates can be as large as ~7,000 to ~12,000 kDa, again overlapping with GSK 2008's range (and falling within claim 1's range). Ex. 1027 at 21 ("Typical Conjugate" of pneumococcal serotype 7F and CRM_{197} is in the range of 9,202 to

11,950 kDa), 30 ("Control" conjugate has a molecular weight of 6,895 kDa); Ex. 1028 (meeting website listing Ex. 1027).

Since the structure of serotype 22F capsular polysaccharide had been known since 1989 (Ex. 1029), a POSITA would have required only routine experimentation to obtain a conjugate molecular weight within GSK 2008's desirable range, *e.g.*, by increasing or decreasing the amount of cross-linking in the conjugate. Ex. 1087, ¶ 115 (citing Ex. 1030 at 4:56-59, referenced by Merck 2011, which discloses that "[t]he degree of crosslinking and overall size of the network or lattice can be regulated by **routine variation of the conditions of the conjugation reaction**.") (emphasis added)).

Finally, a POSITA would have had a reasonable expectation of immunogenicity with respect to a serotype 22F conjugate falling in GSK 2008's disclosed range of about 1,303-9,572 kDa. *Id.*, ¶ 116. The serotype 22F conjugate of GSK 2008 elicited functional antibody. *See* Ex. 1007 at Figures 14, 16, 18, 20 and 22; *id* at 75:6-8 ("19A-dPly and 22F-PhtD administered within the 13-valent conjugate vaccine formulation were shown immunogenic and induced opsono-phagocytic titers in young Balb/c mice (Table 17 and figures 19-20)."), 77:21-23 (same, for young OF1 mice). Likewise, Merck 2011 teaches a serotype 22F conjugate that elicits functional antibody, further supporting the reasonable expectation of immunogenicity. Ex. 1006 at 23:2-4, 30:13-15.

c. "and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a carrier protein,"

In both Merck 2011 and GSK 2008, the disclosed immunogenic serotype 22F conjugates include an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F conjugated to a carrier protein. Ex. 1087, ¶ 117; *see, e.g.,* Ex. 1006 at 1:8-11 ("The present invention provides a multivalent immunogenic composition having 15 distinct polysaccharide-protein conjugates. Each conjugate consists of a capsular polysaccharide prepared from a different serotype of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F or 33F) **conjugated to a carrier protein**, preferably CRM_{197}.") (emphasis added); Ex. 1007 at Abstract ("Specifically, an immunogenic composition for infants is provided comprising a multivalent *Streptococcus pneumoniae* vaccine comprising 2 or more capsular saccharide conjugates from different serotypes, wherein the composition comprises **a serotype 22F saccharide conjugate**.") (emphasis added).

Each of Merck 2011 and GSK 2008 discloses a number of suitable carrier proteins, including CRM_{197}, diphtheria toxoid, tetanus toxoid, detoxified pneumolysin, Protein D and PhtD. Ex. 1087, ¶ 118; *see, e.g.*, Ex. 1006 at 4:26-27 ("In a particular embodiment of the present invention, CRM_{197} is used as the carrier protein."), 5:8-6:10 ("Other suitable carrier proteins include additional inactivated

bacterial toxins such as DT (Diphtheria toxoid), TT (tetanus tox[o]id) or fragment C of TT, . . . *Haemophilus influenzae* protein D, pneumococcal pneumolysin . . . including ply detoxified in some fashion . . ., PhtD, PhtE and fusions of Pht proteins for example PhtDE fusions . . ."; Ex. 1007 at 10:11-16 ("Any *Streptococcus pneumoniae* capsular saccharides present in the immunogenic composition of the invention may be conjugated to a carrier protein independently selected from the group consisting of TT, DT, CRM197, fragment C of TT, PhtD, PhtDE fusions (particularly those described in WO 01/98334 and WO 03/54007), detoxified pneumolysin and protein D.").

d. "and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2."

In view of the individual disclosures of Merck 2011 and GSK 2008, as well as the general knowledge in the art at the time, a POSITA would have been motivated with a reasonable expectation of success to obtain an immunogenic serotype 22F conjugate with a polysaccharide to protein ratio between 0.4 and 2. Ex. 1087, ¶ 119. Merck 2011 and GSK 2008 both disclose the claimed range of conjugate polysaccharide to protein ratios (0.4 to 2), and reflect a POSITA's general understanding that conjugate polysaccharide to protein ratios in the claimed range are typical for immunogenic conjugates. *Id*.

