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. 2017-02131
Patent No. 9,492,559

PATENT OWNER PFIZER INC.'S AMENDED 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 entered on March 13, 2019 (Paper No. 59), the February 4, 2022 Order denying Pfizer's Request for Director Review (Paper No. 68), 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, and a copy of the Order denying Pfizer's Request for Director Review is attached as Exhibit B.

This amended notice of appeal is timely. On May 13, 2019, Pfizer filed a first Notice of Appeal from the Board's Final Written Decision, which was docketed as Federal Circuit Case No. 19-1871. 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. 68). On March 1, 2022, the Federal Circuit issued an Order directing Pfizer to state whether it intended to file a new or amended notice of appeal. *Pfizer Inc. v. Sanofi Pasteur Inc., et al*., No. 19-1871, Dkt. No. 86 (Fed. Cir. Mar. 1, 2022). Pfizer subsequently notified the Court that it intended to file an amended notice of appeal in view of the denial of its request for Director review. *Id.*, Dkt. No. 87 (Fed. Cir. Mar. 8, 2022). This amended notice of appeal is being filed within 63 days after the February 4, 2022 Order denying Pfizer's request for Director review and is therefore timely pursuant to 37 C.F.R. § 90.3(b).

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Pfizer indicates that the issues on appeal include, but are not limited to, the following:

(i) the Board's determination that claims 1-10, 16-19, and 38-45 of U.S. Patent No. 9,492,559 are unpatentable as obvious under 35 U.S.C. § 103;

(ii) the Board's denial of Pfizer's motion to amend concerning proposed substitute claims 46-52;

(iii) the USPTO's denial of Pfizer's request for Director review of the Final Written Decision, including the denial of Pfizer's request to vacate the Final Written Decision and terminate this proceeding in view of the parties' settlement;

(iv) whether the Order denying Pfizer's request for Director review comports with the Appointments Clause of the Constitution, separation of powers, the Supreme Court's decision in *United States v. Arthrex, Inc*., 141 S. Ct. 1970 (2021), the Federal Vacancies Reform Act, and 5 U.S.C. § 553.

Pursuant to 35 U.S.C. § 142 and 37 C.F.R. § 90.2(a), this amended 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 amended notice of appeal is being filed with the United States Court of Appeals for the Federal Circuit. Pursuant to the Federal Circuit's order dated March 1, 2022, no additional docketing fee is required for any amended notice of appeal in this matter. *Pfizer Inc. v. Sanofi Pasteur Inc., et al*., No. 19-1871, Dkt. No. 86 (Fed. Cir. Mar. 1, 2022).

Dated: April 8, 2022

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the above-captioned PATENT OWNER PFIZER INC.'S AMENDED NOTICE OF APPEAL was electronically filed through PTAB E2E and via Express Mail on April 8, 2022 at the following address:

Director of the United States Patent and Trademark Office
Office of the General Counsel
United States Patent and Trademark Office, Mail Stop 8
P.O. Box 1450
Alexandria, VA 22313-1450

The undersigned also hereby certifies that a true and correct copy of the above-captioned PATENT OWNER PFIZER INC.'S AMENDED NOTICE OF APPEAL is being filed via CM/ECF with the Clerk's Office of the United States Court of Appeals for the Federal Circuit on April 8, 2022, in Case No. 19-1871.

The undersigned also hereby certifies that pursuant to 37 C.F.R. § 42.6(e), a true and correct copy of the above-captioned PATENT OWNER PFIZER INC.'S AMENDED NOTICE OF APPEAL is being served by electronic mail and Express Mail on April 8, 2022 to the following attorneys of record for the Petitioner:

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Paper 59
Entered: March 13, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

PFIZER INC.,
Patent Owner.

Case IPR2017-02131
Patent 9,492,559 B2

Before TONI R. SCHEINER, JEFFREY N. FREDMAN, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION AND RELATED ORDERS

Finding claims 1–10, 16–19, and 38–45 Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Denying Patent Owner's Motion to Amend
35 U.S.C. § 326(d) and 37 C.F.R. § 42.221

Denying-in-part and Dismissing-in-part Patent Owner's Motion to Exclude Evidence
37 C.F.R. § 42.64

I. INTRODUCTION

A. Background

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–10, 16–19, and 38–45 of U.S. Patent No. 9,492,559 B2 (Ex. 1001, "the '559 patent"). Paper 1 ("Pet."). Pfizer Inc. ("Patent Owner") filed a Patent Owner's Preliminary Response. Paper 6 ("Prelim. Resp.").

