UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

PFIZER INC.,
Patent Owner.

Case: IPR No. 2017-02132
Patent No. 9,492,559

PATENT OWNER PFIZER'S MOTION TO AMEND

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I. INTRODUCTION

Patent Owner, Pfizer Inc. ("Pfizer") moves to amend certain claims of U.S. Patent 9,492,559 ("the '559 patent") contingent on the outcome of this trial. If the Board finds original independent claim 1 unpatentable, Pfizer requests the Board grant this motion and issue substitute independent claim 46 shown in the attached Claim Listing Appendix. Similarly, if the Board finds dependent claim 2, 3, 4, 9, 41, or 42 unpatentable, Pfizer requests the Board issue substitute claim 47, 48, 49, 50, 51, and 52, respectively, shown in the Claim Listing Appendix.

The motion and accompanying declaration of Dr. Peter Paradiso (EX2045, ¶¶1-95) demonstrate that the substitute claims meet all requirements of 35 U.S.C. § 316(d), 37 C.F.R. § 42.121, and *Western Digital Corp. v. SPEX Technologies, Inc.*, IPR2018-00082, -00084, Paper No. 13 (PTAB Apr. 25, 2018). Each substitute claim is responsive to an asserted ground of unpatentability, none of the amendments seeks to enlarge the scope of the claims or introduce new matter, the amendments present a reasonable number of substitute claims (seven substitute claims in total versus forty-five original claims, twenty-two of which are challenged), and the motion shows the changes sought and the support in the original and benefit applications for each substitute claim.

The motion confirms that the substitute claims are patentable over all prior art known to Pfizer. Having met the statutory requirements of 35 U.S.C. § 316(d)

and 37 C.F.R. § 42.121, as well as its duty of candor, Pfizer is entitled to the substitute claims unless the Board determines that such claims are unpatentable by a preponderance of evidence based on the entirety of the record, including any opposition made by the petitioner. *Western Digital*, IPR2018-00082, Paper No. 13, at *4. This motion goes beyond the threshold statutory and regulatory requirements by showing why the prior art raised in the IPR proceedings challenging the ’559 patent and certain prior art cited during prosecution do not render the substitute claims unpatentable.

II. RELIEF REQUESTED

To the extent the Board finds one or more original claim unpatentable, Pfizer requests that the Board grant this motion to amend with respect to each proposed substitute claim as specified in the attached Claim Listing Appendix.

III. LEVEL OF ORDINARY SKILL IN THE ART

Merck has proposed that the level of a person having ordinary skill in the art 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." Petition, Paper No. 1, at 33. Pfizer adopts this definition for this motion.

IV. CLAIM CONSTRUCTION

Pfizer proposes that the claims terms of the substitute claims be construed by their plain and ordinary meaning. The new proposed limitations, plainly understood, establish patentability of the proposed substitute claims.

V. THE SUBSTITUTE CLAIMS SATISFY C.F.R. § 42.121(a)

Proposed substitute independent claim 46 retains all features of original independent claim 1 and does not enlarge the scope of the original claim. Substitute claim 46 (and therefore dependent substitute claims 47-52) adds the following narrowing limitations to the original claim 1: (i) a limitation that the carrier protein is a "CRM_{197}" protein (previously found in original claim 16); (ii) a limitation that the composition further comprises "glyconconjugates from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F all individually conjugated to CRM_{197}" (from original claims 5, 6, 7, and 8, with the further requirement that all serotypes are individually conjugated to CRM_{197}); (iii) a limitation that the composition comprises "an aluminum salt adjuvant," and (iv) a limitation that "the composition exhibits more than a 2-log increase above baseline in serum IgG levels in New Zealand White Rabbits across all serotypes in the

composition following administration of two equal doses of the composition in the form of an initial dose and a booster dose."

The proposed substitute dependent claims do not enlarge the scope of any original claim. *See* 37 C.F.R. § 42.121(a)(2)(ii). Substitute dependent claims 47-52 amend the dependency recitations of the original claims they will replace. Substitute claim 47 narrows the acetate limitation from original claim 2 by specifying the level of acetate as "0.8" mM acetate per mM polysaccharide. Substitute claims 48-49 narrow the glycoconjugates of original claims 3 and 4 by reciting "wherein said serotypes … are all individually conjugated to CRM_{197}." Substitute claim 50 narrows original claim 9 to conform to the proposed amendments in claim 46. Substitute claims 51 and 52 have been revised to state "22F" polysaccharide in order to conform to the amendments to claim 46.

