UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI PASTEUR INC., SK CHEMICALS CO., LTD,
Petitioner,

v.

PFIZER INC.,
Patent Owner.

Case: IPR No. 2018-00187
Patent No. 9,492,559

PATENT OWNER PFIZER INC.'S NOTICE OF APPEAL

Pursuant to 35 U.S.C. §§ 141(c) and 319 and 37 C.F.R. §§ 90.2(a) and 90.3(b), Patent Owner Pfizer Inc. ("Pfizer") hereby provides notice that it appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision on Remand entered by the Patent Trial and Appeal Board ("Board") on June 10, 2024 (Paper No. 84) and all underlying orders, decisions, rulings, and opinions related thereto that adversely affected Pfizer. A copy of the Final Written Decision is attached as Exhibit A.

On August 2, 2019, Pfizer filed a first Notice of Appeal from the Board's Final Written Decision, which was docketed as Federal Circuit Case No. 19-2224. On August 13, 2019, the Federal Circuit consolidated case No. 19-1871 with 19-1873, 19-1875, 19-1876, and 19-2224. On January 21, 2020, the Federal Circuit vacated the Final Written Decision and remanded the case to the Board for further proceedings in light of *Arthrex, Inc. v. Smith & Nephew, Inc*., 941 F.3d 1320 (Fed. Cir. 2019). On August 17, 2021, the Federal Circuit vacated its January 21, 2020 Order and reinstated the appeal in light of the Supreme Court's decision in *United States v. Arthrex, Inc.*, 141 S. Ct. 1970 (2021). On November 9, 2021, the Federal Circuit remanded the case for the limited purpose of allowing Pfizer the opportunity to request Director review of the Final Written Decision. *Pfizer Inc. v. Sanofi Pasteur Inc., et al*., No. 19-1871, Dkt. No. 53 (Fed. Cir. Nov. 9, 2021).

Pfizer filed a request for Director review on December 10, 2021, which was denied on February 4, 2022 (Paper No. 73). On April 8, 2022, Pfizer filed an Amended Notice of Appeal from the Board's Final Written Decision and the denial of Pfizer's request for Director review. On March 5, 2024, the Federal Circuit (1) affirmed the Board's decisions as to claims 1-45 and proposed substitute claims 46, 47, and 50-52 and (2) vacated the Board's denial of Pfizer's motion to amend as to proposed substitute claims 48 and 49 and remanded the case to the Board to address the patentability of proposed substitute claims 48 and 49. *Pfizer Inc. v. Sanofi Pasteur Inc., et al*., No. 19-1871, Dkt. No. 146 (Fed. Cir. Mar. 5, 2024).

Pursuant to 37 C.F.R. § 90.3(b), this notice of appeal is timely, being filed within 63 days after the Board's June 10, 2024 Final Written Decision on Remand.

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Pfizer indicates that the issues on appeal include that the Board's determination that proposed substitute claims 48 and 49 are unpatentable as obvious under 35 U.S.C. § 103.

Pursuant to 35 U.S.C. § 142 and 37 C.F.R. § 90.2(a), this notice of appeal is being filed simultaneously with the Director of the United States Patent and Trademark Office and the Patent Trial and Appeal Board. In addition, a copy of this notice of appeal is being filed with the Clerk's Office for the United States Court of Appeals for the Federal Circuit along with the required docketing fee.

Dated: August 9, 2024

Respectfully submitted,

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CERTIFICATE OF SERVICE AND FILING

I hereby certify that on August 9, 2024, in addition to being filed and served electronically through the Patent Trial and Appeal Board's P-TACTS System, this **PATENT OWNER PFIZER INC.'S NOTICE OF APPEAL** was filed with and served on the Director of the United States Patent and Trademark Office via e-mail at the following:

Office of the General Counsel
U.S. Patent and Trademark Office
efileSO@uspto.gov

I also hereby certify that on August 9, 2024, this **PATENT OWNER PFIZER INC.'S NOTICE OF APPEAL** and the requisite docketing fees were filed with the Clerk's Office of the United States Court of Appeals for the Federal Circuit via CM/ECF.

I further hereby certify that on August 9, 2024, this **PATENT OWNER PFIZER INC.'S NOTICE OF APPEAL** was served by electronic mail on the following counsel for Petitioner:

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EXHIBIT A

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Paper No. 76
Filed: June 10, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI PASTEUR INC. AND SK CHEMICALS CO., LTD.
and MERCK SHARP & DOHME CORP.,
Petitioners[1],

v.

PFIZER INC.,
Patent Owner.

Case IPR2018-00187, Patent 9,492,559 B2,
Case IPR2017-02131, Patent 9,492,559 B2,
Case IPR2017-02132, Patent 9,492,559 B2

Before JEFFREY N. FREDMAN, RYAN H. FLAX, and TIMOTHY G. MAJORS, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge*.

JUDGMENT[2]
Final Written Decision on Remand
Denying Patent Owner's Motion to Amend
as to Proposed Substitute Claims 48 and 49
35 U.S.C. § 144, 318

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[1] We note that Merck Sharp & Dohme Corp. is no longer an actively participating in IPR2017-02131 and IPR2017-02132. *See, e.g.*, IPR2017-02132, Paper 67 at 1 "Pfizer and Merck resolved their dispute, and Merck withdrew from the appeal."

[2] We exercise our discretion to issue one Decision to be filed in each case. Our rationale for such is indicated below.

I. INTRODUCTION

This case was remanded to the Board by the United States Court of Appeals for the Federal Circuit with instructions that we address the patentability of Patent Owner's proposed substitute claims 48 and 49 to U.S. Patent No. 9,492,559 B2 (Ex. 1001, "the '559 patent"). *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341 (Fed. Cir. 2024); *see* Paper 15 (Patent Owner's Motion to Amend, "Mot. Amend."). The Court stated that:

> we affirm *in toto* the Board's decision at issue in Appeals 2019-1875 and 2019-1876. We further affirm the Board's decisions at issue in Appeals 2019-1871, 2019-1873, and 2019-2224 as to claims 1–45 and proposed substitute claims 46, 47, and 50–52. Claims 1–45 are therefore unpatentable. But we vacate the Board's denials of Pfizer's motions to amend in those decisions as to proposed substitute claims 48 and 49 and remand for further proceedings consistent with this opinion.

Pfizer, 94 F.4th at 1354.[3]

We therefore limit our analysis to proposed substitute claims 48 and 49 (the "Challenged Claims") of the '559 patent. For the reasons discussed herein, we determine that Petitioner has shown, by a preponderance of the evidence, that the Challenged Claims are unpatentable.

[3] The same issues on remand in IPR2018-00187 remain for IPR2017-02131 and IPR2017-02132, and all three of these pending cases are addressed together in both the Federal Circuit's Decision from which these proceedings are remanded, and in this consolidated Final Decision, because the issues presented are substantively identical. *See Pfizer*, 94 F.4th 1341, 1350–54. We generally cite to the record of the IPR2018-00187 proceeding, as it is representative, and will specifically note when we cite to the record in either of the IPR2017-02131 or IPR2017-02132 proceedings.