On March 22, 2018, we instituted an *inter partes* review of all challenged claims. Paper 7 ("Dec. Inst."). On June 18, 2018, Patent Owner filed a Patent Owner's Response to the Petition (Paper 20) ("PO Response") and a Motion to Amend. Paper 22 ("Mot. Amend."). Petitioner filed an Opposition to the Motion to Amend (Paper 31) ("Pet. Opp."), followed by a Reply to the Patent Owner's Response. Paper 33 ("Pet. Reply"). Patent Owner then filed a Reply in Support of the Motion to Amend. Paper 39 ("PO Reply"). Petitioner filed a Sur-Reply to Patent Owner's Motion to Amend. Paper 44 ("Pet. Sur-Reply"). Patent Owner filed a Sur-Reply. Paper 48 ("PO Sur-Reply"). Patent Owner filed a Sur-Sur-Reply in Support of the Motion to Amend. Paper 54 ("PO Sur-Sur-Reply").

Patent Owner filed a Motion to Exclude Evidence. Paper 49. Petitioner filed an Opposition to Motion to Exclude Evidence. Paper 53. Patent Owner filed a Reply in Support of the Motion to Exclude. Paper 54.

On November 13, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 58 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we

determine that Petitioner has shown by a preponderance of the evidence that claims 1–10, 16–19, and 38–45 of the '559 patent are unpatentable. See 35 U.S.C. §316(e). Additionally, the Motion to Exclude Evidence by Patent Owner has been decided below in Section IV and the Motion to Amend has been decided below in Section III.

B. Related Proceedings

We have instituted three additional *inter partes* reviews of claims of the '559 patent in IPR2017-02132, IPR2017-02136, and IPR2017-02138. We also note that IPR2017-00378, IPR2017-00380, and IPR2017-00390 were instituted with respect to U.S. Patent No. 8,562,999, and that several PGR and IPR petitions were also filed with respect to U.S. Patent Nos. 9,399,060 B2 and 8,895,024 B2, which all relate to immunogenic vaccine compositions. Pet. 5.

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 teaches the "etiological agent of pneumococcal diseases, *Streptococcus pneumoniae* (pneumococcus), is a Gram-positive

encapsulated coccus,[1] surrounded by a polysaccharide capsule.[2] 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[3] 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 teaches "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.

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

[2] "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 virulence determinant for pneumococci, as the capsule not only protects the inner surface of the bacteria from complement, but is itself poorly immunogenic." Ex. 1007, 2:10–14.

[3] 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).

D. Illustrative Claims

All of the challenged claims 1–10, 16–19, and 38–45 depend either directly or indirectly from independent claim 1 of the '559 patent.[4] Claims 1, 3, and 40 are illustrative of the challenged claims and recite:

> **1.** An immunogenic composition comprising a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2.
>
> **3.** The immunogenic composition of claim **1**, wherein the composition further comprises a *S. pneumoniae* serotype 15B glycoconjugate and a *S. pneumoniae* serotype 33F glycoconjugate.
>
> **40.** The immunogenic composition of claim **1**, wherein a ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM isolated polysaccharide is at least 0.6.

Ex. 1001, 141:28–34, 141:38–41, 144:14–17.

E. The Instituted Grounds of Unpatentability

We instituted trial based on each challenge to the patentability of the '559 patent presented in the Petition (Pet. 6–7):

[4] Claims 11–15 and 20–37 were not challenged in this proceeding, but were challenged in the related proceedings in IPR2017-02136 and IPR2017-02138.

Reference	Basis	Claims Challenged
Merck 2011,[5] GSK 2008[6]	§ 103(a)	1, 3–10, 16–19, 39, 41, 42, 45
Merck 2011, GSK 2008, PVP 2013[7]	§ 103(a)	2, 40, 43
Merck 2011, GSK 2008, Hsieh 2000[8]	§ 103(a)	38, 44

Petitioner relies on Declarations of Dennis L. Kasper, M.D. Ex. 1004 and Ex. 1096. Patent Owner relies on Declarations of Geert-Jan Boons, Ph.D. Ex. 2040 and Peter Paradiso, Ph.D., Ex. 2044 and Ex. 2063.