With respect to the requirement of 37 C.F.R. § 42.121(a)(2)(i) that amendments be responsive to a ground of unpatentability in the trial, the Board has held that the rule does not require "that every word added to or removed from a claim in a motion to amend must be solely for the purpose of overcoming an instituted ground." *Western Digital*, IPR2018-00082, Paper No. 13, at *6. Each substitute claim contains an amendment that is responsive to one or more grounds of unpatentability at issue in this proceeding. The Board instituted trial on a

ground that claims 1, 9, 41 and 42 (and others) are obvious over Merck 2011 (EX1006) in view of Pfizer 2012 (EX1008), on a ground that claim 2 (and others) are obvious over Merck 2011, Pfizer 2012, and PVP 2013 (EX1009), and on a ground that claims 3 and 4 (and others) are obvious over Merck 2011, Pfizer 2012, and GSK 2008 (EX1007). *See* Decision, Paper No. 7, at 35. As discussed in Section VII below, the features added to substitute claim 46 are neither disclosed nor rendered obvious by Merck 2011, Pfizer 2012, PVP 2013, GSK 2008, or the general knowledge of a POSA either alone or in combination, or any other references raised in related proceedings. As each dependent substitute claim includes the limitations of claim 46, they also contain amendments responsive to an asserted ground of unpatentability in the trial. Thus, 37 C.F.R. § 42.121(a)(2)(i) is satisfied.

This motion presents a total of seven (7) substitute claims as opposed to the forty-five (45) original claims of the ’559 patent, twenty-two of which are challenged here. The substitute claims (46-52) represent one substitute claim per original claim (1-4, 9, 41, and 42, respectively), which is presumptively reasonable. No substitute claims have been proposed with respect to each of original claims 5-8, 16-19, 38-40, and 43-45. Thus, the motion presents a reasonable number of substitute claims and is compliant with the statute,

regulations, and guidance. *See* 35 U.S.C. § 316(d)(1)(B); 37 C.F.R. § 42.121(a)(3); *Western Digital*, IPR2018-00082, Paper No. 13, at *4-5.

VI. THE SUBSTITUTE CLAIMS SATISFY 37 C.F.R. § 42.121(b)

As required by 37 C.F.R. § 42.121(b), this motion is accompanied by an appendix that lists the proposed substitute claims and shows the proposed amendments to each claim in light of the corresponding original claim. This section, per 37 C.F.R. § 42.121(b)(1) and (b)(2), sets forth the support in the original disclosure (Appl. No. 14/597,488, "the '488 application") and in the earlier-filed disclosure to which the claims are entitled to priority (No. 61/929,547, "the '547 application"). As demonstrated in the accompanying Declaration of Dr. Peter Paradiso (EX2045), a POSA would have understood that the disclosures of the non-provisional '488 application and the provisional '547 application support the subject matter of the substitute claims at the respective filing dates of each application.

1. Independent Claim 46

The '488 and '547 applications support the first clause of claim 46, "An immunogenic composition comprising: a *Streptococcus pneumoniae* serotype 22F glycoconjugate." EX2045, ¶16. The '488 and '547 applications disclose "new immunogenic compositions for use in pneumococcal vaccines… typically compris[ing] conjugated capsular saccharide antigens (glycoconjugates), wherein

the saccharides are derived from serotypes of *S. pneumoniae*" wherein "the purified polysaccharides, are capsular polysaccharide from serotypes… 22F… of *S. pneumoniae*…." EX1002 at 2:10-13 and 12:4-8; EX1003 at 14:4-7 and 19:34-37; *see also* EX1002 at 172:2-7 and 10-11; EX1003 at 123:2-7 and 10-11; EX2045, ¶17 (cites to the '488 and '547 applications are in parallel because the disclosures are substantially identical; unless specified otherwise, cites are to IPR page number). The '488 and '547 applications further describe the structure of the 22F polysaccharide. *See* EX1002 at 5:23-24 and 206 (Figure 6); EX1003 at 16:19-20 and 145 (Figure 6); EX2045, ¶18. The '488 and '547 applications also characterize a number of serotype 22F glycoconjugates. *See* EX1002 at 35:20-21, 154:31-32, and 155 (Table 16); EX1003 at 35:5-37:25, 113:12, and 113 (Table 16); EX2045, ¶19. Examples 17 and 18 of the '488 and '547 applications show compositions comprising the glycoconjugates of substitute claim 46 that are immunogenic. *See* EX1002 at 161:4-11, 162:1-8, 162:25-34, 164:2-6, 164:12-165:8, 165:33-166:9, 164 (Table 21), and 166 (Table 22); EX1003 at 118:2-8, 118:22-28, 119:1-9, 119:30-33, 120:2-10, 121:12-22, 120 (Table 21), and 122 (Table 22); EX2045, ¶20; *see also Sanofi v. Pfizer*, IPR2018-00188, Paper No. 10, at *7 (PTAB June 5, 2018).