A. Background

Sanofi Pasteur Inc. and SK Chemicals Co., Ltd. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–45 of the '559 patent. Paper 3 ("Pet."). Pfizer Inc. ("Patent Owner") filed a Patent Owner's Preliminary Response. Paper 8 ("Prelim. Resp.").

On June 5, 2018, we instituted an *inter partes* review of all challenged claims. Paper 10 ("Dec. Inst."). Patent Owner filed a Motion to Amend. Paper 15. Patent Owner then filed a Patent Owner Response to the Petition. Paper 21 ("PO Response"). Petitioner filed an Opposition to the Motion to Amend (Paper 28) ("Pet. Opp."), followed by a Reply to the Patent Owner's Response. Paper 31 ("Pet. Reply"). Patent Owner then filed a Reply in Support of the Motion to Amend. Paper 36 ("PO Reply"). Petitioner filed a Sur-Reply to Patent Owner Motion to Amend. Paper 55 ("Pet. Sur-Reply"). Patent Owner filed a Sur-Reply. Paper 46 ("PO Sur-Reply").

On February 12, 2019, the parties presented arguments at an oral hearing.[4] The hearing transcript has been entered in the record. Paper 59 ("Tr."). We issued a Final Written Decision determining that Petitioner had shown by a preponderance of the evidence that original claims 1–45 and proposed substitute claims 46–52 of the '559 patent were unpatentable. Paper 61.

Patent Owner filed a Notice of Appeal of the Final Written Decision with the Federal Circuit. Paper 63. Patent Owner then filed a Request for

[4] A separate hearing was held for IPR2017-02131 and IPR2017-02132 on November 13, 2018. *See, e.g.*, IPR2017-02131, Paper 58.

Director Review, which was Denied. Papers 72, 73. Patent Owner then filed an amended Notice of Appeal. Paper 74.

On April 29, 2024, the Federal Circuit mandate issued for its decision in which it: (1) affirmed our Final Written Decisions to the extent that claims 1–45 of the '559 patent and proposed substitute claims 46, 47, and 50–52 were found unpatentable and (2) vacated our Final Written Decisions as to proposed substitute claims 48 and 49 of the '559 patent and remanded for further proceedings consistent with its decision. *Pfizer*, 94 F.4th at 1354. The Federal Circuit determined that we abused our discretion because "[i]t does not appear that the Board considered whether, once incorporated, it would have been reasonably expected that the compositions exhibit the claimed 2-log IgG increase across all serotypes[5] recited in proposed claims 48 and 49." *Id*. at 1353. The Federal Circuit explained that it "is hornbook law that administrative agencies must provide a 'reasoned basis' for their actions that is sufficient to permit meaningful judicial review." *Id*. The Federal Circuit therefore remanded for the Board to address whether the record provided sufficient evidence to support an obviousness finding for the 2-log IgG increase required by proposed substitute claims 48 and 49 of the '559 patent. *Id*. at 1352–53.

On May 15, 2024, we conducted a conference call with the parties where the parties agreed that no further briefing or evidence was necessary to address the remand. Paper 83.

[5] A "serotype" is defined as "a group of intimately related microorganisms distinguished by a common set of antigens." *See* https://www.merriam-webster.com/dictionary/serotype.

B. Related Proceedings

A concurrent Petition for *inter partes* review of the '559 patent, IPR2018-00188, was denied institution on June 5, 2018. IPR2018-00188, Paper 10. Four *inter partes* reviews of the '559 patent were filed by Merck Sharp & Dohme Corp. as IPR2017-02131, IPR2017-02132, IPR2017-02136, and IPR2017-02138. *See* Pet. 2. The same issues as in the current proceeding remain for IPR2017-02131 and IPR2017-02132. *Pfizer*, 94 F.4th at 1350–54.

C. The '559 Patent (Ex. 1001)

The '559 patent involves vaccines for "vaccination of human subjects, in particular infants and elderly, against pneumoccocal infections . . . ." Ex. 1001, 1:21–22. "Pneumonia, febrile bacteraemia and meningitis are the most common manifestations of invasive pneumococcal disease, whereas bacterial spread within the respiratory tract may result in middle-ear infection, sinusitis or recurrent bronchitis." *Id*. at 1:28–32. "Pneumonia is by far the most common cause of pneumococcal death worldwide." *Id*. at 1:46–48.

The '559 patent describes that the "etiological agent of pneumococcal diseases, *Streptococcus pneumoniae* (pneumococcus), is a Gram-positive encapsulated coccus,[6] surrounded by a polysaccharide capsule.[7]

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[6] A "coccus" is defined as "a spherical bacterium." *See* https://www.merriam-webster.com/dictionary/coccus.

[7] "Pneumococcus is encapsulated with a chemically linked polysaccharide which confers serotype specificity. There are 90 known serotypes of pneumococci, and the capsule is the principle [sic] virulence determinant for pneumococci, as the capsule not only protects the inner surface of the

Differences in the composition of this capsule permit serological differentiation between about 91 capsular types." *Id*. at 1:49–53. "Pneumococcal conjugate vaccines (PCVs) are pneumococcal vaccines used to protect against disease caused by *S. pneumoniae* (pneumococcus)." *Id*. at 1:59–61. "There are currently three PCV vaccines[8] available on the global market: PREVNAR® (called PREVENAR® in some countries) (heptavalent vaccine), SYNFLORIX® (decavalent vaccine) and PREVNAR 13® (tridecavalent vaccine)." *Id*. at 1:61–65.

The '559 patent states, "there 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." *Id*. at 2:3–6.

D. Challenged Claims

Proposed substitute claims 48 and 49 depend from proposed substitute independent claim 46 of the '559 patent. Paper 15, ii. Claims 46, 48, and 49 recite:

> 46. 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

bacteria from complement, but is itself poorly immunogenic." Ex. 1007, 2:10–14.

[8] The valency of a vaccine refers to the number of different serotypes of bacteria to which the vaccine induces immune response (e.g., a tridecavalent vaccine protects against thirteen different bacterial strains).

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.

48. 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}.

49. 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}.

Mot. Amend., Claims Listing App'x i–ii (underlining identifies proposed additions compared to existing claims, strike-throughs identify proposed deletions compared to those claims).

As noted above, the Federal Circuit affirmed the Board's earlier determination that proposed substitute claim 46 is unpatentable over the asserted prior art. *Pfizer*, 94 F.4th at 1352, 1354 ("[S]ubstantial evidence supports the Board's conclusion that a person of ordinary skill in the art would have had a reasonable expectation of success in arriving at the

composition claimed in proposed claim 46. Therefore, the Board did not abuse its discretion in denying Pfizer's motions to amend as to that claim.").