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review filed before November 13, 2018, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear.[9] 37 C.F.R. § 42.100(b). Under the broadest reasonable interpretation approach, claim

[5] Caulfield et al., WO 2011/100151 A1, published Aug. 18, 2011 ("Merck 2011," Ex. 1006).
[6] Biemans et al., WO 2009/000825 A2, published Dec. 31, 2008 ("GSK 2008," Ex. 1007).
[7] *Pneumococcal Vaccine Polyvalent* 1–6 (Mar. 2, 2013) (revision to *Japan's Minimum Requirements for Biological Products* published on the website of Japan's National Institute of Infectious Diseases) ("PVP 2013," Ex. 1009).
[8] C. L. Hsieh, *Characterization of Saccharide-CRM$_{197}$ Conjugate Vaccines*, 103 DEV. BIOL. 93–104 (2000) ("Hsieh 2000," Ex. 1013).
[9] A recent amendment to this rule does not apply here because the Petition was filed before November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018).

terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms that are in controversy need to be construed and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999).

We determine that the following claim term needs to be discussed.

1. "*immunogenic"*

Independent claim 1, as well as many of the dependent claims, recites the term "immunogenic" as a modifier of the term "composition." In the Decision on Institution, we construed "immunogenic" to require a composition that "elicits functional antibody." Inst. Dec. 7. We also determined that because claim 1 did not specifically require any additional glycoconjugates besides 22F, the "immunogenic" composition only needed to elicit antibodies against the serotype 22F glycoconjugate recited in claim 1. *Id*.

In its Patent Owner's Response, Patent Owner contends "the context within the claim requires that the *composition* is immunogenic, not merely serotype 22F glycoconjugate in isolation." PO Resp. 12. Patent Owner proposes that "immunogenic" be interpreted as "elicits functional antibody against each serotype in the claimed composition." *Id*. Patent Owner asserts that "[w]hen viewed in the full context of the claims and specification, [Petitioner's] . . . proposed construction yields the illogical result of a pneumococcal conjugate vaccine wherein one conjugate (serotype 22F) elicits functional antibody, but other conjugates . . . need not." *Id.* at 14.

Petitioner agrees with our Decision on Institution that a "POSITA would have understood that the 'immunogenic' limitation of independent claim 1 applies to just the serotype 22F conjugate of claim 1." Pet. Reply 23. Petitioner contends:

> no claim of the '559 Patent recites structural characteristics (*e.g.*, molecular weight and/or polysaccharide to protein ratio) for any conjugate other than the serotype 22F conjugate of claim 1. Ex.1105, ¶12. And there is no disclosure in the '559 Patent specification of molecular weights or polysaccharide to protein ratios for any of the 13 conjugates recited in dependent claims 5–8.

Id. at 24.

In performing claim interpretation, we first turn to the language of the claims themselves. While claim 1 recites an immunogenic composition composed solely of the "*Streptococcus pneumoniae* serotype 22F glycoconjugate," claims 3–9 recite the inclusion of glycoconjugates from other *Streptococcus pneumoniae* serotypes and claims 21 and 22 recite inclusion of antigens from other pathogenic bacteria or viruses. While claim 1 does not require the presence of other immunogenic components, claims 3–9, 21, and 22 expressly recite the presence of other immunogenic components. In making a vaccine, there would have been no reason to include these additional antigens other than to induce a protective antibody response for vaccination against the included antigens. Therefore, these dependent claims reasonably support Patent Owner's interpretation that an "immunogenic" composition requires eliciting antibodies against each of the serotypes or other immunogens within the "immunogenic" composition.

Next we turn to the Specification of the '559 patent. When the '559 patent uses the term "immunogenic," the '559 patent identifies "a need for

immunogenic compositions that can be used to induce an immune response against additional *Streptococcus pneumoniae* serotypes." Ex. 1001, 2:10–13. The '559 patent states that multiple serotypes ranging from 7 to 25 may be included in the "immunogenic composition." Ex. 1001, 3:4–6. The '559 patent teaches the "pneumococcal opsonophagocytic assay (OPA), which measures killing of *S. pneumoniae* cells by phagocytic effector cells in the presence of functional antibody and complement, is considered to be an important surrogate for evaluating the effectiveness of pneumococcal vaccines." Ex. 1001, 88:52–56. The '559 patent supports an interpretation of "immunogenic" which requires elicitation of functional antibody for each component in the composition, consistent with the interpretation of Patent Owner.