The ’488 and ’547 applications also provide support for the clause “wherein the 22F glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa.” EX2045, ¶21. The ’488 and ’547 applications disclose that “the serotype 22F glycoconjugate of the invention has a molecular weight of… between 1,000 kDa and 12,500 kDa….” *See* EX1002 at 35:20-34; EX1003 at 35:5-16; *see also* EX1002 at 176:7-12; EX1003 at 126:9-12; EX2045, ¶22. The ’488 application further discloses a range of molecular weights for 22F glycoconjugates within the claimed range in Table 16. *See* EX1002 at 154:31-32 and 155 (Table 16); EX1003 at 113:12 and 113 (Table 16); EX2045, ¶23; *see also Sanofi*, IPR2018-00188, Paper No. 10, at *7.

The ’488 and ’547 applications provide support for “wherein the 22F glycoconjugate… comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a CRM_{197} carrier protein.” EX2045, ¶24. The ’488 and ’547 applications state, “the glycoconjugates from *S. pneumoniae* serotype 22F is conjugated to CRM_{197}.” EX1002 at 92:32-33; EX1003 at 73:15-16; *see also* EX1002 at 4:30-5:1, 8:6-8, 96:11-12, 174:3-4, and 177:14-20; EX1003 at 15:34-35, 17:16-18; 75:35-36, 124:25-26, and 127:4-9; EX2045, ¶25. The ’488 and ’547 applications describe the 22F polysaccharide (*see* EX1002 at 22:30-23:15; EX1003 at 26:24-37) and the CRM_{197} carrier protein (*see* EX1002 at 9:16-27 and 10:1-3;

EX1003 at 18:11-22). EX2045, ¶26. The ’488 and ’547 applications also describe the conjugation process. *See* EX1002 at 29:23-30:15; EX1003 at 30:40-31:22; EX2045, ¶27.

The ’488 and ’547 applications provide support for “wherein the 22F glycoconjugate has … a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2.0.” EX2045, ¶28. The ’488 and ’547 applications describe a number of 22F glycoconjugates within the claimed range of w/w ratios. *See* EX1002 at 154:31-32 and 155 (Table 16); EX1003 at 113:12 and 113 (Table 16); EX2045, ¶29; *see also Sanofi*, IPR2018-00188, Paper No. 10, at *9; *see also id.* at *7-8 and *10. In addition, the ’488 and ’547 applications disclose that the “serotype 22F glycoconjugates of the invention may also be characterized by the ratio (weight/weight) of saccharide to carrier protein.… In other embodiments, the saccharide to carrier protein ratio (w/w) is between 0.5 and 2.… In some such embodiments, the carrier protein is CRM_{197}.” EX1002 at 37:31-38:8; EX1003 at 36:28-37; *see also* EX1002 at 176:13-15; EX1003 at 126:13-15; EX2045, ¶30; EX2013, 77:21-78:4.

The ’488 and ’547 applications also provide support for the “composition comprising… glycoconjugates from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F all individually conjugated to CRM_{197}.”

EX2045, ¶31. The '488 and '547 applications state, "the glycoconjugates… are all individually conjugated to CRM_{197}." EX1002 at 93:19-20; EX1003 at 73:32-33; *see also* EX1002 at 92:30-31; EX1003 at 75:23-24; EX2045, ¶32. The '488 and '547 applications disclose that "the glycoconjugate from *S. pneumoniae* serotype 22F is conjugated to CRM_{197}… the glycoconjugates from *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F are conjugated to CRM_{197}… the glycoconjugates from *S. pneumoniae* serotypes 1, 5 and 7F are conjugated to CRM_{197}… the glycoconjugates from *S. pneumoniae* serotypes 6A and 19A are conjugated to CRM_{197}… the glycoconjugate from *S. pneumoniae* serotype 3 is conjugated to CRM_{197}…." EX1002 at 96:11-30; EX1003 at 75:35-76:10; *see also* EX1002 at 88:13-23, 92:18-29, and 94:10-95:9; EX1003 at 71:16-24, 73:4-12, and 74:13-75:3; EX2045, ¶33. The 16vPnC and 20vPnC vaccines in Examples 15-18 describe glycoconjugates wherein serotypes are "all individually conjugated to CRM_{197}." EX1002 at 161:4-11 and 162:1-8; EX1003 at 118:2-8 and 118:22-28; EX2045, ¶34.

The '488 and '547 applications provide support for the "composition comprising… an aluminum salt adjuvant." EX1002 at 107:3-10, 161:20-25, 162:17-23, 187:12-22, and 197:61-198:2; EX1003 at 80:32-38, 118:16-20, 118:35-40, and 134:13-21; EX2045, ¶35.