Merck 2011 discloses pre-conjugation ratios between 0.2 and 2, which a POSITA would have considered indicative of a final conjugate ratio in that same

range. *Id.*, ¶ 120 (citing Ex. 1006 at 17:24-25). For example, Table 1 of GSK 2008 discloses pre-conjugation ratios that are similar to the final conjugate ratios disclosed in Table 2. Ex. 1007 at 52:15-53:1, 54:27-55:1. Indeed, Example 13 of the '559 Patent itself employs a pre-conjugation ("input") ratio of 1 to achieve serotype 22F conjugates in the claimed polysaccharide to protein ratio (and molecular weight) range - using the same reductive amination chemistry and carrier protein (CRM_{197}) of Merck 2011's Examples. Ex. 1001 at 115:58-61. Notably, the pre-conjugation ratios of Merck 2011 resulted in an average polysaccharide to protein ratio in the conjugates of approximately 1 (~32 μg of polysaccharide and ~32 μg of protein), squarely in the claimed range. Ex. 1006 at 19:3-8 (Table 1).

GSK 2008 discloses claim 1's polysaccharide to protein ratio of 0.4 to 2: "Preferably the ratio of carrier protein to *S. pneumoniae* saccharide is . . . between 1:2 and 2.5:1 . . . (w/w)," which translates to a polysaccharide to protein ratio of 1:2.5 to 2:1, *i.e.*, 0.4 to 2. Ex. 1007 at 20:24-26. GSK 2008's Table 2 specifically discloses an immunogenic serotype 22F conjugate (PS22F-PhtD) with a protein to polysaccharide ratio of 2.17, which translates to a polysaccharide to protein ratio of 1/2.17 or 0.46 - squarely within claim 1's range. *Id.* at 54:27-55:1. (A POSITA would have understood that, unless otherwise specified, the ratio of polysaccharide to carrier protein is a weight to weight ratio, consistent with GSK 2008's disclosure

of other polysaccharide to protein ratios. Ex.1087 ¶ 121 (citing Ex. 1007 at 14:15-18, 20:24-26, 27:31-28:2).)

In fact, a POSITA would have had a reasonable expectation of successfully obtaining conjugates with the claimed polysaccharide to protein ratios **that were also** within the claimed molecular weight range, using standard conjugation chemistry. *Id*., ¶ 122. Notably, every conjugate disclosed in GSK 2008's Table 2 with a molecular weight in the range of 1,000 to 12,500 kDa (as required by the claim) features a polysaccharide to protein ratio within the claimed range of 0.4 to 2. Ex. 1007 at 54:27-55:1.

Merck 2011 and GSK 2008 reflect a POSITA's general understanding that conjugate polysaccharide to protein ratios in the claimed range (0.4 to 2) are typical for immunogenic conjugates. Ex. 1087, ¶ 123. For example, the "Biological Products Standards" published on the website of Japan's National Institute of Infectious Diseases as of January 6, 2013 includes a monograph directed to "Adsorbed Pneumococcal 7-valent Conjugate Vaccine (Non-toxic Diphtheria Toxin Mutant)," *i.e.*, a 7-valent pneumococcal CRM_{197} conjugate vaccine. Ex. 1085 at 20-24. That monograph specifies the acceptable range of "Saccharide content/protein ratio" (which a POSITA would have understood to be a w/w ratio) for each of the seven disclosed conjugates:

Capsular serotype	Saccharide content/protein ratio
4	0.9 ~ 2.1
6 B	0.4 ~ 0.9
9 V	1.2 ~ 2.3
14	1.4 ~ 2.6
18 C	0.7 ~ 1.8
19 F	0.4 ~ 1.1
23 F	0.3 ~ 1.0

Id. at 23. Each disclosed ratio overlaps to a large extent with the claimed ratio of 0.4 to 2, consistent with the general understanding in the art as of January 21, 2014 of typical immunogenic conjugate ratios. Ex. 1087, ¶ 124.