E. The Remaining Grounds of Unpatentability

During trial, Petitioner asserted that proposed substitute claims 48 and 49 were unpatentable as obvious (Papers 28, 55), as summarized here:

Reference	Basis	Claims Challenged
Merck-086,[9] Hausdorff,[10] GSK-711,[11] General knowledge in the art	§ 103	48, 49

Petitioner relies on the Declaration of Andrew Lees, Ph.D. Ex. 1005. Petitioner also relies on the Declaration of Dr. Loek Van Alphen, Ph.D. Ex. 1101. Patent Owner relies on the Declaration of Dr. Peng Wang, Ph.D. Ex. 2058. Patent Owner also relies on the Declarations of Dr. Peter Paradiso, Ph.D. Exs. 2051, 2074. Patent Owner submitted a Declaration from Dr. Kasper in the instant proceeding from the 02131 proceeding. Ex. 2037. In the 02131 proceeding, Dr. Kasper and Dr. Paradiso each had two additional Declarations that were filed by Patent Owner. 02131, Exs.

[9] Caulfield et al., US 2011/0195086 A1, published Aug. 11, 2011 ("Merck-086," Ex. 1008). The -02131 and -02132 proceedings relied upon the substantively similar Caulfield et al., US 2011/100151 A1, published Aug. 18, 2011.

[10] Hausdorff et al., US 2012/0237542 A1, published Sept. 20, 2012 ("Hausdorff," Ex. 2027). The -02131 and -02132 proceedings also relied on this reference.

[11] Biemans et al., WO 2007/071711 A2, published June 28, 2007 ("GSK-711," Ex. 1007). The -02131 and -02132 proceedings relied upon the substantively similar Biemans et al., WO 2009/000825 A2, published Dec. 30, 2008.

1096, 1105, 2044, 2063.

II. ANALYSIS

A. Claim Interpretation

As discussed in the Final Written Decision, and left undisturbed by the Federal Circuit Decision, upon review of the parties' arguments and the evidence before us, we maintain our conclusion that the claim term "immunogenic," as it is used in the '559 patent and recited by proposed substitute claims 46, 48, and 49, requires that a functional antibody be elicited against each immunogen contained in the respective composition. Paper 61, 7–9. Consequently, for proposed substitute claims 48 and 49, the term "immunogenic" requires that functional antibodies be elicited against each immunogen specifically recited and required.

B. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art;[12] and (4) where in evidence,

[12] Petitioner states that the person of ordinary skill in the art at the time of the invention "would have had a Ph.D. or equivalent degree in chemistry, immunology, or other biological sciences or an MD and at least 2 years of experience in glycoconjugate vaccine research and development, or would

objective indicia of obviousness or non-obviousness.[13] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

Id. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established

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have an M.S. degree and at least 4 years of relevant experience." Pet. 26 (citing Ex. 1005 ¶ 77). Patent Owner "does not dispute Sanofi's proposed level of skill for the person having ordinary skill in the art." PO Response 8. We agree with the parties regarding the level of ordinary skill in the art. *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

[13] Neither Petitioner nor Patent Owner presents evidence on the fourth Graham factor.

functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

"A petitioner bears the burden of persuasion to show, by a preponderance of the evidence, that any proposed substitute claims are unpatentable." 37 C.F.R. § 42.121(d)(2); *see also Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 15 at 4 (PTAB Feb. 25, 2019) (precedential) (citing *Aqua Prods. Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017); *Bosch Auto. Serv. Sols. LLC v. Iancu*, 878 F.3d 1027 (Fed. Cir. 2017)).

We analyze the patentability of the challenged claims in accordance with the above-stated principles.

C. Obviousness Analysis

Petitioner asserts that proposed substitute claims 48 and 49 are unpatentable as obvious over the combination of Merck-086, Hausdorff, and GSK-711, in view of the knowledge of the ordinarily skilled artisan. Pet. Opp. 10–21; *see also* Pet. Sur-Reply 6–12. To support its challenge to the patentability of these claims, Petitioner proffers witness testimony in the declaration of Dr. Van Alphen and the deposition of Dr. Paradiso. Ex. 1101; Ex. 1105. Patent Owner opposes this challenge. PO Reply 6–12. To support its opposition to the challenge, Patent Owner proffers witness testimony in the two declarations of Dr. Paradiso (Ex. 2051; Ex. 2074).

Based on our review of the parties' arguments and the evidence of record, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of substitute claims 48 and 49 would have been obvious over Merck-086, Hausdorff, and GSK-711, in view of the

general knowledge of an ordinarily skilled artisan. We address the prior art, Petitioner's position, and Patent Owner's arguments below.

1. *Merck-086 (Ex. 1008)*

Merck-086, the prior art status of which is not contested, teaches "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}." Ex. 1008 ¶ 2; *see also* 02131 Ex. 1006, 1:7–11. Merck-086 teaches "conjugates containing serotypes 22F and 33F provide[] robust antibody responses demonstrat[ing] the feasibility of expanding coverage of pneumococcal serotypes. . . ." Ex. 1008 ¶ 15; *see also* 02131 Ex. 1006, 4:2–4. Merck-086 teaches the pneumococcal conjugate vaccine (PCV) with "induced high OPA[14] GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine." Ex. 1008 ¶ 114; *see also* 02131 Ex. 1006, 23:3–4.

Merck-086 teaches "purified polysaccharides are chemically activated to make the saccharides capable of reacting with the carrier protein. . . . Coupling to the protein carrier (*e.g.*, CRM_{197}) can be by reductive amination via direct amination to the lysyl groups of the protein." Ex. 1008 ¶¶ 23, 25; *see also* 02131 Ex. 1006, 6:11–12, 6:22–23. Merck-086 teaches the "concentrated saccharide was mixed with CRM_{197} carrier protein in a 0.2 – 2 to 1 charge ratio. The blended saccharide-CRM_{197} mixture was filtered

[14] Opsonophagocytosis. Ex. 1008 ¶ 114.

through a 0.2 μm filter." Ex. 1008 ¶ 94; *see also* 02131 Ex. 1006, 17:24–25. Table 1 of Merck-086 shows a vaccine formulation comprising 32 μg of total polysaccharide and 32 μg of CRM_{197} carrier protein, with the total polysaccharide being composed of 2 μg of 14 serotypes, including 22F, and 4 μg of serotype 6B. Ex. 1008 ¶ 104; *see also* 02131 Ex. 1006, 19:5–8.

Merck-086 teaches that formulations containing 15 serotypes of the pneumococcal conjugate vaccine (PCV-15) "were evaluated in 4 studies in adult New Zealand White Rabbits (NZWRs) using a compressed immunization regimen in which rabbits received a full human dose of vaccine at day 0 and day 14." Ex. 1008 ¶ 115; *see also* 02131 Ex. 1006, 23:15–17. The results are provided in Table 4 below.

Table 4

Fold-rise (Post-dose 2:Pre-dose 1) in IgG Responses to Non-Prevnar™ Serotypes of PCV-15 Lead Formulations Tested in NZWR

Serotype	NZWR-1	NZWR-2	NZWR-3	NZWR-4
1	14.9	30.5	55.1	59.9
3	33.6	16.2	61.5	28.5
5	12.8	70.2	112.0	134.0
6A	21.3	77.8	143.0	123.0
7F	42.0	83.8	194.0	108.0
19A	40.5	79.1	450.0	314.0
22F	45.7	87.8	243.0	135.0
33F	21.7	47.9	98.8	69.4

Merck 2011 Table 4.