The ’488 and ’547 applications provide support for “the composition exhibits more than a 2-log increase above baseline in serum IgG levels in New Zealand White Rabbits across all serotypes in the composition following administration of two equal doses of the composition in the form of an initial dose and a booster dose.” EX2045, ¶36. The ’488 and ’547 applications disclose that New Zealand white rabbits immunized on week 0 and boosted with the same dose on week 2 exhibited an increase in serum IgG levels of more than 2-logs above baseline. EX1002 at 162:25-34, 164:2-6, and 164 (Table 21); EX1003 at 119:1-9, 119:30-33, and 120 (Table 21); *see also* EX1002 at 164:12-165:8, 165:33-166:9, and 166 (Table 22); EX1003 at 120:2-10, 121:12-22, and 122 (Table 22); EX2045, ¶37.

2. Dependent Claims

The ’488 and ’547 applications provide support for the “immunogenic composition of claim 46, wherein the glycoconjugate comprises at least 0.8 mM acetate per mM polysaccharide,” as recited in claim 47, disclosing at least 0.8 mM acetate per mM polysaccharide. *See* EX1002 at 36:22-28; EX1003 at 33:10-16 and 35:35-40; EX2045, ¶38.

The ’488 and ’547 applications provide support for the “immunogenic composition of claim 46, wherein the composition further comprises a *S. pneumoniae* serotype 15B glycoconjugate and a *S. pneumoniae* serotype 33F

glycoconjugate, wherein said serotypes 15B and 33F are all individually conjugated to CRM_{197}" as recited in claim 48, disclosing immunogenic compositions comprising 22F, 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 15B, and 33F glycoconjugates, where serotypes 15B and 33F are individually conjugated to CRM_{197}. *See* EX1002 at 89:11-13, 90:13-18, 91:15-22, 92:3-8, 92:12-17, 93:19-20, 94:10-18, and 96:11-15; EX1003 at 72:3-4, 72:12-14, 72:24-27, 72:34-37, 72:39-73:3, 73:32-33, and 75:35-38; *see also* EX1002 at 88:13-30 and 92:30-31; EX1003 at 71:16-30, 74:13-21, and 75:23-24; EX2045, ¶39. The '488 and '547 applications further show that the compositions recited in claim 48 are immunogenic. *See* EX1002 at 161:4-11, 162:25-28, 164:2-6, 164 (Table 21), 162:1-8, 164:12-165:2, 165:33-166:9, 166 (Table 22), and 172:22-31; EX1003 at 118:2-8, 119:1-4, 119:30-33, 120 (Table 21), 118:22-28, 120:2-5, 121:12-22, 122 (Table 22), and 123:22-30; EX2045, ¶40.

The '488 and '547 applications provide support for the "immunogenic composition of claim 48, 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, wherein said serotypes 12F, 10A, 11A, and 8 are all individually conjugated to CRM_{197}," as recited in claim 49, disclosing

immunogenic compositions comprising serotype 22F, 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 15B, 33F, 12F, 10A, 11A, and 8 glycoconjugates, where serotypes 12F, 10A, 11A, and 8 are individually conjugated to CRM_{197}. *See* EX1002 at 88:13-89:4, 92:12-17, 92:30-31, 93:19-20, 94:10-30, and 96:11-21; EX1003 at 71:16-38, 72:39-73:3, 73:32-33, 74:13-33, 75:23-24, and 75:35-76:2; EX2045, ¶41. The '488 and '547 applications show that the compositions recited in claim 49 are immunogenic. *See* EX1002 at 162:1-8, 164:12-165:2, 165:33-166:9, 166 (Table 22), and 172:25-31; EX1003 at 118:22-28, 120:2-5, 121:12-22, 122 (Table 22), and 123:25-30; EX2045, ¶42.

The '488 and '547 applications provide support for the "immunogenic composition of claim 46, wherein the immunogenic composition is a 14, 15, 16, 17, 18, 19 or 20-valent pneumococcal conjugate composition," as recited in claim 50, disclosing immunogenic compositions from 14-20 valents. *See* EX1002 at 4:3-27, 93:32-94:8, 94:10-95:32, 96:11-12, and 97:1-2; EX1003 at 15:15-33, 74:3-11, 74:13-75:22, 75:35-36, and 76:16-21; EX2045, ¶43. The '488 and '547 applications show that the composition recited in claim 50 is immunogenic. *See* EX1002 at 161:4-11, 162:25-28, 164:2-6, 164 (Table 21), 162:1-8, 164:12-165:2, 165:33-166:9, 166 (Table 22), and 173:24-25; EX1003 at 118:2-8, 119:1-4,

119:30-33, 120 (Table 21), 118:22-28, 120:2-5, 121:12-22, 122 (Table 22), and 124:17-18; EX2045, ¶44.