2. Claim 11

a. The immunogenic composition of claim 1, wherein said immunogenic composition further comprises a buffer, a salt, a divalent cation, a non-ionic detergent, a cryoprotectant, an anti-oxidant, or a combination thereof.

Merck 2011 discloses 15-valent immunogenic compositions (including an immunogenic serotype 22F conjugate), which include histidine buffer. Ex. 1087, ¶ 125; *see, e.g.*, Ex. 1006 at 18:24-27 (the 15 conjugates of Example 3 are combined in "sodium chloride and L-histidine, pH 5.8, containing buffer"), 11:31-12:6 ("Each 0.5 mL dose is formulated to contain: . . . L-histidine buffer."), 3:6-9 (same formulation), 15:16-17 ("In a preferred embodiment, the vaccine composition is formulated in L-histidine buffer with sodium chloride.").

3. Claim 12

a. "The immunogenic composition of claim 11, wherein the composition further comprises a buffer."

Claim 12 limits the composition of claim 11 to one in which the composition includes a buffer. Merck 2011 discloses 15-valent immunogenic compositions (including an immunogenic serotype 22F conjugate), which include histidine buffer. Ex. 1087, ¶ 126; *see, e.g.*, Ex. 1006 at 18:24-27 (the 15 conjugates of Example 3 are combined in "sodium chloride and L-histidine, pH 5.8, containing buffer"), 11:31-12:6 ("Each 0.5 mL dose is formulated to contain: . . . L-histidine buffer."), 3:6-9 (same formulation), 15:16-17 ("In a preferred embodiment, the vaccine composition is formulated in L-histidine buffer with sodium chloride.").

4. Claim 13

a. "The immunogenic composition of claim 12, wherein the buffer is phosphate, succinate, histidine or citrate."

Claim 13 limits the composition of claim 12 to one in which the recited buffer is selected from the commonly-used phosphate, succinate, histidine and citrate buffers. Merck 2011 discloses 15-valent immunogenic compositions (including an immunogenic serotype 22F conjugate), which include histidine buffer. Ex. 1087, ¶ 127; *see, e.g.*, Ex. 1006 at 18:24-27 (the 15 conjugates of Example 3 are combined in "sodium chloride and L-histidine, pH 5.8, containing buffer"), 11:31-12:6 ("Each 0.5 mL dose is formulated to contain: . . . L-histidine

buffer."), 3:6-9 (same formulation), 15:16-17 ("In a preferred embodiment, the vaccine composition is formulated in L-histidine buffer with sodium chloride.").

5. Claim 14

a. "A syringe filled with the immunogenic composition of claim 1."

Merck 2011 discloses that "[t]he composition of the invention can be formulated as . . . pre-filled syringes." Ex. 1006 at 13:1-2; *see* Ex. 1087, ¶ 128.

6. Claim 23

a. "The immunogenic composition of claim 1, wherein said immunogenic composition further comprise[s] at least one adjuvant."

Merck 2011 discloses 15-valent immunogenic compositions that contain at least one adjuvant. Ex. 1087, ¶ 129; *see, e.g.*, Ex. 1006 at 7:28-10:25 (disclosing "[s]uitable adjuvants to enhance effectiveness of the composition"); *see also id*. at 18:24-29 (the 15 conjugates are mixed with aluminum phosphate adjuvant), 11:31-12:6 ("Each 0.5 mL dose is formulated to contain: . . . 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant . . ."), 3:6-9 (same formulation), 3:1-2 ("In a particular embodiment of the invention, the adjuvant is aluminum phosphate."), 10:13-14 ("In certain embodiments, the adjuvant is a CpG-containing nucleotide sequence, for example, a CpG-containing oligonucleotide.").

7. Claim 24

a. "The immunogenic composition of claim 23, wherein said at least one adjuvant is selected from the group consisting of aluminum, calcium phosphate, a liposome, an oil-in-water emulsion, and poly(D,L-lactide-co-glycolide) (PLG) microparticles or nanoparticles."

