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 1-10, 16-19, and 38-45 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. 1004), there is a reasonable likelihood that Petitioner will prevail in establishing that claims 1-10, 16-19, and 38-45 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.

Sole independent claim 1 of the '559 Patent recites an "immunogenic composition" that includes "a *Streptococcus pneumoniae* serotype 22F glycoconjugate." 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 nothing inventive 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, including sole independent claim 1. 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 3-10, 16-19, 39, 41-42 and 45 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: PVP 2013 (Ex. 1009) (claims 2, 40 and 43, amount of acetate per polysaccharide), and Hsieh 2000 (Ex. 1013) (claim 38, molecular size distribution of conjugates; claim 44, degree of conjugation).

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 1-10, 16-19, and 38-45 of the '559 Patent, and respectfully submits that the claims are unpatentable based on the following grounds:

Ground 1. Claims 1, 3-10, 16-19, 39, 41-42 and 45 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. Claims 2, 40 and 43 are unpatentable as obvious under post-AIA § 103 over Merck 2011 (Ex. 1006) in view of GSK 2008 (Ex. 1007), PVP 2013 (Ex. 1009) and the general knowledge of a POSITA.

Ground 3. Claims 38 and 44 are unpatentable as obvious under post-AIA § 103 over Merck 2011 (Ex. 1006) in view of GSK 2008 (Ex. 1007), Hsieh 2000 (Ex. 1013) 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

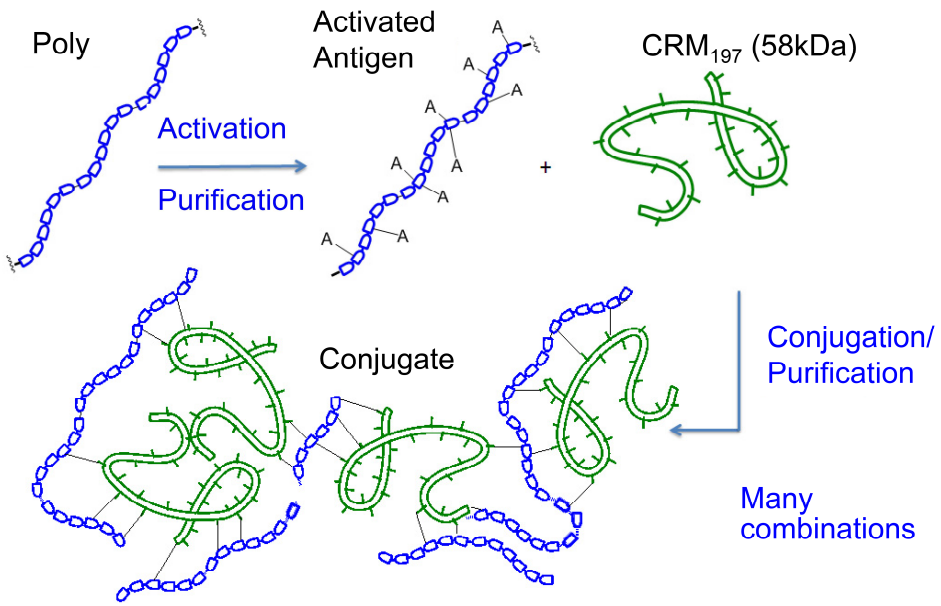
A vaccine prevents infectious diseases by priming the immune system prior to exposure to disease-causing organisms (*i.e.*, pathogens), such as bacteria, viruses or parasites. Ex. 1004, ¶ 19. When the source of infection is encapsulated bacteria (*i.e.*, bacteria covered in a shell of polysaccharides (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.*, ¶¶ 20-22 (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*., ¶ 23 (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 conjugation to such proteins ("carrier proteins"), a robust antibody-mediated response against the polysaccharides can be achieved in very young children. *Id*., ¶¶ 24-26 (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*., ¶ 27 (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*., ¶¶ 28-29 (citing Ex. 1063; Ex. 1064; Ex. 1065).

[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 Petitioner at the bottom of each Exhibit (and designated "IPR PAGE __/__").

2. Cross-linking of Polysaccharide-Protein Conjugates

Common chemistries for preparing polysaccharide-protein conjugates are based on "reductive amination" or "CDAP." *Id.*, ¶ 30. 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., ¶¶ 31-33 (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.*, ¶ 34 (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.*, ¶ 35 (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.*, ¶ 36. 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.*, ¶ 37. The earliest version utilizes the most prevalent polysaccharide serotypes. *Id.* Over time, later vaccine versions incorporate additional clinically-relevant serotypes for broader protection. *Id.* ¶¶ 37-39 (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*., ¶ 40. 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*., ¶ 41 (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*., ¶¶ 41-43 (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*., ¶ 44 (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.*, ¶ 45. 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.*, ¶ 46 (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.*, ¶ 47 (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. 1004, ¶ 50. 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 2-10, 16-19, and 38-45 of the '559 Patent recite the following additional features of the immunogenic composition of claim 1:

- preservation of acetate groups known to be contained in pneumococcal serotype 22F capsular polysaccharide (claims 2, 40 and 43);
- inclusion of additional well-known pneumococcal conjugates (claims 3-9);

- use of common carrier proteins such as CRM_{197}, the standard practice of conjugating polysaccharides individually to CRM_{197}, and a wide range of possible degrees of conjugation (claims 10, 16-17 and 44);
- wide ranges of polysaccharide and carrier protein doses (claims 18-19);
- the typical molecular size distribution of pneumococcal conjugates (claim 38);
- the standard requirement of minimizing free polysaccharide after conjugation (claim 39);
- basic reductive amination chemistry, commonly used for generating saccharide-protein conjugates (claims 41-42); and
- a wide range of molecular weights of serotype 22F capsular polysaccharide (claim 45).

Ex. 1004, ¶ 55.

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, 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. 1004, ¶ 50.

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 1-3 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.

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. 1004, ¶ 73.

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. 1004, ¶ 75.

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. 1004, ¶ 78.

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. 1004, ¶ 79.

2. GSK 2008

Grounds 1-3 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. 1004, ¶ 81.

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. 1004, ¶ 82.

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. 1004, ¶ 85.

GSK 2008 claims and discloses both directly- and indirectly-linked immunogenic serotype 22F conjugates. *Id*. 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. 1004, ¶ 86.

3. PVP 2013

Ground 2 of this Petition further relies on the "Pneumococcal Vaccine Polyvalent" revision to Japan's "Minimum Requirements for Biological Products" ("PVP 2013"), published on the website of Japan's National Institute of Infectious Diseases ("NIID") as of March 2, 2013. Ex. 1009. PVP 2013 is an archived copy that is currently accessible via the Wayback Machine, and the authenticity of PVP 2013 is evidenced by the affidavit of Christopher Butler, dated May 2, 2017. Ex. 1024 at 1-2, 346-352; *see, e.g., Creston*, IPR2015-01460, Paper 14 at 12-15. PVP 2013 was publicly accessible via a link on the NIID's webpage.[2] Because PVP 2013 was published as of March 2, 2013, before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under post-AIA § 102(a)(1).

Japan's "Minimum Requirements for Biological Products" specifies "the manufacturing methods, descriptive definitions, quality, storage, test methods, etc.

[2] An archived copy of a contemporaneous NIID webpage linking to PVP 2013 is also accessible via the Wayback Machine. Ex. 1024 at 4.

of vaccines, antitoxins, blood products and other biological products for human use . . ." Ex. 1024 at 9. PVP 2013 specifies the minimum requirements for a 23-valent pneumococcal polysaccharide vaccine (*e.g.*, Pneumovax® 23) which contains purified capsular polysaccharides from pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. Ex. 1009 at 1. One parameter specified in PVP 2013 is "O-acetate content (O-acetyl/polysaccharide unit molar ratio)." *Id*. at 3. For serotype 22F, the required "O-acetate content" is "0.5 - 1.5." *Id*. at 4; Ex. 1004, ¶ 88.

4. Hsieh 2000

Ground 3 of this Petition relies on Hsieh, "Characterization of Saccharide-CRM_{197} Conjugate Vaccines," *Dev. Biol.* 103:93-104 (2000) ("Hsieh 2000"). Ex. 1013. Because Hsieh 2000 was published in 2000, before the earliest possible priority date of the '559 Patent (January 21, 2014), it is prior art under post-AIA § 102(a)(1).

Hsieh 2000 is a paper written by Patent Owner, which discloses methods for characterizing CRM_{197} conjugate vaccines, including multivalent pneumococcal conjugate vaccines prepared by reductive amination. Hsieh 2000 discloses that "[s]ize exclusion chromatography (SEC) with either CL-2B or CL-4B sepharose is used" to assess molecular size. *Id*. at 6. For pneumococcal conjugates, "[a]s a

qualitative measurement, a percent value of less than 0.3 K_d can be used to indicate the quantity of high molecular fraction in the conjugate." *Id;* Ex. 1004, ¶ 91.

With respect to free saccharide levels, Hsieh 2000 discloses that "the amount should be kept to a minimum and be consistent." Ex. 1013 at 8. To that end, "[u]n-reacted saccharide is normally removed to a great extent in the purification steps of the manufacturing process." *Id.*; Ex. 1004, ¶ 92.

Hsieh 2000 also discloses the typical extent of conjugation for CRM_{197} conjugates, and how to measure it:

> It is essential to demonstrate the covalent linkage of the saccharide to the carrier protein. . . . For pneumococcal conjugates, . . . it is possible to demonstrate the reduction of lysine content of the protein as it reacts with the saccharide. Therefore, the reduction of lysine marker can be indicative of the formulation of the covalent bonds and the consistency of the conjugate reaction. For saccharide-CRM_{197} conjugates, there is a limited number of exposed lysines on surface CRM_{197}, which can participate in the conjugation reaction. **The loss of lysine has been relatively consistent in the range of 6-9**.