The ’488 and ’547 applications provide support for the “immunogenic composition of claim 46, wherein said 22F glycoconjugate is prepared using reductive amination,” as recited in claim 51, disclosing that the serotype 22F glycoconjugate of the invention is prepared using reductive amination. *See* EX1002 at 30:11-15 and 33:25-34:18; EX1003 at 31:19-22 and 33:35-34:17; EX2045, ¶45. The ’488 and ’547 applications show that the serotype 22F glycoconjugates of the immunogenic formulations of Examples 17 and 18 are prepared using reductive amination. *See* EX1002 at 152:19-153:4, 153:33-154:22, 161:4-11, 162:25-33, 162:1-8, and 164:12-165:7; EX1003 at 111:23-31, 112:23-113:3, 118:2-8, 119:1-8, 118:22-28, and 120:2-9; *see also* EX1002 at 177:21-22; EX1003 at 127:10-11; EX2045, ¶46.

As shown above for claim 51, the ’488 and ’547 applications provide support for the preamble of claim 52, “The immunogenic composition of claim 51, wherein said reductive amination comprises….” The ’488 and ’547 applications also provide support for “(a) oxidation of the 22F polysaccharide to form an activated 22F polysaccharide.” EX2045, ¶47. The ’488 and ’547 applications describe the procedure for “Oxidation of Isolated *S. pneumoniae* serotype 22F

capsular polysaccharide" for the serotype 22F glycoconjugate of the immunogenic formulations of Examples 17 and 18. *See* EX1002 at 152:19-153:2; EX1003 at 111:23-29; *see also* EX1002 at 153:3-4; EX1003 at 111:30-31; EX2045, ¶48. The '488 and '547 applications provide support for "(b) reduction of the activated 22F polysaccharide and CRM_{197} to form the glycoconjugate," disclosing specific steps for the reductive amination process used to form the serotype 22F glycoconjugate of the immunogenic formulations of Examples 17 and 18. *See* EX1002 at 153:33-154:22 and EX1003 at 112:23-113:3; EX2045, ¶49.

VII. THE PROPOSED SUBSTITUTE CLAIMS ARE PATENTABLE OVER THE PRIOR ART

Pfizer does not bear the burden of persuasion for the patentability of the proposed substitute claims. *See Aqua Products, Inc. v. Matal*, 872 F.3d 1290, 1327 (Fed. Cir. 2017). Merck bears the burden of proving that the substitute claims are unpatentable. *See Bosch Automotive Service Solutions LLC v. Matal*, 878 F.3d 1027, 1040 (Fed. Cir. 2017). The substitute claims are patentable over all material prior art references known to Patent Owner. Below, Pfizer addresses certain prior art references that have been presented in IPR proceedings challenging the '559 patent and cited during prosecution. Pfizer is not aware of any other prior art that it believes is material to the substitute claims.

1. The Substitute Claims Are Patentable over Merck 2011 in view of Pfizer 2012 and the "General Knowledge" Identified by the Petition in IPR2017-02132

Substitute claim 46 reflects a primary object of the invention described in the '559 patent -- to provide a vaccine that protects against *S. pneumoniae* serotypes found in Prevnar13® and additional serotypes not found in Prevnar13®. *See* EX1001 at 2:15-23 (cites to EX1001 are column:line number); EX2045, ¶57. Prevnar13® is a conjugate vaccine containing *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, individually conjugated to CRM_{197}. *See* EX2033 at 5; EX2045, ¶57. Substitute claim 46 recites a composition comprising a serotype 22F-CRM_{197} glycoconjugate (with molecular weight and polysaccharide/carrier protein characteristics previously specified in claim 1) combined with thirteen glycoconjugates from the same serotypes as Prevnar13®, all of which are individually conjugated to CRM_{197}. EX2045, ¶57. In addition, claim 46 requires that the composition exhibits "more than a 2-log increase above baseline in serum IgG levels in New Zealand White Rabbits across all serotypes in the composition following administration of two equal doses of the composition in the form of an initial dose and a booster dose" (hereinafter "2-log IgG Increase"). EX2045, ¶58. The 2-log IgG Increase limitation is supported in the specification, particularly in Examples 17 and 18. *See* EX1001 at 123:35-36, 124:60-61, and Tables 21-22); EX2045, ¶58; *see also* Section VI. A 2-log IgG Increase across all

serotypes is an indicator of an efficacious multivalent vaccine. EX2045, ¶59 (citing EX2027 at 19 (Table 3, 13vPnC +$AlPO_4$, Ratio Wk4:Wk0) and 20 (Table 5, 13vPnC, Ratio Wk4:Wk0)). The vaccines of the invention were the first instance of a composition comprising the glycoconjugates of Prevnar13® plus an additional serotype 22F glycoconjugate that exhibited the claimed 2-log IgG Increase. EX2045, ¶59.