Claim 24 limits the composition of claim 23 to one in which the "at least one adjuvant" is selected from a group of common adjuvants, including aluminum. Merck 2011 discloses that, "[i]n a particular embodiment of the invention, the adjuvant is aluminum phosphate." Ex. 1006 at 3:1-2; *see also id*. at 18:24-29 (the 15 conjugates are mixed with aluminum phosphate adjuvant), 11:31-12:6 ("Each 0.5 mL dose is formulated to contain: . . . 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant . . ."), 3:6-9 (same formulation); Ex. 1087, ¶ 130.

8. Claim 25

a. "The immunogenic composition of claim 24, wherein said adjuvant is an aluminum adjuvant selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide."

Claim 25 limits the composition of claim 24 to one in which the "aluminum adjuvant" is selected from a group of common adjuvants, including aluminum phosphate. Merck 2011 discloses that, "[i]n a particular embodiment of the invention, the adjuvant is aluminum phosphate." Ex. 1006 at 3:1-2; *see also id*. at 18:24-29 (the 15 conjugates are mixed with aluminum phosphate adjuvant), 11:31-

12:6 ("Each 0.5 mL dose is formulated to contain: . . . 0.125 mg of elemental aluminum (0.5 mg aluminum phosphate) adjuvant . . ."), 3:6-9 (same formulation); *see* Ex. 1087, ¶ 131.

9. Claim 26

a. "The immunogenic composition of claim 23, wherein said at least one adjuvant is a CpG Oligonucleotide."

Claim 26 limits the composition of claim 23 to one in which the "at least one adjuvant" is a CpG oligonucleotide. Merck 2011 discloses that, "[i]n certain embodiments, the adjuvant is a CpG-containing nucleotide sequence, for example, a CpG-containing oligonucleotide . . ." Ex. 1006 at 10:13-14; *see* Ex. 1087, ¶ 132.

10. Claim 27

a. "The immunogenic composition of claim 1, wherein said immunogenic composition is formulated in liquid form."

Merck 2011 discloses that, "[i]n a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation." Ex. 1006 at 11:31-32; *see* Ex. 1087, ¶ 133.

11. Claim 28

a. "The immunogenic composition of claim 1, wherein said immunogenic composition is formulated in a lyophilized form."

Based on GSK 2008 and the general knowledge of a POSITA, a POSITA would have been motivated with a reasonable expectation of success to formulate

the immunogenic composition of claim 1 in lyophilized form to improve stability. Ex. 1087, ¶ 134. GSK 2008 explains that "[t]he vaccines of the present invention [*i.e.*, which include immunogenic serotype 22F conjugates] may be stored in solution or lyophilized," and that "[l]yophilizing may result in a more stable composition (vaccine) . . ." Ex. 1007 at 41:5-10.

12. Claim 29

a. "A container filled with the immunogenic composition of claim 1."

A POSITA would have understood that the immunogenic compositions of Merck 2011/GSK2008 would have been provided in a container. Ex. 1087, ¶ 135. For example, Merck 2011 discloses that "[t]he composition of the invention can be formulated as single dose vials, multidose vials or as pre-filled syringes." Ex. 1006 at 13:1-2.

13. Claim 30

a. "A method of preventing, treating or ameliorating an infection, disease or condition associated with *S. pneumoniae* in a subject comprising administering to the subject an effective amount of the immunogenic composition of claim 1."

Merck 2011 teaches administering an effective amount of the disclosed 15-valent pneumococcal conjugate compositions "to protect or treat a human susceptible to pneumococcal infection":

> The compositions and formulations of the present invention can be used **to protect or treat a human susceptible to pneumococcal infection**, by means of administering the vaccine via a systemic or mucosal route. In one embodiment, the present invention provides a method of inducing an immune response to a *S. pneumoniae* capsular polysaccharide conjugate, comprising **administering to a human an immunologically effective amount** of an immunogenic composition of the present invention. In another embodiment, the present invention provides a method of vaccinating a human against a pneumococcal infection, comprising the step of **administering to the human an immuno[lo]gically effective amount** of a immunogenic composition of the present invention.

Ex. 1006 at 10:27-11:3 (emphasis added); *see also id*. at 11:7-10. A POSITA would have had a reasonable expectation of success; like the '559 Patent (Ex. 1001 at 116:50-117:58, 123:1-45, 124:49-125:34), Merck 2011 and GSK 2008 demonstrate immunogenicity against serotype 22F by generation of functional antibody against that serotype in animal studies. Merck 2011 (Ex. 1006) at 22:29-23:13; GSK 2008 (Ex. 1007) at 75:6-8, 77:21-23, Figures 14, 16, 18, 20 and 22. Ex. 1087, ¶ 136.