Ex. 1013 at 8 (emphasis added); Ex. 1004, ¶ 93.

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. 1004, ¶ 59. 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."[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 a different claim constructions in district courts, where a different claim construction standard applies.

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. 1004, ¶ 64.

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*., ¶ 65. 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 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. 1004, ¶ 68; *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."[4] Ex. 1004, ¶ 70.

[4] 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 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.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Claims 1, 3-10, 16-19, 39, 41-42 and 45 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. 1004, ¶ 100. 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 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 a POSITA 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*., ¶ 101. 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 3-10, 16-19, 39, 41-42 and 45 recite only additional features of 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*., ¶ 102.

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. 1004, ¶ 103. Merck 2011 is directed to immunogenic multivalent pneumococcal conjugate compositions that include a serotype 22F conjugate. *Id*. at ¶ 104; *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. 1004, ¶ 105. 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. 1004, ¶ 106. 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. 1004, ¶ 106. 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*., ¶ 107. 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. 1004, ¶ 107. 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. 1004, ¶ 108 (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. 1004, ¶ 109 (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. 1004, ¶ 110 (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*., ¶ 111. 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. 1004, ¶ 112; *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. 1004, ¶ 113; *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. 1004, ¶ 114. 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*., ¶ 115 (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. 1004, ¶ 116 (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*., ¶ 117. 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. 1004, ¶ 118. 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. 1004, ¶ 119.

2. Claim 3

a. "The immunogenic composition of claim 1, wherein the composition further comprises a *S. pneumoniae* serotype 15B glycoconjugate and a *S. pneumoniae* serotype 33F glycoconjugate."

The 15-valent immunogenic compositions of Merck 2011 include conjugates of serotypes 22F and 33F. *See, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and **33F** individually **conjugated to $\mathbf{CRM_{197}}$**.") (emphasis added). Based on GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to additionally include a serotype 15B conjugate. Ex. 1004, ¶ 120.

GSK 2008 discloses compositions with conjugates of serotypes 22F, 15B and 33F, as required by the claim: "For example, the immunogenic composition comprises at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 *S. pneumoniae* capsular saccharides from different serotypes conjugated to PhtD or fusion protein thereof. For example serotypes **22F** and 1, 2, 3, 4, 5, 6 or 7 further selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, **15**, 17F, 18C, 19A, 19F, 20, 23F and

33F are conjugated to PhtD." Ex. 1007 at 27:20-24 (emphasis added); *see also id*. at 8:29-31, 9:17-23. A POSITA would have understood that "serotype 15" in GSK 2008 includes all serotypes within serogroup 15, including serotype 15B as claimed. Ex. 1004, ¶ 121. Moreover, the claimed serotypes were well-known to be prevalent and had already been included in the Pneumovax® 23 polysaccharide vaccine. *Id*. (citing Ex. 1031 at 2; Ex. 1054 at 4).

3. Claim 4

a. "The immunogenic composition of claim 3, wherein the composition further comprises a *S. pneumoniae* serotype 12F glycoconjugate, a *S. pneumoniae* serotype 10A glycoconjugate, a *S. pneumoniae* serotype 11A glycoconjugate and a *S. pneumoniae* serotype 8 glycoconjugate."

Claim 4 adds conjugates of serotypes 12F, 10A, 11A and 8 to the immunogenic composition of claim 3. Based on GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to include conjugates of serotypes 12F, 10A. 11A and 8. Ex. 1004, ¶ 122. GSK 2008 discloses compositions with conjugates of serotypes 22F, 15B, 33F, 12F, 10A, 11A and 8, as required by the claim: "For example, the immunogenic composition comprises at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 *S. pneumoniae* capsular saccharides from different serotypes conjugated to PhtD or fusion protein thereof. For example serotypes **22F** and 1, 2, 3, 4, 5, 6 or 7 further selected from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, **8**, 9N, 9V, **10A**, **11A**, **12F**, 14, **15**, 17F, 18C, 19A, 19F, 20, 23F and

33F are conjugated to PhtD." Ex. 1007 at 27:20-24 (emphasis added); *see also id*. at 8:29-31, 9:17-23. A POSITA would have understood that "serotype 15" in GSK 2008 includes all serotypes within serogroup 15, including serotype 15B as claimed. Ex. 1004, ¶ 122. Moreover, the claimed serotypes were well-known to be prevalent and had already been included in the Pneumovax® 23 polysaccharide vaccine. *Id*. (citing Ex. 1031 at 2; Ex. 1054 at 4).

4. Claim 5

a. "The immunogenic composition of claim 1 further comprising glycoconjugates from *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F."

The 15-valent immunogenic compositions of Merck 2011 include conjugates of serotypes 22F, 4, 6B, 9V, 14, 18C, 19F and 23F. Ex. 1004, ¶ 123; *see, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, **4**, 5, 6A, **6B**, 7F, **9V**, **14**, **18C**, 19A, **19F**, **22F**, **23F** and 33F individually **conjugated to CRM_{197}**.") (emphasis added).