During prosecution of the '559 patent, the Examiner cited art that disclosed both the 22F conjugate and other conjugates to address the claimed compositions for dependent claims. *See* Ex. 1002, 419–20. The Examiner allowed the claims after amendment to include the ranges for molecular weight and ratio of polysaccharide to carrier protein. *See* Ex. 1002, 451, 467. The Examiner did not address the claim construction issue.

Petitioner's Declarant, Dr. Boons, interprets claim 1 to require that serotype "22F should elicit functional antibodies. But also if other antigens are being included, those should also elicit a functional antibody response." Ex. 1109, 36:7–10. In contrast, Patent Owner's Declarant, Dr. Kasper was asked if

> a composition containing a 22F glycoconjugate, 12F glycoconjugate, 10A glycoconjugate, 11A glycoconjugate, and a serotype 8 glycoconjugate and that composition showed functional antibody with respect to the 22F glycoconjugate but

> not with respect to the other conjugates . . . , is it your view that Claim 4 would be met?

Ex. 2013, 16:6–12. Dr. Kasper answered "I think that interpretation is consistent with Claim 4." *Id.* at 16:16–17.

Accordingly, upon review of the parties' arguments and the evidence before us, including the claims, specification, and prosecution history of the '559 patent, we conclude that the term "immunogenic," as it is used in that patent, is reasonably construed as requiring that functional antibody be elicited against each immunogen contained in the composition. Consequently, for claim 1 of the '559 patent, which recites a single immunogen, serotype 22F, only functional antibodies to serotype 22F are required to meet the claim limitation. However, for claim 3 of the '559 patent that requires serotypes 22F, 15B, and 33F, functional antibodies against all three serotypes are required. Similarly for other claims, the term "immunogenic" requires functional antibodies be elicited against any immunogens 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;[10] and, (4) where in evidence, objective indicia of nonobviousness.[11] *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

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[10] Petitioner states that the level of skill in the art at the time of the invention

> 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.

Pet. 27–28 (citing Ex. 1004 ¶ 59). Patent Owner "does not dispute . . . the level of skill in the art proposed by Merck." PO Resp. 5. We agree with both 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).

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

> 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.

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

Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

C. Obviousness over Merck 2011 and GSK 2008

Petitioner contends that claims 1, 3–10, 16–19, 39, 41, 42, and 45 are unpatentable under 35 U.S.C. § 103(a) as obvious over Merck 2011, GSK 2008, and the general knowledge of an ordinary artisan. Pet. 33. The thrust of Patent Owner's position is that the cited prior art does not teach or suggest compositions with 22F glycoconjugates that are immunogenic, within the claimed molecular weight ranges, and within the claimed polysaccharide to carrier protein conjugate ratios. PO Resp. 1–2, 15–53. Based on our review of the arguments and the evidence of record, we determine that Petitioner demonstrates, by a preponderance of the evidence,

that the subject matter of claims 1, 3–10, 16–19, 39, 41, 42, and 45 would have been obvious over Merck 2011, GSK 2008, and the general knowledge of an ordinary artisan. After providing a discussion of the prior art and Petitioner's position, we will address Patent Owner's arguments.

1. *Merck 2011 (Ex. 1006)*

Merck 2011 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. 1006, 1:7–11. Merck 2011 teaches "conjugates containing serotypes 22F and 33F provide[] robust antibody responses demonstrat[ing] the feasibility of expanding coverage of pneumococcal serotypes . . . ." Ex. 1006, 4:2–3. Merck 2011 teaches the pneumococcal conjugate vaccine (PCV) with "induced high OPA[12] GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine." Ex. 1006, 23:3–4.

Merck 2011 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. 1006, 6:11–23. Merck 2011 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 through a 0.2 μm filter." Ex. 1006, 17:24–25. Table 1 of Merck 2011 shows a vaccine formulation

[12] Opsonophagocytosis.

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. 1006, 19:5–9.

2. *GSK 2008*

GSK 2008 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, 8:5–19. GSK 2008 teaches "*Streptococcus pneumoniae* capsular saccharides . . . may be conjugated to a carrier protein independently selected from the group consisting of . . . CRM197. . . ." Ex. 1007, 10:12–14. GSK 2008 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 reductive amination methods. . . ." Ex. 1007, 17:1–28. GSK 2008 teaches "22F-PhtD administered within the 13-valent conjugate vaccine formulation [was] . . . shown immunogenic and induced opsono-phagocytic titers in young OF1 mice." Ex. 1007, 77:21–22.