14. Claim 31

a. "A method of preventing an infection caused by *S. pneumoniae* in a subject comprising administering to the subject an effective amount of the immunogenic composition of claim 1."

Merck 2011 teaches administering an effective amount of the disclosed 15-valent pneumococcal conjugate compositions "to protect . . . a human susceptible to pneumococcal infection":

> The compositions and formulations of the present invention can be used **to protect** or treat **a human susceptible to pneumococcal infection**, by means of administering the vaccine via a systemic or mucosal route. In one embodiment, the present invention provides a method of inducing an immune response to a *S. pneumoniae* capsular polysaccharide conjugate, comprising **administering to a human an immunologically effective amount** of an immunogenic composition of the present invention. In another embodiment, the present invention provides a method of vaccinating a human against a pneumococcal infection, comprising the step of **administering to the human an immuno[lo]gically effective amount** of a immunogenic composition of the present invention.

Ex. 1006 at 10:27-11:3 (emphasis added); *see also id.* at 11:7-10. A POSITA would have had a reasonable expectation of success; like the '559 Patent (Ex. 1001 at 116:50-117:58, 123:1-45, 124:49-125:34), Merck 2011 and GSK 2008 demonstrate immunogenicity against serotype 22F by generation of functional antibody against that serotype in animal studies. Merck 2011 (Ex. 1006) at 22:29-

23:13; GSK 2008 (Ex. 1007) at 75:6-8, 77:21-23, Figures 14, 16, 18, 20 and 22. Ex. 1087, ¶ 137.

15. Claim 32

a. "The method of claim 30, wherein the subject is a human being less than 2 years of age."

Merck 2011 discloses that, "[i]n certain embodiments, the human patient is an infant (less than 1 year of age) . . ." Ex. 1006 at 12:8-9; *see* Ex. 1087, ¶ 138.

16. Claim 33

a. "The method of claim 30, wherein the subject is a human adult 50 years of age or older."

Merck 2011 discloses that, "[i]n other embodiments, the human patient is an elderly patient (> 65 years)." Ex. 1006 at 12:9-10; *see* Ex. 1087, ¶ 139.

17. Claim 35

a. "The method of claim 30, wherein the immunogenic composition is administered in a single dose schedule."

Merck 2011 discloses that, "[i]n one embodiment of the methods of the present invention, a composition of the present invention is administered as a single inoculation." Ex. 1006 at 12:13-14; *see* Ex. 1087, ¶ 140.

18. Claim 36

a. "The method of claim 30, wherein the immunogenic composition is administered in a multiple dose schedule."

Merck 2011 discloses that, "[i]n another embodiment, the vaccine is administered twice, three times or four times or more, adequately spaced apart." Ex. 1006 at 12:14-15; *see* Ex. 1087, ¶ 141.

19. Claim 37

a. "A method of inducing an immune response to *S. pneumoniae* serotype 22F in a subject comprising the step of administering an effective amount of the immunogenic composition of claim 1."

Merck 2011 discloses that, "[i]n one embodiment, the present invention provides a method of inducing an immune response to a *S. pneumoniae* capsular polysaccharide conjugate, comprising administering to a human an immunologically effective amount of an immunogenic composition of the present invention." Ex. 1006 at 10:29-32; *see also id*. at 3:3-5, 3:27-29. A POSITA would have had a reasonable expectation of success; like the '559 Patent (Ex. 1001 at 116:50-117:58, 123:1-45, 124:49-125:34), Merck 2011 and GSK 2008 demonstrate immunogenicity against serotype 22F by generation of functional antibody against that serotype in animal studies. Merck 2011 (Ex. 1006) at 22:29-23:13; GSK 2008 (Ex. 1007) at 75:6-8, 77:21-23, Figures 14, 16, 18, 20 and 22. Ex. 1087, ¶ 142.