5. Claim 6

a. "The immunogenic composition of claim 1 further comprising glycoconjugates from *S. pneumoniae* serotypes 1, 5 and 7F."

The 15-valent immunogenic compositions of Merck 2011 include conjugates of serotypes 22F, 1, 5 and 7F. Ex. 1004, ¶ 124; *see, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile

liquid formulation of pneumococcal capsular polysaccharides of serotypes **1**, 3, 4, **5**, 6A, 6B, **7F**, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F individually **conjugated to CRM_{197}**.") (emphasis added).

6. Claim 7

a. "The immunogenic composition of claim 1 further comprising glycoconjugates from *S. pneumoniae* serotypes 6A and 19A."

The 15-valent immunogenic compositions of Merck 2011 include conjugates of serotypes 22F, 6A and 19A. Ex. 1004, ¶ 125; *see, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, **6A**, 6B, 7F, 9V, 14, 18C, **19A**, 19F, **22F**, 23F and 33F individually **conjugated to CRM_{197}**.") (emphasis added).

7. Claim 8

a. The immunogenic composition of claim 1 further comprising at least one glycoconjugate from *S. pneumoniae* serotype 3.

The 15-valent immunogenic compositions of Merck 2011 include conjugates of serotypes 22F and 3. Ex. 1004, ¶ 126; *see, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, **3**, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F individually **conjugated to CRM_{197}**.") (emphasis added).

8. Claim 9

a. The immunogenic composition of claim 1, wherein the immunogenic composition is an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20-valent pneumococcal conjugate composition.

The immunogenic compositions of Merck 2011 include a 15-valent pneumococcal conjugate composition. Ex. 1004, ¶ 127; *see, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F individually conjugated to CRM_{197}.").

9. Claim 10

a. "The immunogenic composition of claim 1, wherein the carrier protein is selected from the group consisting of DT (Diphtheria toxin), TT (tetanus toxoid), CRM_{197}, other DT mutants, PD (*Haemophilus influenzae* protein D), and immunologically functional equivalents thereof."

A POSITA would have been motivated with a reasonable expectation of success to construct the immunogenic serotype 22F conjugate of claim 1 with CRM_{197} carrier protein. Ex. 1004, ¶ 128. Both Merck 2011 and GSK 2008 disclose CRM_{197} as a suitable carrier protein, and the Examples of Merck 2011 include an immunogenic serotype 22F CRM_{197} conjugate. *See, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of

serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F individually **conjugated to CRM_{197}**.") (emphasis added), 15:26-30:15 (Examples); Ex. 1007 at 10:12:16 ("Any *Streptococcus pneumoniae* capsular saccharides present in the immunogenic composition of the invention may be conjugated to . . . CRM197 . . ."); *see also id.* at 11:34-12:22.

10. Claim 16

a. "The immunogenic composition of claim 10, wherein said carrier protein is CRM_{197}."

A POSITA would have been motivated with a reasonable expectation of success to construct the immunogenic serotype 22F conjugate of claim 1 with CRM_{197} carrier protein. Ex. 1004, ¶ 129. Both Merck 2011 and GSK 2008 disclose CRM_{197} as a suitable carrier protein, and the Examples of Merck 2011 include an immunogenic serotype 22F CRM_{197} conjugate. *See, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F individually **conjugated to CRM_{197}**.") (emphasis added), 15:26-30:15 (Examples); Ex. 1007 at 10:12:16 ("Any *Streptococcus pneumoniae* capsular saccharides present in the immunogenic composition of the invention may be conjugated to . . . CRM197 . . ."); *see also id.* at 11:34-12:22.

11. Claim 17

a. "The immunogenic composition of claim 16, wherein said polysaccharide is individually conjugated to CRM_{197}."

A POSITA would have been motivated with a reasonable expectation of success to individually conjugate the polysaccharide of claim 1 to CRM_{197} carrier protein. Merck 2011 discloses 15-valent immunogenic compositions (including an immunogenic serotype 22F conjugate), wherein each of the 15 capsular polysaccharides is "individually conjugated to CRM_{197}." Ex. 1004, ¶ 130; *see, e.g.*, Ex. 1006 at 11:31-33 ("In a particular embodiment of the present invention, the PCV-15 vaccine is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F **individually conjugated to CRM_{197}**.") (emphasis added); *see also id.* at 8:1-2 ("These pneumococcal conjugates are prepared by separate processes and bulk formulated into a single dosage formulation.").

GSK 2008 likewise discloses that "the saccharides may each be separately conjugated to different molecules of the protein carrier (each molecule of protein carrier only having one type of saccharide conjugated to it)." Ex. 1004, ¶ 131; Ex. 1007 at 11:30-32. GSK 2008 also discloses CRM_{197} as a suitable carrier protein. *See, e.g., id.* at 10:12-16 ("Any *Streptococcus pneumoniae* capsular saccharides

present in the immunogenic composition of the invention may be conjugated to . . . CRM197 . . ."); *see also id.* at 11:34-12:22.