This table summarizes the "fold-rise in antibody levels to the non-Prevnar® serotypes from Day 0 to Day 28 (Post-dose 2, PD-2)" from Merck-086's NZWR studies. Ex. 1008 ¶ 117; *see also* 02131 Ex. 1006, 24:20–28.

In the NZWR-3 and NZWR-4 studies in Table 4 of Merck-086, serotype 22F exhibits a greater than 2-log increase above baseline in New Zealand White Rabbits with values of 243.0 and 135.0, while in the NZWR-1 and NZWR-2 studies in Table 4, serotype 22F exhibits less than 2-log increases of 45.7 and 87.8. *See* Ex. 1008 ¶ 117; *see also* 02131 Ex. 1006, 24:20–28.

2. *Hausdorff (Ex. 2027)*

Hausdorff, also uncontested as prior art, teaches "a multivalent immunogenic composition, wherein the capsular polysaccharides are from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9v, 14, 18C, 19A, 19F and 23F of *Streptococcus pneumoniae*, the carrier protein is CRM_{197}, and the adjuvant is an aluminum-based adjuvant." Ex. 2027 ¶ 8. Hausdorff teaches a starting "saccharide/protein ratio of 2:1." Ex. 2027 ¶ 89. Hausdorff teaches that "[s]ize exclusion chromatography media (CL-4B) was used to profile the relative molecular size distribution of the conjugate." Ex. 2027 ¶ 92.

Hausdorff "examined the ability of the 13vPnC vaccine with $AlPO_4$ adjuvant to elicit vaccine serotype-specific immune responses. The pneumococcal serotypes represented in the 13vPnC vaccine include types 1, 3, 4, 5, 6A, 68, 7F, 9V, 14, 18C, 19A, 19F and 23F." Ex. 2027 ¶ 230. Hausdorff teaches:

> New Zealand White rabbits were immunized intramuscularly at week 0 and week 2 with the planned human clinical dose of each polysaccharide (2 μg of each PS, except 4 μg of 6B) formulated with or without $AlPO_4$ (100 μg/dose). Sera were collected at various time points. Serotype specific IgG was measured by ELISA and functional activity was assessed by OPA.

Ex. 2027 ¶ 230.

Table 3 of Hausdorff shows that each of the thirteen tested serotypes produced an immune response with more than a 2-log increase above baseline serum IgG levels in New Zealand White Rabbits after administration of the two equal doses; this table is reproduced below:

TABLE 3

Rabbit IgG Immune Responses (GMTs) Following Immunization with Two Doses of 13-valent Pneumococcal Glycoconjugate

	Diluent with $ALPO_4$[a]			13vPnC[a]			13vPnC + $ALPO_4$[a]		
Serotype	Week 0	Week 4	Ratio Wk4:Wk0	Week 0	Week 4 (95% CI)	Ratio Wk4:Wk0	Week 0	Week 4 (95% CI)	Ratio Wk4:Wk0
1	<100	<100	1.0	50	5,926 (2,758-12,733)	119	50	11,091 (5,327-23,093)	222
3	<100	<100	1.0	50	6,647 (2,773-15,932)	133	58	16,443 (7,096-38,106)	284
4	<100	<100	1.0	50	13,554 (8,031-22,875)	271	50	29,183 (15,342-55,508)	584
5	134	<100	0.4	50	5,859 (2,450-14,009)	117	50	16,714 (6,959-40,140)	334
6A	141	<100	0.4	74	22,415 (11,987-41,914)	303	83	63,734 (21,141-192,146)	768
6B	<100	<100	1.0	57	8,108 (3,564-18,444)	142	54	23,505 (11,286-48,955)	435
7F	3,859	579	0.2	171	43,591 (26,931-70,557)	444	143	84,888 (46,445-155,151)	496
9V	289	995	3.4	205	15,780 (7,193-34,616)	125	208	43,331[b] (23,256-71,510)	217
14	437	177	0.4	61	6,906 (3,416-13,962)	113	70	16,076 (9,649-26,785)	322
18C	<100	<100	1.0	50	21,283 (15,770-28,725)	426	50	35,040 (24,708-49,692)	701
19A	<100	<100	1.0	121	113,599 (54,518-236,707)	939	144	280,976 (119,587-660,167)	1,951
19F	<100	<100	1.0	50	14,365 (7,346-28,090)	287	50	24,912 (9,243-67,141)	498
23F	<100	<100	1.0	50	5,323 (1,894-14,962)	106	50	15,041 (4,711-48,018)	301

[a]GMTs of pooled sera consisted of equal volumes of serum from each individual rabbit within a group
[b]Statistically different (p = 0.022) from treatment group without $ALPO_4$

Table 3 shows that the ratio of increase in immune response from week 4 to week 0, both with and without aluminum phosphate adjuvant, was higher than a 2-log increase of 100 for every single serotype tested. Ex. 2027 ¶ 231, Table 3.

3. *GSK-711 (Ex. 1007)*

GSK-711, which is also uncontested to be prior art, teaches "the multivalent pneumococcal vaccine of the invention will be selected from the following 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." Ex. 1007, 7:1–3; *see also* 02131 Ex. 1007, 8:29–31. GSK 2008 teaches conjugation of polysaccharides to the carrier protein CRM_{197} (*see* Ex. 1007, 10:4–6; *see also* 02131 Ex. 1007, 10:13–15) and teaches, "[p]referably the ratio of carrier protein to *S. pneumoniae* saccharide is between 1:5 and 5:1." Ex. 1007, 19:1; *see also* 02131 Ex. 1007, 20:24. GSK-711 further teaches, in claim 61, an "immunogenic composition of any preceding claim wherein the average size (e.g. M_w) of the saccharides is above 50 kDa, e.g[.], 50-1600. . . ." Ex. 1007, 82; *see also* 02131 Ex. 1007, 94, claim 61.

GSK-711 teaches a *Streptococcus pneumoniae* vaccine comprising "capsular saccharide antigens (preferably conjugated), wherein the saccharides are derived from at least ten serotypes of *S. pneumoniae*" that may include an "*S. pneumoniae* saccharide conjugate of 22F." Ex. 1007, 6:4, 24–26[15]; *see also* 02131 Ex. 1007, 8:19–20, 7:31. GSK-711 teaches, "*Streptococcus pneumoniae* capsular saccharides . . . may be conjugated to a carrier protein independently selected from the group consisting of . . . CRM197. . . ." Ex. 1007, 8:18–20; *see also* 02131 Ex. 1007, 10:12–14. GSK-711 teaches "saccharide conjugates present in the immunogenic compositions of the invention may be prepared by any known coupling technique" and specifically, conjugates "can also be prepared by direct

[15] We refer to the original page numbers in Ex. 1007.

reductive amination methods. . . ." Ex. 1007, 15:9–10; 16:1; *see also* 02131 Ex. 1007, 17:1–2, 17:28. GSK-711 teaches "22F-PhtD[16] administered within the 13-valent conjugate vaccine formulation [was] shown immunogenic in old C57BI mice." Ex. 1007, 67:36–37; *see also* 02131 Ex. 1007, 70:17–18.