B. Claim 15 Is Invalid as Obvious over Merck 2011 In View of GSK 2008, the '787 Patent and the General Knowledge of a POSITA

1. Claim 15

a. "The syringe of claim 14, wherein the syringe is siliconized or made of glass."

Based on Patent Owner's '787 Patent (Ex. 1010), a POSITA would have been motivated with a reasonable expectation of success to include the immunogenic composition of claim 1 in a syringe that is siliconized and/or made of glass. Ex. 1087, ¶ 143. Merck 2011 discloses that "[t]he composition of the invention can be formulated as . . . pre-filled syringes." Ex. 1006 at 13:1-2. The '787 Patent discloses pneumococcal polysaccharide-protein conjugate formulations in siliconized containers, including glass syringes; the formulations inhibit protein aggregation caused by the silicone oil. *See, e.g.*, Ex. 1010 at 13:34-14:23. A POSITA designing a pneumococcal conjugate composition based on Merck 2011/GSK 2008 would have considered the teachings of the '787 Patent relating to suitable containers for such compositions. Ex. 1087, ¶ 144.

The '787 Patent discloses silicone oil in a syringe "to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel (i.e., silicone oil improves the syringeability of the formulation)." Ex. 1010 at 2:25-29. Furthermore, most of the examples of siliconized syringes in the '787 Patent are made of glass. *Id.* at 20:9-12 ("3 mL BD HYPAK™ SCF™ glass syringe with

w4432 grey stoppers"), 23:34-38 (referencing "ready to use (single-dose) Becton Dickinson® (BD) Hypak Type 1 borosilicate glass syringes treated with Dow Corning® medical grade DC 360 silicone"), 29:48-56 ("syringes with higher silicone levels" include "BD Hypak syringe (control 1)"). Ex. 1087, ¶ 145.

C. Claims 20-21 Are Invalid as Obvious over Merck 2011 In View of GSK 2008, Obaro 2002 and the General Knowledge of a POSITA

1. Claim 20

a. "The immunogenic composition of claim 1, wherein said immunogenic composition further comprises an antigen from other pathogens."

Based on Obaro 2002 (Ex. 1040), a POSITA would have been motivated with a reasonable expectation of success to include an antigen from a pathogen other than pneumococcus in the immunogenic composition of claim 1. Ex. 1087, ¶ 146. As an initial matter, a POSITA would have understood that combining distinct individual vaccines (*e.g.*, pneumococcal and non-pneumococcal vaccinations) into a single composition is desirable, to enhance protection against disease and minimize the number of injections to a patient, particularly for infants. *Id.*; *see, e.g.*, Ex. 1007 at 43:1-11. Obaro 2002 reports the safety and immunogenicity of Patent Owner's 9-valent pneumococcal CRM_{197}-conjugate vaccine ("PnCV") when given in combination with a vaccine ("TETRAMUNE") containing diphtheria toxoid, tetanus toxoid, whole cell pertussis, and CRM197-conjugated *Haemophilus influenzae* type B oligosaccharide. Ex. 1040 at 2. The

authors conclude that "[t]he combination of TETRAMUNE and PnCV is safe and immunogenic." *Id*. at 1. Given the teaching of Obaro 2002, as well as the demonstrated immunogenicity of serotype 22F conjugates in the multivalent compositions of Merck 2011 and GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to combine the immunogenic serotype 22F conjugates of Merck 2011/GSK 2008 with the claimed "antigen from other pathogens." Ex. 1087, ¶ 146.

2. Claim 21

a. "The immunogenic composition of claim 20, wherein said antigen is selected from the group consisting of a diphtheria toxoid (D), a tetanus toxoid (T), a pertussis antigen (P), an acellular pertussis antigen (Pa), a hepatitis B virus (HBV) surface antigen (HBsAg), a hepatitis A virus (HAV) antigen, a conjugated *Haemophilus influenzae* type b capsular saccharide (Hib), and an inactivated poliovirus vaccine (IPV) antigen."