12. Claim 18

a. "The immunogenic composition of claim 1, wherein each dose of said immunogenic composition comprises 0.1 µg to 100 µg of the polysaccharide."

Merck 2011 discloses that, "[g]enerally, each dose will comprise 0.1 to 100 µg of each polysaccharide." Ex. 1006 at 11:19-20; *see also id*. at 11:33-12:1 ("Each 0.5 mL dose is formulated to contain: 2 µg of each saccharide [including serotype 22F], except for 6B at 4 µg . . ."); Ex. 1004, ¶ 132.

13. Claim 19

a. "The immunogenic composition of claim 1, wherein each dose of said immunogenic composition comprises 10 µg to 150 µg of the carrier protein."

Merck 2011 discloses that "[e]ach 0.5 mL dose is formulated to contain: . . . about 32 µg CRM_{197} carrier protein . . ." Ex. 1006 at 11:33-12:2; *see* Ex. 1004, ¶ 133.

14. Claim 39

a. "The immunogenic composition of claim 1, wherein the glycoconjugates comprise less than about 50% of free polysaccharide compared to a total amount of polysaccharide."

A POSITA would have been motivated with a reasonable expectation of success to purify the conjugates of claim 1 such that they contain less than about

50% of free polysaccharide. Ex. 1004, ¶ 134. Merck 2011 discloses that "infants and young children respond poorly to unconjugated [*i.e.*, free] pneumococcal polysaccharides." Ex. 1006 at 1:25-26. And, Merck 2011 discloses that generation of functional antibody was assessed with respect to "a formulation of PCV-15 using a bulk conjugation process that minimized free (unconjugated) polysaccharide and unconjugated CRM_{197}." *Id*. at 22:16-18. This is consistent with the standard practice in the art. Ex. 1004, ¶ 134; *see, e.g.*, Ex. 1085 at 21-22 ("The ratio of free saccharide with respect to the total saccharide . . . must be below the value listed in the following table [*i.e.*, at most 40%] for each capsular serotype."); Ex. 1034 at 36:58-61 ("Accordingly, in the production of serotype 19A conjugates, . . . **a preferred free saccharide level [is] below about 20-25%**.") (emphasis added); Ex. 1013 at 8 (With respect to free saccharide levels, "the amount should be kept to a minimum and be consistent."). The claimed subject matter would have been especially obvious over GSK 2008, in which every conjugate listed in Table 2 (including serotype 22F conjugates) has less than 12% free polysaccharide. Ex. 1007 at 54:27-55:1.

15. Claim 41

a. "The immunogenic composition of claim 1, wherein said glycoconjugate is prepared using reductive amination."

Merck 2011 discloses that, "[i]n one embodiment, prior to formulation, each pneumococcal capsular polysaccharide antigen is individually purified from *S. pneumoniae*, activated to form reactive aldehydes, and then covalently conjugated using **reductive amination** to the carrier protein CRM_{197}." Ex. 1006 at 7:17-20 (emphasis added); *see also id*. at 6:22-26, 16:25-18:22; Ex. 1004, ¶ 135. GSK 2008 likewise discloses that "[t]he conjugates can also be prepared by direct reductive amination methods . . ." Ex. 1007 at 17:28-30; Ex. 1004, ¶ 136.

16. Claim 42

a. "The immunogenic composition of claim 41, wherein said reductive amination comprises: (a) oxidation of the polysaccharide to form an activated polysaccharide and (b) reduction of the activated polysaccharide and a carrier protein to form the glycoconjugate."

Claim 42 limits the composition of claim 41 to one in which the reductive amination involves activating the polysaccharide by oxidation, followed by reduction of the activated polysaccharide and a carrier protein to form the recited conjugate. A POSITA would have understood that the reductive amination of Merck 2011/GSK 2008, by definition, involves the claimed steps. Ex. 1004, ¶ 137.

Merck 2011 discloses that its reductive amination includes "activation of pneumococcal polysaccharide by reaction with any oxidizing agent" and "conjugation is carried out by reacting a mixture of the activated polysaccharide and carrier protein with a reducing agent." Ex. 1006 at 6:15-26; *see also id*. at 16:25-18:22; Ex. 1004, ¶ 138.

GSK 2008 likewise discloses the claimed steps. Ex. 1004, ¶ 139. GSK 2008 discloses oxidation with, *e.g.*, periodate, to form an activated polysaccharide: "On a saccharide, in general the following groups can be used for a coupling: OH, COOH or NH2. Aldehyde groups can be generated after different treatments known in the art such as: periodate, acid hydrolysis, hydrogen peroxide, etc." Ex. 1007 at 19:9-11. GSK 2008 further discloses reduction with sodium cyanoborohydride (NaCNBH3) to form the conjugate: "Saccharide-aldehyde + NH2-Prot ----> Schiff base + NaCNBH3 ----> conjugate[.]" *Id*. at 19:16.