The Petition in IPR2017-02132 asserts that original claim 1 and certain dependent claims are obvious over Merck 2011 (EX1006) in view of Pfizer 2012 (EX1008) and the general knowledge of a POSA. IPR2017-02132, Paper No. 1, at 38-54; *see also* IPR2017-02132, EX1005 at ¶¶ 103-130 (cited in support of the petition). The substitute claims are not rendered obvious by this combination of prior art. EX2045, ¶60. Merck 2011 does not show a composition comprising the recited serotype-CRM_{197} glycoconjugates which exhibits the claimed 2-log IgG Increase. EX2045, ¶60. While Merck 2011 provides no IgG data in New Zealand White Rabbits ("NZWR") against baseline values, it does provide, in Fig. 2, serotype-specific GMC IgG data for serotypes 1, 3, 5, 6A, 7F, 19A, 22F and 33F after administration of two doses to Infant Rhesus Monkeys (IRM). *See* EX1006 at 5:13-14 and 24:23-25; EX2045, ¶61. Merck 2011 states, "PD-2 responses to [serotypes 1, 3, 5, 6A, 7F, 19A, 22F and 33F] were all at least 10-fold higher than

baseline (pre-vaccination) IgG concentrations. *See* EX1006 at 24:24-25; EX2045, ¶62. The data in Fig. 2 shows that the composition did not exhibit more than a 2-log increase in serum IgG levels in IRM following the two immunizations for serotypes 1, 3, 5, 6A, 7F, 19A, and 22F. EX2045, ¶63. In addition, the data provides no information as to serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, which are also recited in substitute claim 46. EX2045, ¶64.

Merck 2011 provides certain data from experiments in NZWRs which would cause a POSA to doubt whether the PCV-15 vaccine in Merck 2011 could exhibit the 2-log IgG Increase. EX2045, ¶65. Merck 2011 Table 3 shows a post-dose 2 IgG response ratio of PCV-15 vs. Prevnar® (7vPnC) for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. *See* EX1006 at 25:14-26:14; EX2045, ¶65. The data shows that for several serotypes, IgG values induced by PCV-15 were less than those induced by Prevnar®, including a low 0.27 ratio for serotype 18C (NZWR-4). *See* EX1006 at 26 (Table 3); EX2045, ¶66. Merck 2011 acknowledges the problem, stating that PCV-15 demonstrated >2.5-fold lower IgG than Prevnar® in 2 of 4 experiments for serotype 23F. *See* EX1006 at 26:13-14; EX2045, ¶67.

Table 5 of Merck 2011 shows post-dose 2 IgG titers with Prevnar®, 1X human dose of PCV-15, and 2X human dose of PCV-15. *See* EX1006 at 27:11-28:3; EX2045, ¶68. The Table 5 data shows that PCV-15 in both 1X and 2X dose

volumes elicited IgG titers lower than found with Prevnar® for serotypes 4, 6B, 14, 18C, 19F, and 23F. *See* EX1006 at Table 5; EX2045, ¶69. The same was true for serotypes 6A and 19A even though Prevnar® does not contain glycoconjugates of these serotypes. *See* EX1006 at Table 5; EX2045, ¶70.

Table 6 of Merck 2011 shows post-dose 2 IgG titers of PCV-15 formulated with 1x, 2x, or 0x aluminum adjuvant in NZWRs. EX1006 at 30-31. The Table 6 data shows that PCV-15 formulated with 1x or 2x aluminum adjuvant elicited IgG titers lower than found with Prevnar® for serotypes 4, 18C, 19F and 23F. *See* EX1006 at Table 6; EX2045, ¶71.

Taken individually and collectively, the IRM and NZWR data in Merck 2011 would suggest to a POSA that the PCV-15 vaccine disclosed in Merck 2011 would not meet the 2-log IgG Increase limitation for all serotypes required by substitute claim 46 and would not be an efficacious multivalent vaccine because of the reduced immune response and evidence of immune interference. EX2045, ¶72.

Pfizer 2012 (EX1008) does not disclose any *S. pneumoniae* serotype glyconconjugates, any multivalent glycoconjugate compositions, or any immunogenicity data whatsoever. EX2045, ¶73. With the knowledge of Merck 2011 and Pfizer 2012, a POSA would not have had a reasonable expectation of success in generating a composition exhibiting the 2-log IgG Increase that includes

the glycoconjugates specified in substitute claim 46. EX2045, ¶74. Multivalent conjugate development often encounters unforeseen obstacles that can affect the IgG levels elicited in animals in pre-clinical testing. EX2045, ¶75. POSAs would have understood that multivalent pneumococcal vaccines present additional complexities with regard to their synthesis, as each serotype is chemically distinct, effectively requiring the optimization of the manufacture of multiple individual vaccines. *See* EX1035 at 1-2; EX2045, ¶76. Given that Merck 2011 casts doubt as to whether the vaccines in Merck 2011 would meet the 2-log IgG Increase required by substitute claim 46 and Pfizer 2012 has no disclosure regarding the limitation, a POSA would have no expectation of success in generating a composition with these properties based on the disclosures of Merck 2011, Pfizer 2012, and the general knowledge of a POSA. EX2045, ¶77.