GSK-711 teaches: "Preferably the ratio of carrier protein to *S. pneumoniae* saccharide is between 1:5 and 5:1; e.g. between 1:0.5–4:1, 1:1–3.5:1, 1.2:1–3:1, 1.5:1–2.5:1; e.g. between 1:2 and 2.5:1; 1:1 and 2:1 (w/w)." Ex. 1007, 19:1–3; *see also* 02131 Ex. 1007, 20:24–26. Table 2 of GSK-711 teaches fourteen different conjugates—the smallest conjugate size was PS4-PD of 1303 kDa and the largest conjugate size was PS9V-PD of 9572 kDa. Ex. 1007, 53, Table 2; *see also* 02131 Ex. 1007, 54–55, Table 2. GSK-711 discloses a conjugate of serotype 22F, with a carrier/PS ratio of 2.17, but does not determine the conjugate size. Ex. 1007, 53, Table 2; *see also* 02131 Ex. 1007, 54–55, Table 2.

GSK-711 claims a conjugate where "the average size (e.g. M_w) of the 22F saccharide is between 50 and 800 kDa. . . ." Ex. 1007, 81, claim 56; *see also* 02131 Ex. 1007, 93, claim 56. GSK-711 further teaches, in claim 61, an "immunogenic composition of any preceding claim wherein the average size (e.g. M_w) of the saccharides is above 50 kDa, e.g., 50–1600. . . ." Ex. 1007, 82; *see also* 02131 Ex. 1007, 94, claim 61.

[16] "22F-PhtD" is a term used by GSK-711 for capsular saccharide 22F conjugated to a polyhistidine triad carrier protein, specifically PhtD. Ex. 1007, 8:25–29.

GSK-711 teaches, "immunogenic conjugates prone to hydrolysis may be stabilised by the use of larger saccharides for conjugation. The use of larger polysaccharides can result in more cross-linking with the conjugate carrier and may lessen the liberation of free saccharide from the conjugate." Ex. 1007, 12:31–34; *see also* 02131 Ex. 1007, 14:18–21. GSK-711 teaches, "that saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease." Ex. 1007, 13:1–3; *see also* 02131 Ex. 1007, 14:23–25. GSK-711 recommends optimization for larger size saccharide-protein conjugates, limited only by a requirement to be "filterable through a 0.2 micron filter. . . ." Ex. 1007, 13:12; *see also* 02131 Ex. 1007, 14:34.

4. *Analysis*

The Federal Circuit determined, regarding the glycoconjugate size limitation required in original claim 1, and proposed substitute claims 46, 48, and 49, that

> both GSK-711 and Merck-086 disclose methods for preparing *S. pneumoniae* glycoconjugates and teach that the polysaccharides can be sized to improve the filterability of the conjugated product. . . . Expert testimony further supported the notion that, at the time of the invention, conjugation techniques and conditions were routine such that a person of ordinary skill in the art would have understood the claimed molecular weight to be "typical of immunogenic conjugates." *Id.* at *11. That evidence therefore supports the Board's conclusion that "conjugate size is a result[-]effective variable associated with improved stability of conjugates and good immune response, limited only by filter size, thereby rendering 'optimization within the grasp of one of ordinary skill in the art.'" *Sanofi Decision* at *13 (quoting [*In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012)].

Pfizer, 94 F.4th at 1348 (second alteration in original). The Federal Circuit further stated, regarding the 2-log IgG increase requirement in proposed substitute claim 46, that both "Merck-086 and Hausdorff clearly demonstrated that the claimed 2-log IgG increase could be achieved across various serotypes in a multivalent composition, which is consistent with the disclosure in the prior art that new glycoconjugates could be added to multivalent compositions without negatively affecting the components already within the vaccine." *Id*. at 1352.

As noted above, the Federal Circuit remanded for analysis of the 2-log IgG increase requirement recited in proposed substitute claims 48 and 49.

a. Petitioner's position

Petitioner asserts, specific to claims 48 and 49, that:

> All of the additional serotypes recited in claims 48-49 were already included in Pneumovax®23, which is Merck's 23-valent pneumococcal vaccine, approved by the FDA more than 30 years ago. Ex. 1017, 1. Therefore, those serotypes had long been recognized as immunologically important. Before Pfizer's earliest possible filing date, a POSA looking to improving Prevnar13® would be motivated to add those additional serotypes from Pneumovax®23. Van Alphen Decl., ¶97.

Pet. Opp. 23. Petitioner further asserts, "in January 2014, it would also have been obvious for a POSA to use CRM_{197} based conjugates to add these new serotypes to a multivalent PCV composition. It was the consensus in the field that CRM_{197} was 'preferred' for multivalent conjugate vaccines and had been tested in increasing valencies." *Id*. at 24. Petitioner asserts "CRM_{197} based conjugates make it possible to induce good immunity to new serotypes '**without negatively affecting**' the immunogenicity of other serotypes in the existing products. *Supra* III(A)(2)(iii)(b); Van Alphen Decl., ¶¶74-78." *Id*.

Petitioner asserts, "[a]s of January 2014, Merck's all CRM_{197} PCV15 already included a 33F-CRM_{197} conjugate recited in claim 48 and induced robust IgG and functional antibody responses in monkeys and rabbits including a 98.8-fold IgG increase above baseline, which is almost a 2-log increase. Ex. 1008, [0117], Table 4." Pet. Opp. 24. Petitioner asserts that Patent Owner's expert, "Dr. Paradiso indicated that he did not believe immune interference would be an issue for a 21-valent and that immune interference may become 'a diminishing issue' as the valency increases. Ex. 1105, 224:23-225:14." *Id*.

Petitioner asserts:

> Therefore, as of January 2014, a POSA would have had a reasonable expectation-of-success that a 16-valent and a 20-valent immunogenic composition recited in claims 48 and 49, respectively, could be made and able to exhibit more than a 2-log IgG increase above baseline in NZWRs across all serotypes by routine 25 optimization as taught in Hausdorff. Van Alphen Decl., ¶¶97-102. Thus, claims 48 and 49 are obvious over the prior art.

Pet. Opp. 24–25.

b. Patent Owner's position

Patent Owner asserts that Petitioner "acknowledges that Merck-086 does not report increases over baseline for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F (the serotypes of Prevnar®) in its multivalent composition. See Opp. at 15; EX2074 at ¶13." PO Reply 6–7. Patent Owner asserts:

> Even if a POSA[17] could have tripled the IgG-fold increases of the PCV-15 in Merck-086 through routine optimization, as

[17] Patent Owner uses the acronym "POSA" to refer to the person of ordinary skill in the art.

> Sanofi asserts (*see* Opp. at 14-15), a POSA would have no basis to believe that the tripled unknown values would meet the claimed 2-log IgG Increase across all serotypes.