17. Claim 45

a. "The immunogenic composition of claim 1, wherein the polysaccharide has a molecular weight of between 10 kDa and 2,000 kDa."

A POSITA would have been motivated with a reasonable expectation of success to construct the conjugate of claim 1 with a serotype 22F polysaccharide between 10 and 2,000 kDa. Ex. 1004, ¶ 140. GSK 2008 discloses that the serotype 22F polysaccharide can be, *e.g.*, "between 50 and 800 kDa." Ex. 1007 at

93 (claim 56). And, in the conjugates disclosed in Table 2, the serotype 22F polysaccharide is 159-167 kDa. *Id*. at 54:27-55:1. 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.

B. Claims 2, 40 and 43 Are Invalid as Obvious over Merck 2011 in View of GSK 2008, PVP 2013, and the General Knowledge of a POSITA

The minimum acetate content of the pneumococcal conjugates recited in dependent claims 2, 40 and 43 would have been obvious in further view of PVP 2013 (Ex. 1009). Ex. 1004, ¶ 141. PVP 2013 specifies the minimum requirements for a 23-valent pneumococcal polysaccharide vaccine (*e.g.*, Pneumovax® 23), which contains purified capsular polysaccharides from pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. Ex. 1009 at 1. Because the immunogenicity of a conjugate depends in large part on the immunogenicity of the included polysaccharide, a POSITA would have considered the teachings of PVP 2013 when designing the pneumococcal conjugate compositions of Merck 2011/GSK 2008; that combination incorporates many of the same polysaccharides as PVP 2013 (including from serotype 22F). Ex. 1004, ¶ 141.

1. Claim 2

a. "The immunogenic composition of claim 1, wherein the glycoconjugate comprises at least 0.1 mM acetate per mM polysaccharide."

Based on PVP 2013, a POSITA would have been motivated with a reasonable expectation of success to preserve the claimed amount of acetate in the serotype 22F conjugate of claim 1. Ex. 1004, ¶ 142. PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an "O-acetyl/polysaccharide unit molar ratio" of "0.5 - 1.5"; that entire specified range meets the claimed ratio of "at least 0.1." Ex. 1009 at 4.

Notably, as of January 21, 2014, a POSITA would have understood that O-acetyl groups can contribute to the immunogenicity of pneumococcal polysaccharides. Ex. 1004, ¶ 143 (citing Ex. 1086). Absent a specific showing that O-acetyl groups are not required for immunogenicity of serotype 22F polysaccharide (a showing that has not been made to date), a POSITA would have been motivated to preserve the O-acetyl groups. *Id*.

A POSITA would have had a reasonable expectation of success in maintaining at least 0.1 mM acetate per mM polysaccharide. *Id*., ¶144 That amounts to maintaining the O-acetyl groups on 10% of the polysaccharide repeating units (vs. the 80% of native repeating units that contain an O-acetyl group). *Id*. (citing Ex. 1001 at 15:67-16:2; Ex. 1029 at 1).

Notably, the '559 Patent emphasizes (but does not claim) the use of high pressure homogenization as the preferred method for sizing of serotype 22F polysaccharide while preserving the native O-acetyl groups:

> In a preferred embodiment, the size of the purified polysaccharide is reduced by high pressure homogenization. . . . The high pressure homogenization process is particularly appropriate for reducing the size of the purified serotype 22F polysaccharide while preserving the structural features of the polysaccharide, such as the presence of O-acetyl groups.

Ex. 1001 at 16:31-42. Merck 2011 discloses that such homogenization was used to size the polysaccharides: "The dissolved polysaccharide was passed through a mechanical homogenizer with pressure preset from 0-1000 bar." Ex. 1006 at 17:5-6.

The '559 Patent also suggests (but does not claim) an "aprotic solvent" - *i.e.*, a solvent, such as DMSO, that cannot donate protons - for the serotype 22F conjugation reaction (reductive amination) to prevent the potential loss of O-acetyl groups:

> The conjugation of activated serotype 22F polysaccharide with a protein carrier by reductive amination in dimethylsulfoxide (DMSO) is suitable to preserve the O-acetyl content of the polysaccharide as compared, for example, to reductive amination in aqueous phase where the level of O-acetylation of the polysaccharide may be

significantly reduced. Therefore in a preferred embodiment, step (c) and step (d) are carried out in DMSO.