GSK 2008 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, 20:24–26. Table 2 of GSK 2008 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, 54–55, Table 2. GSK 2008 discloses a conjugate of serotype 22F, with a carrier/PS ratio of 2.17, but does not determine the conjugate size. Ex. 1007, 55, Table 2.

GSK 2008 claims a conjugate where "the average size (e.g. M_w) of the 22F saccharide is between 50 and 800 kDa. . . ." Ex. 1007, 93 (claim 56). GSK 2008 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, 94.

GSK 2008 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, 14:18–21. GSK 2008 teaches "that saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease." Ex. 1007, 14:23–25. GSK 2008 recommends optimization for larger size saccharide-protein conjugates, limited only by a requirement to be "filterable through a 0.2 micron filter . . . ." Ex. 1007, 14:34.

3. *Analysis*

Petitioner asserts "Merck 2011 and GSK 2011 disclose immunogenic compositions that include a conjugate of pneumococcal serotype 22F" and that "Merck 2011 demonstrates immunogenicity against serotype 22F by the generation of functional antibody against that serotype." Pet. 34–35 (citing Ex. 1004 ¶ 103; Ex. 1006, 23:2–4). Petitioner asserts: "Based on the GSK 2008 disclosure of pneumococcal conjugates between 1,303-9,572 kDa, a POSITA would have been motivated with a reasonable expectation of success to construct the serotype 22F conjugate of Merck 2011/GSK 2008 in that approximate molecular weight range." Pet. 36 (citing Ex. 1004 ¶ 106). Petitioner also asserts "Merck 2011 and GSK 2008 both disclose the claimed

range of conjugate polysaccharide to protein ratios (0.4 to 2), and reflect a POSITA's general understanding that conjugate polysaccharide to protein ratios in the claimed range are typical for immunogenic conjugates." Pet. 42 (citing Ex. 1004 ¶ 114).

Petitioner's Declarant, Dr. Kasper, states that a "POSITA would have considered the disclosure of pre-conjugation polysaccharide to CRM_{197} ratios in the range of 0.2 to 2 indicative of a final conjugate ratio in that range." Ex. 1004 ¶ 115 (citing Ex. 1006, 17:24–25). Dr. Kasper notes "the pre-conjugation ratios of Merck 2011 resulted in an average polysaccharide to protein ratio in the conjugates of approximately 1 (~32 μg of polysaccharide and ~32 μg of protein), squarely in the claimed range." Ex. 1004 ¶ 115 (citing Ex. 1006, 19:3–8). Dr. Kasper also notes "a POSITA's general understanding that conjugate polysaccharide to protein ratios in the claimed range (0.4 to 2) are typical for immunogenic conjugates" and cites a monograph disclosing ratios of saccharide to protein in a pneumococcal CRM_{197} conjugate vaccine with seven serotypes, concluding that each "disclosed ratio overlaps to a large extent with the claimed ratio of 0.4 to 2, consistent with the general understanding in the art as of January 21, 2014 that such ratios are typical for immunogenic conjugates." Ex. 1004 ¶¶ 118–19 (citing Ex. 1085, 20–24).

Dr. Kasper states "GSK 2008 discloses that '[p]referably the ratio of carrier protein to *S. pneumoniae* saccharide is . . . between 1:2 and 2.5:1 . . . (w/w),' which translates to a polysaccharide to protein ratio of 1:2.5 to 2:1, *i.e.*, the claimed polysaccharide to protein ratio of 0.4 to 2." Ex. 1004 ¶ 116 (quoting Ex. 1007, 20:24–26). Dr. Kasper also states "Table 2 of GSK 2008 discloses an immunogenic serotype 22F conjugate (PS22F-PhtD) with a

protein to polysaccharide ratio of 2.17, which translates to a polysaccharide to protein ratio of 1/2.17 or 0.46 - squarely within the claimed range." Ex. 1004 ¶ 116 (citing Ex. 1007, 54:27 to 55:1). Dr. Kasper also relies upon a monograph that "specifies the acceptable range of 'Saccharide content/protein ratio' (which a POSITA would have understood to be a w/w ratio)" and that "[e]ach disclosed ratio overlaps to a large extent with the claimed ratio of 0.4 to 2 . . . ." Ex. 1004 ¶¶ 118–19 (citing Ex. 1085, 20–24).