The Petition in IPR2017-02132 also relies on GSK 2008 (EX1007). GSK 2008 does not show any compositions exhibiting the 2-log IgG Increase, nor does it suggest such a composition could be made with a reasonable expectation of success. Example 2 of GSK 2008 describes 10-, 11-, and 13-valent pneumococcal conjugate compositions that were made and a prophetic 14-valent pneumococcal conjugate composition that "may be made." *See* EX1007 at 56:2-10; EX2045, ¶78. GSK 2008 does not disclose that any composition or vaccine combining all of the

serotype glycoconjugates in substitute claim 46 was made or tested. The conjugates in Example 2 of GSK 2008 use different carrier proteins, including protein D and PhtD, but do not use CRM_{197}. *See* EX1007 at 55-56; EX2045, ¶79.

GSK 2008 does not provide any data regarding IgG levels in NZWR and nothing in the immunogenicity data provided would have led a POSA to conclude that the compositions in GSK 2008 would exhibit the 2-log IgG Increase recited in substitute claim 46. EX2045, ¶80. GSK 2008 provides IgG levels in several types of mice (Tables 15-18) and guinea pigs (Table 19) following three doses (tables use "post III") of 11- and 13-valent compositions. *See* EX1007 at 71-82; EX2045, ¶81. GSK 2008 does not report baseline levels or IgG levels following administration of two doses. *See* EX1007 at 71-82; EX2045, ¶81.

The Petition in IPR2017-02132 further relies on PVP 2013 (EX1009) and Hsieh 2000 (EX1013), neither of which contain nor suggest the missing disclosures discussed above. EX2045, ¶82. Therefore the substitute claims are patentable over the prior art asserted in IPR2017-02132.

2. The Substitute Claims Are Patentable over Merck 2011 in view of GSK 2008 and the "General Knowledge" Identified by the Petition in IPR2017-02131

The Petition in IPR2017-02131 asserts that original claim 1 and certain dependent claims are obvious over Merck 2011 (EX1006) in view of GSK 2008 (EX1007) and the general knowledge of a POSA. IPR2017-02131, Petition, Paper

No. 1, at 33-56 (EX2036); *see also* IPR2017-02131, EX1004 at ¶¶ 100-140 (cited in support of the petition) (EX2037). The substitute claims are not rendered obvious by this combination of prior art. EX2045, ¶83. Merck 2011 and GSK 2008 do not disclose the limitations of the substitute claims as shown in Section VII.1 above.

With the knowledge of Merck 2011 and GSK 2008, a POSA would not have had a reasonable expectation of success in generating a composition exhibiting the 2-log IgG Increase that includes the glycoconjugates specified in substitute claim 46. EX2045, ¶84. The Petition in IPR2017-02131 also relies on Pfizer 2012 (EX1008), which does not disclose the limitations of the substitute claims as shown in Section VII.1 above. EX2045, ¶85. The Petition in IPR2017-02131 further relies on PVP 2013 (EX1009) and Hsieh 2000 (EX1013), neither of which contain nor suggest the missing disclosures discussed above. EX2045, ¶85. Therefore the substitute claims are patentable over the prior art asserted in IPR2017-02131.

3. The Substitute Claims Are Patentable over GSK-711 in view of Merck-086 and the "General Knowledge" Identified by the Petition in IPR2018-00187

The Petition in IPR2018-00187 asserts that original claim 1 and certain dependent claims are obvious over WO 2007/071711 ("GSK-711") (EX2030) in view of U.S. Pat. App. 2011/0195086 ("Merck-086") (EX2031) and the general

knowledge of a POSA. IPR2018-00187, Paper No. 3, at 30-66 (EX2038); *see also* IPR2018-00187, EX1005 at ¶¶ 122-222 (cited in support of the petition) (EX2039). The substitute claims are not anticipated or rendered obvious by this combination of prior art. First, GSK-711 is substantially similar to GSK 2008, which does not disclose the limitations of the substitute claims as shown in Section VII.1 above. EX2045, ¶86. Second, Merck-086 is substantially similar to Merck 2011, which does not disclose the limitations of the substitute claims as shown in Section VII.1 above. *Id.* Neither GSK-711 nor Merck-086 discloses or suggests the limitations of substitute claim 46 for the same reasons discussed in Section VII.1 above regarding GSK 2008 and Merck 2011, respectively. *Id.*

With the knowledge of GSK-711 and Merck-086, a POSA would not have had a reasonable expectation of success in generating a composition that including the glycoconjugates specified in substitute claim 46 that exhibits the 2-log IgG Increase for all serotypes. EX2045, ¶87. The Petition in IPR2018-00187 also relies on Lees 2008 (EX1035), PVP 2013 (EX1009), Pfizer-605 (EX1034), and WO 2011/110531 (EX2032), none of which contain or suggest the missing disclosures discussed above. EX2045, ¶88. Therefore the substitute claims are patentable over the prior art asserted in IPR2018-00187.