Id. at 7 (citing Ex. 2074 ¶ 14). Patent Owner asserts "Table 4 of Merck-086 shows that serotypes 1 and 3 (required by all proposed substitute claims) and 33F (required by proposed substitute claim 48) of PCV-15 of Merck-086 never achieved a 2-log IgG Increase across four separate groups of NZWR." *Id*. (citing Ex. 2074 ¶ 16). Patent Owner asserts "Figure 2 of Merck-086 shows that after two doses, the vaccine failed to elicit a 2-log IgG Increase in serum IgG levels in IRM for at least serotypes 1, 3, 5, 6A, 7F, 19A, and 22F." *Id*. at 8 (citing Ex. 2051 ¶ 67). Patent Owner asserts "[l]acking any supporting disclosure in the art, Sanofi instead alleges that a POSA would have been motivated to 'optimize' the PCV-15 described by Merck-086 to achieve the 2-log increase, but Dr. Van Alphen admits that this is based on hindsight." *Id*. at 7–8 (citing Ex. 2073, 115:17–116:23).

Patent Owner asserts a "POSA would have had no reasonable expectation of success that Merck-086's vaccine could achieve the 2-log IgG Increase for all serotypes, which is required for a showing of obviousness." *Id*. at 8. Patent Owner asserts "Hausdorff does not describe the Table 3 results as optimizing Table 5. EX2074 at ¶18. Rather, the studies reflected in Tables 3 and 5 were different experiments aimed at entirely different comparisons." *Id*. at 8–9 (citing Ex. 2074 ¶ 18). Patent Owner asserts "a POSA would not have been able to optimize the baseline because it is not feasible to procure NZWR with a specific baseline or exclude certain NZWR from experiments." *Id*. at 9 (citing Ex. 2073, 68:15–69:14; 75:2–24).

Patent Owner asserts "Merck-086 is silent on the baseline values corresponding to the experiments of Tables 3 and 4, and does not report observing anomalous data that would suggest that IgG ratios below 100 (i.e., 2-log) might be due to presence of abnormally high baseline values." *Id*. at 9 (citing Ex. 2074 ¶ 21). Patent Owner asserts that, in Merck-086, "responses could not be further optimized by adjustment of dose because 'there did not appear to be a significant benefit in increasing the amount of polysaccharide-conjugate in the vaccine.'" *Id*. at 10 (citing Ex. 1008 ¶ 118; Ex. 2074 ¶ 22). Patent Owner asserts regarding optimization of assay conditions that a "POSA would not have had any such expectation." *Id*. at 10 (citing Ex. 2074 ¶ 24). Patent Owner asserts that, "[g]iven that Merck-086 shows that its formulations were unable to meet the required 2-log IgG Increase even after optimization attempts, a POSA would not have expected they could be routinely optimized further." *Id*. at 11 (citing Ex. 2074 ¶ 27). Patent Owner asserts "a POSA would have concluded that PCV-15 of Merck-086 likely suffered from immune interference." *Id*. (citing Ex. 2074 ¶ 28).

Patent Owner also asserts "[l]ong felt need for the immunogenic compositions of the proposed substitute claims and the failure of others to formulate a composition eliciting the efficacy associated with the 2-log IgG Increase further demonstrate that the proposed substitute claims are not obvious.'" *Id*. at 11–12. Patent Owner asserts "Pfizer's 16- and 20-valent pneumococcal conjugate vaccines, embodiments of the proposed substitute claims, meet the long felt need for coverage of serotypes 22F (claim 46), 33F, and 15B (claim 48) with a 2-log IgG increase maintained for all

serotypes in the vaccine." *Id*. at 12 (citing Ex. 2074 ¶ 30). Patent Owner asserts "[t]o date, there are no licensed vaccines that cover the serotypes required by claim 46 and its dependent claims." *Id*. (citing Ex. 2074 ¶ 31).

c. Proposed Substitute Claims 48 and 49 would have been Obvious

(1) Prior Art Teaches the Disputed Claim Limitation

We agree with Petitioner that the asserted prior art teaches the claim limitations.

We find Merck-086 teaches "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}." Ex. 1008 ¶ 2; *see also* 02131 Ex. 1006, 1:7–11.

That is, Merck-086 teaches a multivalent composition that lacks one of the capsular polysaccharides required by proposed substitute claim 48, i.e., serotype 15B, and that lacks the capsular polysaccharides of serotypes 12F, 10A, 11A, and 8 required by proposed substitute claim 49.

We find GSK-711 teaches "the multivalent pneumococcal vaccine of the invention will be selected from the following serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15[B], 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F." Ex. 1007, 7:1–3; *see also* 02131 Ex. 1007, 8:29–31. GSK 2008 also teaches conjugation of polysaccharides to the carrier protein CRM_{197}. *See* Ex. 1007, 10:4–6; *see also* 02131 Ex. 1007, 10:12–15.

Thus, GSK-711 teaches all of the capsular polysaccharide serotypes required by proposed substitute claims 48 and 49 i.e., specifically reciting the capsular polysaccharides of serotypes 15, 33F, 12F, 10A, 11A, and 8. Ex. 1007, 7:1–3; *see also* 02131 Ex. 1007, 8:29–31.

Finally, we find Hausdorff "examined the ability of the 13vPnC vaccine with $AlPO_4$ adjuvant to elicit vaccine serotype-specific immune responses. The pneumococcal serotypes represented in the 13vPnC vaccine include types 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F." Ex. 2027 ¶ 230. Hausdorff teaches:

> New Zealand White rabbits were immunized intramuscularly at week 0 and week 2 with the planned human clinical dose of each polysaccharide (2 μg of each PS, except 4 μg of 6B) formulated with or without $AlPO_4$ (100 μg/dose). Sera were collected at various time points. Serotype specific IgG was measured by ELISA and functional activity was assessed by OPA.

Ex. 2027 ¶ 230. Table 3 of Hausdorff shows that each of the thirteen tested serotypes produced an immune response with more than a 2-log increase above baseline serum IgG levels in New Zealand White Rabbits after administration of the two equal doses for every single serotype tested. Ex. 2027 ¶ 231, Table 3.

Viewing the evidence as a whole, we determine that a preponderance of the evidence demonstrates that it would have been obvious to incorporate serotypes 15B, 33F, 12F, 10A, 11A, and 8—conjugated to CRM_{197}, with molecular weights and saccharide to protein ratios falling in the claimed ranges, as rendered obvious by Merck-086 and GSK-711, into a pneumococcal vaccine with the serotypes also disclosed by Hausdorff, with

a reasonable expectation of success in obtaining a 2-log increase above baseline in serum IgG levels as required by the challenged claims.