Based on Obaro 2002, a POSITA would have been motivated with a reasonable expectation of success to include an antigen from a pathogen recited in claim 21 in the immunogenic composition of claim 1. Ex. 1087, ¶ 147. As an initial matter, a POSITA would have understood that combining distinct individual vaccines (*e.g.*, pneumococcal and non-pneumococcal vaccinations) into a single composition is desirable, to enhance protection against disease and minimize the number of injections to a patient, particularly for infants. *Id.*; *see, e.g.*, Ex. 1007 at

43:1-11. Obaro 2002 reports the safety and immunogenicity of Patent Owner's 9-valent pneumococcal CRM_{197}-conjugate vaccine ("PnCV") when given in combination with a vaccine ("TETRAMUNE") containing diphtheria toxoid, tetanus toxoid, whole cell pertussis, and CRM197-conjugated *Haemophilus influenzae* type B oligosaccharide. Ex. 1040 at 2. The authors conclude that "[t]he combination of TETRAMUNE and PnCV is safe and immunogenic." *Id*. at 1. Given the teaching of Obaro 2002, as well as the demonstrated immunogenicity of serotype 22F conjugates in the multivalent compositions of Merck 2011 and GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to combine the immunogenic serotype 22F conjugates of Merck 2011/GSK 2008 with at least one of the claimed antigens from different pathogens. Ex. 1087, ¶ 147.

D. Claim 22 Is Invalid as Obvious over Merck 2011 In View of GSK 2008, Sigurdardottir 2008 and the General Knowledge of a POSITA

1. Claim 22

a. "The immunogenic composition of claim 1, wherein said immunogenic composition further comprises a conjugated *N. meningitidis* serogroup A capsular saccharide (MenA), a conjugated *N. meningitidis* serogroup W135 capsular saccharide (MenW135), a conjugated *N. meningitidis* serogroup Y capsular saccharide (MenY), or a conjugated *N. meningitidis* serogroup C capsular saccharide (MenC)."

Based on Sigurdardottir 2008 (Ex. 1011), a POSITA would have been motivated with a reasonable expectation of success to include a meningococcal serogroup C conjugate in the immunogenic composition of claim 1. Ex. 1087, ¶ 148. As an initial matter, a POSITA would have understood that combining distinct individual vaccines (*e.g.*, pneumococcal and non-pneumococcal vaccinations) into a single composition is desirable, to enhance protection against disease and minimize the number of injections to a patient, particularly for infants. *Id.*; *see, e.g.*, Ex. 1007 at 43:1-11. Sigurdardottir 2008 "evaluated safety and immunogenicity of a combined 9-valent pneumococcal and meningococcal C conjugate vaccine ["9vPnC-MnCC"], administered according to either a two- or a three-dose primary immunization schedule, followed by a booster dose." Ex.1011 at 2. The authors conclude that, for both immunization schedules, 9vPnC-MnCC is safe and immunogenic. *Id.* at 8. Given the teaching of Sigurdardottir 2008, as well

as the demonstrated immunogenicity of serotype 22F conjugates in the multivalent compositions of Merck 2011 and GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to combine the immunogenic serotype 22F conjugates of Merck 2011/GSK 2008 with the claimed meningococcal serogroup C conjugate. Ex. 1087, ¶ 148.

E. Claim 34 Is Invalid as Obvious over Merck 2011 In View of GSK 2008, MMWR 2012 and the General Knowledge of a POSITA

1. Claim 34

a. "The method of claim 30, wherein the subject is an immunocompromised human."

Based on MMWR 2012 (Ex. 1012), a POSITA would have been motivated with a reasonable expectation of success to practice the method of claim 30 (taught by the combination of Merck 2011 and GSK 2008) in an immunocompromised human. Ex. 1087, ¶ 149. Authored by the Centers for Disease Control and Prevention ("CDC"), "the MMWR series is the agency's primary vehicle for scientific publication of timely, reliable, authoritative, accurate, objective, and useful public health information and recommendations." Ex. 1025 at 1. MMWR 2012 discloses the "recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ⩾19 years with immunocompromising conditions . . ." Ex. 1012 at 12. A POSITA developing the pneumococcal conjugate

compositions of Merck 2011/GSK 2008 would have considered the teachings of MMWR regarding the recommended use of a previously-licensed pneumococcal conjugate composition. Ex. 1087, ¶ 149. Based on MMWR 2012, as well as the demonstrated immunogenicity of the serotype 22F conjugates of Merck 2011 and GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to practice the method of claim 30 (taught by the combination of Merck 2011 and GSK 2008) in an immunocompromised human. *Id*.