Ex. 1001 at 24:11-18. It was well-known in the art that certain O-acetyl groups (depending on the polysaccharide and site of the O-acetyl group) can be labile and susceptible to changes in pH, *i.e.*, changes in the concentration of free protons in the solvent. Ex. 1004, ¶ 146 (citing Ex. 1035 at 6 and Ex. 1086 at 2). DMSO was commonly used in the art to preserve O-acetylated polysaccharides. *Id*. (citing Ex. 1036 at 2 ("Dimethyl sulfoxide (DMSO) extractions have been found to result in a water-soluble form of xylan, which retains the acetyl groups present in the native state. This native-like xylan is more likely to result in production of antibodies specific to the native structures found in xylans in situ in the cell wall.")). And, the prior art had already disclosed the use of a DMSO solvent in a reductive amination reaction for the preparation of serotype 22F conjugates. *Id*. (citing Ex. 1037 at 14-16 (claims 1, 9, 52) (claiming the preparation of a pneumococcal serotype 22F conjugate by reductive amination in DMSO); Ex. 1038 at 15 (claims 2-4) (same); Ex. 1039 at [0056] (". . . **DMSO conjugation was conducted for serotypes** 6A, 6B, 7F, 19A, 19F, **22F**, 23F, and 33F.") (emphasis added), [0017] ("The conjugation is achieved by reductive amination.")).

2. Claim 40

a. "The immunogenic composition of claim 1, wherein a ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM isolated polysaccharide is at least 0.6."

Claim 40 requires a ratio of at least 0.6 of acetate in the polysaccharide of the serotype 22F conjugate vs. acetate in the originally-isolated (*i.e.*, native) serotype 22F polysaccharide. In other words, claim 40 requires that at least 60% of the acetate in the native polysaccharide be preserved in the polysaccharide of the conjugate. Ex. 1004, ¶ 147. Based on PVP 2013, a POSITA would have been motivated with a reasonable expectation of success to preserve the claimed amount of acetate in the serotype 22F conjugate of Merck 2011/GSK 2008. *Id*.

As explained for claim 2, a POSITA would have been motivated with a reasonable expectation of success in view of PVP 2013 to obtain a serotype 22F conjugate with an "O-acetyl/polysaccharide unit molar ratio" of "0.5 - 1.5." *Id*., ¶ 148; Ex. 1009 at 4. Given that the O-acetyl content of native 22F capsular polysaccharide was known to be approximately 0.8 (Ex. 1029 at 1), it would have been obvious that the "ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM isolated polysaccharide" would have been 0.625-1.875; that entire specified range meets the claim limitation of "at least 0.6." Ex. 1004, ¶ 148.

3. Claim 43

a. "The immunogenic composition of claim 42, wherein the ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM polysaccharide in the activated polysaccharide is at least 0.6."

Claim 43 limits the composition of claim 42 (in which the serotype 22F conjugate is prepared by reductive amination) to one in which the serotype 22F conjugate has a ratio of at least 0.6 of acetate in the polysaccharide of the conjugate vs. acetate in the activated polysaccharide. In other words, claim 43 requires that at least 60% of the acetate in the activated polysaccharide be preserved in the polysaccharide of the conjugate. Ex. 1004, ¶ 149. Based on PVP 2013, a POSITA would have been motivated with a reasonable expectation of success to preserve the claimed amount of acetate in the serotype 22F conjugate of claim 42. *Id*.

As explained for claim 2, a POSITA would have been motivated with a reasonable expectation of success, in view of PVP 2013, to obtain a serotype 22F conjugate with an "O-acetyl/polysaccharide unit molar ratio" of "0.5 - 1.5." *Id*., ¶ 150; Ex. 1009 at 4. Given that the O-acetyl content of native 22F capsular polysaccharide was known to be approximately 0.8 (Ex. 1029 at 1), it would have been obvious to a POSITA that the "ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM polysaccharide in the activated

polysaccharide" would have been at least 0.625-1.875; that entire specified range meets the claim limitation of "at least 0.6." Ex. 1004, ¶ 150.

C. Claims 38 and 44 Are Invalid as Obvious over Merck 2011 In View of GSK 2008, Hsieh 2000, and the General Knowledge of a POSITA

The molecular size distribution of the conjugate of dependent claim 38, and degree of conjugation of dependent claim 44, would have been obvious in further view of Hsieh 2000 (Ex. 1013). Ex. 1004, ¶ 151. Hsieh 2000 is a paper written by Patent Owner, which discloses methods for characterizing CRM_{197} conjugate vaccines, including multivalent pneumococcal conjugate vaccines prepared by reductive amination; Hsieh 2000 would have been considered by a POSITA designing the pneumococcal conjugate compositions of Merck 2011/GSK 2008. *Id*.

1. Claim 38

a. "The immunogenic composition of claim 1, wherein at least 30% of the glycoconjugates have a K_d below or equal to 0.3 in a CL-4B column."