4. The Substitute Claims Are Patentable over Prior Art Cited During Prosecution

Substitute claim 46 is also novel and non-obvious over the relevant prior art raised during prosecution. During prosecution, a third-party submission identified four references: US 2013/0266609 ("Boutriau'609") (EX2025), US2012/0052088 ("Davis") (EX2026), US2013/0273098 ("Blue") (EX2001), and US2012/0237542 ("Hausdorff") (EX2027). *See* EX1002 at 386-403. None of these references teaches or suggests a vaccine that includes the glycoconjugates specified in substitute claim 46 and that exhibits the 2-log IgG Increase. EX2045, ¶¶89.

Boutriau'609, Davis, and Blue do not show or suggest a composition comprising the recited serotype-CRM_{197} glycoconjugates which exhibits the claimed 2-log IgG Increase. EX2045, ¶90. Boutriau'609, Davis, and Blue provide no IgG data in New Zealand White Rabbits ("NZWR") or any immunogenicity data that would suggest the vaccines therein could meet the 2-log IgG Increase limitation. EX2045, ¶91. Boutriau'609, Davis, and Blue provide a list of pneumococcal serotypes that may be used for the pneumococcal conjugate, and CRM_{197} as a potential carrier protein for the conjugate. *See* EX2025 at 2 (paragraph 0023) and 4 (paragraph 0059), EX2026 at 19 (paragraphs 0089-0092), EX2001 at 1 (Abstract), 10 (paragraph 0011), and 13-14 (paragraph 0055); EX2045, ¶92. However, Boutraiu'609, Davis, and Blue fail to disclose the claimed

molecular weights or w/w ratios required for a 22F-CRM_{197} glycoconjugate. EX2045, ¶93. Hausdorff does not disclose a 22F-CRM_{197} glycoconjugate with the molecular weight or w/w ratios specified in claim 46. EX2045, ¶94. The sole Office Action in prosecution did not include any new substantive prior art, other than US2004/0202668 ("Boutriau'668") (EX2028), which has the same defective disclosure as Boutriau'609 and Davis. EX2045, ¶95.

VIII. CONCLUSION

For the foregoing reasons, Pfizer requests that the Board grant this motion to amend as to the substitute claims.

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Respectfully submitted,

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CLAIM LISTING APPENDIX

Proposed amended claims are shown in marked-up form below. Underlining and strikethrough text show the modifications to the original claim being made in the corresponding substitute claim.

I. Proposed Substitute Claims

Claim 46 (substitute for original claim 1, if found unpatentable): An immunogenic composition comprising:

a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the 22F 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 CRM_{197} carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2;

glycoconjugates from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F all individually conjugated to CRM_{197};

an aluminum salt adjuvant; and

wherein the composition exhibits more than a 2-log increase above baseline in serum IgG levels in New Zealand White Rabbits across all serotypes in the composition following administration of two equal doses of the composition in the form of an initial dose and a booster dose.

Claim 47 (Substitute for original claim 2, if found unpatentable): The immunogenic composition of claim ~~1~~ 46, wherein the glycoconjugate comprises at least ~~0.1~~ 0.8 mM acetate per mM polysaccharide.

Claim 48 (Substitute for original claim 3, if found unpatentable): The immunogenic composition of claim ~~1~~ 46, wherein the composition further comprises a *S. pneumoniae* serotype 15B glycoconjugate and a *S. pneumoniae* serotype 33F glycoconjugate, wherein said serotypes 15B and 33F are all individually conjugated to CRM_{197}.

Claim 49 (Substitute for original claim 4, if found unpatentable): The immunogenic composition of claim ~~3~~ 48, 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, wherein said serotypes 12F, 10A, 11A and 8 are all individually conjugated to CRM_{197}.

Claim 50 (Substitute for original claim 9, if found unpatentable): The immunogenic composition of claim ~~1~~ 46, wherein the immunogenic composition is a ~~an 8, 9, 10, 11, 12, 13,~~ 14, 15, 16, 17, 18, 19 or 20-valent pneumococcal conjugate composition.

Claim 51 (Substitute for original claim 41, if found unpatentable): The immunogenic composition of claim ~~1~~ 46, wherein said 22F glycoconjugate is prepared using reductive amination.

Claim 52 (Substitute for original claim 42, if found unpatentable): The immunogenic composition of claim ~~41~~ 51, wherein said reductive amination comprises:

(a) oxidation of the 22F polysaccharide to form an activated 22F polysaccharide; and

(b) reduction of the activated 22F polysaccharide and CRM_{197} to form the glycoconjugate.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner Motion to Amend and related exhibits were served on June 18, 2018, by filing this document through the Patent Trial and Appeal Board End to End System as well as delivering a copy via electronic mail upon the following attorneys of record for the Petitioner:

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