As to reasons to include serotype 22F and 33F in such a composition, we find Merck-086 states "the addition of new polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses [and] demonstrates the feasibility of expanding coverage of pneumococcal serotypes not covered by existing pneumococcal vaccines." Ex. 1008 ¶ 15; *see also* 02131 Ex. 1006, 4:1–4. GSK-711 states

> the presence of 22F in a childhood pneumococcal vaccine will be advantageous in inducing herd immunity in the population such that the onset of serious elderly disease caused by this serotype (such as pneumonia and/or invasive pneumococcal disease (IPD) and/or exacerbations of chronic obstructive pulmonary disease (COPD)) may be prevented or reduced in severity.

Ex. 1007, 4:18–22; *see also* 02131 Ex. 1007, 5:5–9. GSK-711 further contemplates a "23 valent (such as 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. 1007, 7:28–30; *see also* 02131 Ex. 1007, 9:21–23. GSK-711 explains "the present invention is an improved method to elicit a (protective) immune response in infants (defined as 0-2 years old in the context of the present invention) by administering a safe and effective amount of the vaccine." Ex. 1007, 41:21–23; *see also* 02131 Ex. 1007, 43:14–16.

Thus, both Merck-086 and GSK-711 provide specific reasons to incorporate serotypes 22F, 33F, 8, 10A, 11A, 12F, and 15B into a pneumococcal vaccine to provide robust antibody responses that will provide herd immunity and reduce disease in human populations.

(2) Reasonable Expectation of Success for 2-log increase for immune compositions of claims 48 and 49

As to the issue of immune interference and a reasonable expectation of success in obtaining a 2-log increase, we find Table 3 of Hausdorff shows that a composition with thirteen of the fourteen serotypes that were required by proposed substitute claim 46, conjugated with CRM_{197}, produced an immune response with more than a 2-log increase above baseline serum IgG levels in New Zealand White Rabbits after administration of the two equal doses with or without the aluminum salt adjuvant. Ex. 2027 ¶ 231, Table 3.

Thus, we find there would have been a reasonable expectation of success in the inclusion of serotypes 22F, 33F, 8, 10A, 11A, 12F, and 15B in Hausdorff's pneumococcal vaccine composition while retaining the 2-log increased immune response of the thirteen serotypes and also retaining a 2-log increase in the immune response to the added serotypes. We note that Patent Owner does not identify any particularized evidence drawn to the seven serotypes recited in the challenged claims showing any expected difference in the behavior of these serotypes from the fourteen serotypes already included in the Hausdorff composition.

Dr. Van Alphen testifies that

> Hausdorff showed that its 13-valent PCV composition (13vPnPC) achieved a 2-Log IgG Increase or higher across all serotypes (at least in one study). . . . Hausdorff also demonstrated that its 13vPnPC composition successfully achieved the 2-Log IgG Increase across all serotypes by routine optimization. Specifically, Hausdorff reported several studies examining the immune response to the 13vPnPC composition in NZWRs.

Ex. 1101 ¶¶ 59–60. Dr. Van Alphen further testifies that the data in Hausdorff "demonstrated that for a reasonably immunogenic multivalent PCV composition, a 2-Log IgG Increase from baseline across all the serotypes can be achieved by routine optimization of test conditions, for example, the baseline (using different animals), the dose or adjuvant amounts, and others." Ex. 1101 ¶ 61. Similarly, in the 02131 proceeding, Dr. Kasper stated "[w]ith conjugates on CRM_{197} it has been possible to induce good immunity to new serotypes **without negatively affecting the components already in the vaccine**." 02131, Ex. 1096 ¶ 43 (citing 02131, Ex 1091, 3). Dr. Kasper noted "the 15-valent composition of Merck 2011 consistently elicited more IgG against serotype 9V than Prevnar®, which would not have been expected if immune interference were occurring." 02131, Ex. 1096 ¶ 46 (citing Ex. 2006, 24, Table 4).

The optimization rationale is supported by Merck-086, which shows that PCV-15, a composition comprising all of Hausdorff's thirteen serotypes and further including serotypes 22F and 33F, resulted in a 2-log increase for serotype 22F in two of four studies in New Zealand White Rabbits, and less than a 2-log increase in the other two studies. *See* Ex. 1008 ¶¶ 7, 117, Table 4; *see also* 02131, Ex. 1006, 24, Table 4. While Merck-086 mentions immune interference in the background section relating to prior art formulations, Patent Owner does not identify any teaching or suggestion in Merck-086 that immune interference occurred in PCV-15. Ex. 1008 ¶ 6; *see also* 02131, Ex. 1006, 2:13–15.

We are also unpersuaded by Patent Owner's assertion that "a POSA would not have been able to optimize the baseline because it is not feasible

to procure NZWR with a specific baseline or exclude certain NZWR from experiments." PO Reply 9. Dr. Van Alphen testifies, "[t]here was a clear motivation to further increase the IgG levels above the baseline for all serotypes as serum IgG levels are one of the indicators of immunogenicity of vaccine." Ex. 1101 ¶ 51 (citing Ex. 1053, 100–101). Dr. Van Alphen further testifies with regard to Hausdorff that "for a reasonably immunogenic multivalent PCV composition, a 2-Log IgG Increase from baseline across all the serotypes can be achieved by routine optimization of test conditions, for example, the baseline (using different animals)." Ex. 1101 ¶ 61.

Dr. Van Alphen's optimization reasoning is supported by the cross-examination testimony of Patent Owner's own expert witness. Dr. Paradiso, in response to the question "what are some of the factors that would impact the level of the baseline," testified "previous exposure to the bacteria or previous immunization, two that come to mind." Ex. 1105, 104:11–18; *Cf.* 02131, Ex. 1104, 74:17–18 ("I would agree that there is variability in the results from the rabbit assay."); *see also* 02131, Ex. 1104, 75:11–13 ("I would say one of the sources of the variability was what you raised with relation to preexisting titers."). Thus, Dr. Paradiso's statements supports Petitioner's position that the baseline could be routinely reduced by selecting germ-free animals that were never immunized or increased by selecting exposed animals already subjected to immunization, rendering the baseline as a results optimizable variable known in the prior art. Ex. 1101 ¶ 61; Ex. 1105, 104:11–18.

We recognize that Patent Owner correctly notes that Merck-086 only obtained a 2-log increase of serum IgG levels in serotype 22F conjugates in two of the four arms. PO Reply 7–8.[18] However, "'[o]bviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*.'" *In re Kubin*, 561 F.3d at 1360 (*quoting In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). Evidence that all of the Merck-086 experiments showed a greater than 1-log increase in serum IgG levels and half of the experiments showed a greater than 2-log increase supports the determination that there was a reasonable expectation of success. *See* Ex. 1008 ¶¶ 7, 117, Table 4; *see also* 02131, Ex. 1006, 24, Table 4.