F. 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.

X. CONCLUSION

Petitioner respectfully submits that it has established a reasonable likelihood that it will prevail as to the obviousness of claims 11-15 and 20-37 of the '559 Patent. Petitioner respectfully requests that this Petition be granted, *inter partes* review be instituted, and claims 11-15 and 20-37 of the '559 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: September 20, 2017

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CLAIM LISTING APPENDIX

1. An immunogenic composition comprising a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2.

11. The immunogenic composition of claim 1, wherein said immunogenic composition further comprises a buffer, a salt, a divalent cation, a non-ionic detergent, a cryoprotectant, an anti-oxidant, or a combination thereof.

12. The immunogenic composition of claim 11, wherein the composition further comprises a buffer.

13. The immunogenic composition of claim 12, wherein the buffer is phosphate, succinate, histidine or citrate.

14. A syringe filled with the immunogenic composition of claim 1.

15. The syringe of claim 14, wherein the syringe is siliconized or made of glass.

20. The immunogenic composition of claim 1, wherein said immunogenic composition further comprises an antigen from other pathogens.

21. The immunogenic composition of claim 20, wherein said antigen is selected from the group consisting of a diphtheria toxoid (D), a tetanus toxoid (T), a pertussis antigen (P), an acellular pertussis antigen (Pa), a hepatitis B virus (HBV) surface antigen (HBsAg), a hepatitis A virus (HAV) antigen, a conjugated *Haemophilus influenzae* type b capsular saccharide (Hib), and an inactivated poliovirus vaccine (IPV) antigen.

22. The immunogenic composition of claim 1, wherein said immunogenic composition further comprises a conjugated *N. meningitidis* serogroup A capsular saccharide (MenA), a conjugated *N. meningitidis* serogroup W135 capsular saccharide (MenW135), a conjugated *N. meningitidis* serogroup Y capsular saccharide (MenY), or a conjugated *N. meningitidis* serogroup C capsular saccharide (MenC).

23. The immunogenic composition of claim 1, wherein said immunogenic composition further comprise[s] at least one adjuvant.

24. The immunogenic composition of claim 23, wherein said at least one adjuvant is selected from the group consisting of aluminum, calcium phosphate, a liposome, an oil-in-water emulsion, and poly(D,L-lactide-co-glycolide) (PLG) microparticles or nanoparticles.

25. The immunogenic composition of claim 24, wherein said adjuvant is an aluminum adjuvant selected from the group consisting of aluminum phosphate, aluminum sulfate and aluminum hydroxide.

26. The immunogenic composition of claim 23, wherein said at least one adjuvant is a CpG Oligonucleotide.

27. The immunogenic composition of claim 1, wherein said immunogenic composition is formulated in liquid form.

28. The immunogenic composition of claim 1, wherein said immunogenic composition is formulated in a lyophilized form.

29. A container filled with the immunogenic composition of claim 1.

30. A method of preventing, treating or ameliorating an infection, disease or condition associated with *S. pneumoniae* in a subject comprising administering to the subject an effective amount of the immunogenic composition of claim 1.

31. A method of preventing an infection caused by *S. pneumoniae* in a subject comprising administering to the subject an effective amount of the immunogenic composition of claim 1.

32. The method of claim 30, wherein the subject is a human being less than 2 years of age.

33. The method of claim 30, wherein the subject is a human adult 50 years of age or older.

34. The method of claim 30, wherein the subject is an immunocompromised human.

35. The method of claim 30, wherein the immunogenic composition is administered in a single dose schedule.

36. The method of claim 30, wherein the immunogenic composition is administered in a multiple dose schedule.

37. A method of inducing an immune response to *S. pneumoniae* serotype 22F in a subject comprising the step of administering an effective amount of the immunogenic composition of claim 1.

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §42.24(d), the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,492,559 contains, as measured by the word processing system used to prepare this paper, 12,842 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: September 20, 2017

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,492,559, along with all exhibits and other supporting documents, was served on September 20, 2017, by FedEx overnight delivery at the following address:

Pfizer Inc.
Attn: Legal Patent Department, Chief IP Counsel
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which is the correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 9,492,559.

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