Based on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to obtain at least 30% of the conjugates of claim 1 with a K_d below or equal to 0.3 in a CL-4B column. Ex. 1004, ¶ 152. Consistent with GSK 2008's disclosure of high molecular weight conjugates, Hsieh 2000 discloses that pneumococcal conjugates should generally have a K_d below or equal to 0.3 in a CL-4B column: "For pneumococcal conjugate, . . . [a]s a qualitative

measurement, a percent value of less than 0.3 K_d can be used to indicate the quantity of high molecular fraction in the conjugate." Ex. 1013 at 6. Based on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to obtain a serotype 22F conjugate in which the majority of the conjugates (and certainly "at least 30% of the glycoconjugates" as claimed) have a K_d below or equal to 0.3 in a CL-4B column. Ex. 1004, ¶ 152; *see also* Ex. 1034 at 36:58-61 ("Accordingly, in the production of serotype 19A conjugates, a preferred value for conjugate molecular size is about 70% 0.3 K_d . . ."); Ex. 1085 at 23 (each conjugate of the 7-valent vaccine must contain at least 30% saccharide with "0.3 or less in Kd value").

2. Claim 44

a. "The immunogenic composition of claim 1, wherein the degree of conjugation of said glycoconjugate is between 2 and 15."

Based on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to construct the conjugate of claim 1 with a "degree of conjugation" between 2 and 15. Ex. 1004, ¶ 153. The '559 Patent defines "degree of conjugation" as "the number of lysine residues in the carrier protein (*e.g.*, CRM_{197}) that become conjugated to the saccharide which can be characterized as a range of conjugated lysines." Ex. 1001 at 26:35-39. Hsieh 2000 discloses a degree of conjugation for pneumococcal CRM_{197} conjugates in the

range of 6-9, entirely within the claimed range. Ex. 1013 at 8. Based on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to obtain a serotype 22F CRM_{197}-conjugate with a degree of conjugation in the range of 6-9, entirely within the claimed range of 2-15. Ex. 1004, ¶ 153.

D. 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 1-10, 16-19, and 38-45 of the '559 Patent. Petitioner respectfully requests that this Petition be granted, *inter partes* review be instituted, and claims 1-10, 16-19, and 38-45 of the '559 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: September 19, 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.

2. The immunogenic composition of claim 1, wherein the glycoconjugate comprises at least 0.1 mM acetate per mM polysaccharide.

3. The immunogenic composition of claim 1, wherein the composition further comprises a *S. pneumoniae* serotype 15B glycoconjugate and a *S. pneumoniae* serotype 33F glycoconjugate.

4. The immunogenic composition of claim 3, wherein the composition further comprises a *S. pneumoniae* serotype 12F glycoconjugate, a *S. pneumoniae* serotype 10A glycoconjugate, a *S. pneumoniae* serotype 11A glycoconjugate and a *S. pneumoniae* serotype 8 glycoconjugate.

5. The immunogenic composition of claim 1 further comprising glycoconjugates from *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

6. The immunogenic composition of claim 1 further comprising glycoconjugates from *S. pneumoniae* serotypes 1, 5 and 7F.

7. The immunogenic composition of claim 1 further comprising glycoconjugates from *S. pneumoniae* serotypes 6A and 19A.

8. The immunogenic composition of claim 1 further comprising at least one glycoconjugate from *S. pneumoniae* serotype 3.

9. The immunogenic composition of claim 1, wherein the immunogenic composition is an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20-valent pneumococcal conjugate composition.

10. The immunogenic composition of claim 1, wherein the carrier protein is selected from the group consisting of DT (Diphtheria toxin), TT (tetanus toxoid), CRM_{197}, other DT mutants, PD (*Haemophilus influenzae* protein D), and immunologically functional equivalents thereof.

16. The immunogenic composition of claim 10, wherein said carrier protein is CRM_{197}.

17. The immunogenic composition of claim 16, wherein said polysaccharide is individually conjugated to CRM_{197}.

18. The immunogenic composition of claim 1, wherein each dose of said immunogenic composition comprises 0.1 μg to 100 μg of the polysaccharide.

19. The immunogenic composition of claim 1, wherein each dose of said immunogenic composition comprises 10 μg to 150 μg of the carrier protein.

38. The immunogenic composition of claim 1, wherein at least 30% of the glycoconjugates have a K_d below or equal to 0.3 in a CL-4B column.

39. The immunogenic composition of claim 1, wherein the glycoconjugates comprise less than about 50% of free polysaccharide compared to a total amount of polysaccharide.

40. The immunogenic composition of claim 1, wherein a ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM isolated polysaccharide is at least 0.6.

41. The immunogenic composition of claim 1, wherein said glycoconjugate is prepared using reductive amination.

42. The immunogenic composition of claim 41, wherein said reductive amination comprises: (a) oxidation of the polysaccharide to form an activated polysaccharide and (b) reduction of the activated polysaccharide and a carrier protein to form the glycoconjugate.

43. The immunogenic composition of claim 42, wherein the ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM polysaccharide in the activated polysaccharide is at least 0.6.

44. The immunogenic composition of claim 1, wherein the degree of conjugation of said glycoconjugate is between 2 and 15.

45. The immunogenic composition of claim 1, wherein the polysaccharide has a molecular weight of between 10 kDa and 2,000 kDa.

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, 13,712 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 19, 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 19, 2017, by FedEx overnight delivery at the following address:

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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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