We note that "this is not the case where the prior art teaches merely to pursue a 'general approach that seemed to be a promising field of experimentation' or 'gave only general guidance as to the particular form of the claimed invention or how to achieve it.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) (*quoting O'Farrell*, 853 F.2d at 903; *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1167 (Fed. Cir. 2006)). Here, both Merck-086 and GSK-711 specifically suggested incorporation of additional serotype conjugates linked to CRM_{197} into a pneumococcal vaccine that was already composed of other known serotypes, including all

[18] We note that in the Patent Owner Reply in related IPR2017-02131, Patent Owner supported this same argument with annotated Figures 3 and 4 of a reference called Merck 2011 (Ex. 1006 in IPR2017-02131) to identify particular experimental results that did not satisfy the 2-log increase. IPR2017-02131, PO Reply 3–4 (Paper 39). Merck 2011 and Merck-086 both claim priority from provisional application 61/302,726 and are drawn to 15-valent vaccine compositions.

of the thirteen serotypes disclosed by Hausdorff. Ex. 1008 ¶ 15; *see also* 02131 Ex. 1006, 4:2–4; Ex. 1007, 5:18–22; 02131, Ex. 1007, 4:30–34; Ex. 2027 ¶ 231, Table 3.

We recognize, but find unpersuasive, Patent Owner's assertion that "a POSA would have concluded that PCV-15 of Merck-086 likely suffered from immune interference." PO Reply 11 (citing Ex. 2074 ¶ 28).

Paradiso 2009 supports the position that immune interference would not necessarily have been expected with the addition of a serotype 22F-CRM_{197} conjugate to the thirteen serotype composition of Hausdorff because Paradiso 2009 states "[c]onjugate vaccine formulations using the carrier protein CRM_{197} have been tested in increasing valencies . . . [and] [w]ith conjugates on CRM_{197} it has been possible to induce good immunity to new serotypes without negatively affecting the components already in the vaccine." Ex. 1107, 3.

We also conclude that even if some degree of immune interference resulted from the addition of new serotype conjugates, Dr. Van Alphen states "the overall benefit of the new multivalent conjugate vaccine composition based on both epidemiology consideration and regulatory consideration could outweigh the reduced immune response to a particular serotype and the new multivalent conjugate vaccine could still be efficacious and approved." Ex. 1101 ¶ 80. Dr. Alphen further testified that "there's no reason to think about immune interference, because CRM was used for many new vaccines, and the development was fast and without any chance for interference." Ex. 2073, 133:19–22. This is consistent with Patent Owner's expert, Dr. Paradiso, who answered "Correct" in response to a

question asking "one of the trade-offs that you would consider is whether a reduced immune response with respect to an individual serotype in the multivalent immunogenic composition made it worth – still worthwhile or not worthwhile to develop the vaccine, correct?" Ex. 1105, 82:20–83:2.

Thus, we find that a preponderance of the evidence supports a determination that there would have been a reasonable expectation of success in obtaining a pneumococcal vaccine composition as required by claim 48 and 49 with 2-fold increases in IgG responses in New Zealand White Rabbits because Merck-086 itself exemplifies 2-fold increases in IgG responses in New Zealand White Rabbits for other serotype conjugates, and because Paradiso-2009 supports the position that inclusion of an additional serotype conjugates into the thirteen serotype composition of Hausdorff would not have been expected to result in immune interference. Ex. 1008 ¶ 15; ; *see also* 02131 Ex. 1006, 4:2–4; Ex. 1107, 3 ("[w]ith conjugates on CRM_{197} it has been possible to induce good immunity to new serotypes without negatively affecting the components already in the vaccine.")

We have considered, but are not persuaded by Patent Owner's assertion that evidence of a long-felt and unmet need supports non-obviousness because, as Petitioner points out, Patent Owner "fails to produce any objective evidence that the need for the immunogenic compositions of the [proposed] substitute claims, specifically eliciting the 2-log IgG Increase [was] an art-recognized problem." Pet. Sur-Reply 10. Indeed, we agree with Petitioner that Patent Owner provides no objective evidence establishing any of the three elements necessary to establish a long felt and unmet need: (i) the need must have been a persistent one that was

recognized by ordinarily skilled artisans (ii) the long-felt need must not have been satisfied by another before Appellants' invention; and (iii) the invention must, in fact, satisfy the long-felt need. *In re Gershon*, 372 F.2d 535, 538 (CCPA 1967); *Newell Companies, Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988); *In re Cavanagh*, 436 F.2d 491, 496 (CCPA 1971).

We also agree with Petitioner that there is no evidence that the PCV-15 vaccine disclosed in Merck-086 "failed at any specific effort to formulate a composition eliciting the 2-log IgG Increase." Pet. Sur-Reply 11 (emphasis omitted). Patent Owner's citation to post-filing date evidence in Exhibit 2072 (PO Reply 12) is also unavailing because that exhibit teaches that "PCV15 is likely to provide additional protection against diseases caused by 22F and 33F." Ex. 2072, 8. While we recognize that Exhibit 2072 also teaches reduced immunogenicity of certain strains in PCV15, Patent Owner provides no objective evidence that these reductions resulted in levels below the 2-log increase required by proposed substitute claim 46. *See* Ex. 2072, 5–6. Thus, there is no objective evidence that the PCV-15 vaccine did not satisfy the asserted long-felt need.

Lastly, Patent Owner does not provide objective evidence that the claimed invention satisfies the alleged need because Patent Owner acknowledges that "[t]o date, there are no licensed vaccines that cover the serotypes required by [proposed substitute] claim 46 and its dependent claims." PO Reply 12. To the extent that Patent Owner asserts that the only way to satisfy the alleged long-felt need is by a licensed vaccine, rather than by a disclosed composition such as PCV-15, Patent Owner has not

established with objective evidence that the compositions of proposed substitute claims 48, and 49 are such licensed vaccines. We do not, however, take such a narrow view of the requirements of satisfying the long-felt and unmet need consideration, but instead find that the prior art's PCV-15 itself can reasonably be identified as satisfying the alleged long-felt need consistent with Dr. Paradiso's statement that PCV-15 and Prevnar 13 would show "[c]omparability using the WHO standard." Ex. 1116, 43:10. Thus, even if we credit the claimed composition as also satisfying the alleged long-felt need, there is no evidence that it was not previously satisfied by PCV-15.

V. CONCLUSION

We conclude on remand that Petitioner has shown by a preponderance of the evidence that proposed substitute claims 48 and 49 are unpatentable as obvious over the combination of GSK-711, Merck-086, and Hausdorff, in view of the knowledge of the ordinary artisan.

Motion to Amend Outcome[19]	**Claim(s)**
Original Claims Cancelled by Amendment	
Substitute Claims Proposed in the Amendment	48, 49
Substitute Claims: Motion to Amend Granted	
Substitute Claims: Motion to Amend Denied	48, 49
Substitute Claims: Not Reached	

[19] This table addresses only those issues remaining in the proceeding following the Federal Circuit's remand, as all remaining aspects of the Board's decisions were affirmed "*in toto*." *See Pfizer*, 94 F.4th at 1354.

VI. ORDER

For the reasons given, it is

ORDERED that Patent Owner's Motion to Amend is denied as to proposed substitute claims 48 and 49, as these claims are unpatentable;

FURTHER ORDERED, because this is a final written decision, the parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2018-00187 (Patent 9,492,559 B2)
IPR2017-02131 (Patent 9,492,559 B2)
IPR2017-02132 (Patent 9,492,559 B2)

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