Dr. Kasper states "the conjugate molecular weights that were determined (for every conjugate of the underlying 10-valent composition) ranged from 1,303-9,572 kDa, squarely within the claimed molecular weight range." Ex. 1004 ¶ 106. Dr. Kasper states "GSK 2008 discloses that the serotype 22F polysaccharide in its immunogenic conjugates can be, *e.g.*, 'between 50 and 800 kDa.'" Ex. 1004 ¶ 107 (quoting Ex. 1007, 93).

Dr. Kasper states the ordinary artisan would "have been motivated to stay roughly within the upper limit of molecular weights disclosed in GSK 2008, because 'excessive modifications to the PS or protein molecules can have an adverse impact on immunogenicity.'" Ex. 1004 ¶ 108 (quoting Ex. 1035, 8). Dr. Kasper also notes that "both Merck 2011 and GSK 2008 disclose a sterile filtration step through a 0.2 μm filter, which sets an upper limit on conjugate molecular weight." Ex. 1004 ¶ 108 (citing Ex. 1006, 16:30–31 and Ex. 1007, 14:13–15).

Dr. Kasper states a "POSITA's motivation and reasonable expectation of success would have been further supported by the fact that Patent Owner disclosed in a scientific meeting in 2012 that the 'Typical Mass (kDa)' for a glycoconjugate is '500-5000,' largely overlapping with the range recited in

GSK 2008 (and claim 1)." Ex. 1004 ¶ 109 (citing Ex. 1008, 6). Dr. Kasper states "Patent Owner even disclosed in a scientific meeting in 2007 that its own pneumococcal conjugates can be as large as ~7,000 to ~12,000 kDa, again overlapping with the range of GSK 2008 (and completely within the claimed range)." Ex. 1004 ¶ 109 (citing Ex. 1027, 21). Dr. Kasper states:

> Because the structure of serotype 22F capsular polysaccharide had been known to the art since 1989 (Ex. 1029), a POSITA would have required only routine experimentation to obtain a conjugate molecular weight within the desirable range disclosed in GSK 2008, *e.g*., by increasing or decreasing the amount of cross-linking in the conjugate.

Ex. 1004 ¶ 110 (citing Ex. 1030, 4:56–59).

Having reviewed the cited evidence, and the record as a whole, we find that Petitioner has accurately described the above stated teachings of Merck 2011 and GSK 2008. We adopt these stated facts as our own. *See* Pet. 33–55. We focus our remaining analysis on Patent Owner's arguments that the cited combination fails to teach or suggest an immunogenic composition including: (1) a serotype 22F glycoconjugate having a molecular weight of between 1000 kDa and 12,500 kDa; and (2) a polysaccharide to carrier protein ratio (w/w) of between 0.4 and 2.

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

Patent Owner asserts:

> Claim 1 and each of the challenged claims that depend therefrom require that the recited serotype 22F glycoconjugate "has a molecular weight of between 1,000 kDa and 12,500 kDa." EX1001 at claim 1. Merck 2011, GSK 2008, and the general knowledge do not alone or in combination teach or suggest this limitation.

PO Resp. 15.

i. Optimization

Patent Owner asserts a "POSA would have understood that a number of variables can affect polysaccharide activation, conjugation, and the final molecular weight of a glycoconjugate" and "[d]ue to these variables, a POSA 'couldn't predict what the outcome would be' with regard to the molecular weight of an uncharacterized serotype 7F glycoconjugate." PO Resp. 16 (citing Ex. 2040 ¶ 54).

Patent Owner further asserts that "[d]etermining the appropriate molecular weight for a specific serotype glycoconjugate was not a matter of 'routine optimization' of existing reductive amination procedures as of January 21, 2014." PO Resp. 17 (citing Ex. 2040 ¶ 55). Patent Owner asserts "each serotype glycoconjugate was designed using different protocols, and resulted in serotype glycoconjugates having different properties, thereby demonstrating that each serotype glycoconjugate needed to be evaluated on a case-by-case basis." PO Resp. 18 (citing Ex. 1007, Table 2).

Patent Owner asserts "[t]here is no overlap between the molecular weights in GSK 2008 and the '559 claims." PO Resp. 19. Patent Owner asserts:

> The serotype 22F glycoconjugates of GSK 2008 were treated in an alkaline pH of 9.0 (EX1007 at 51:5-8; 52:18-22), and as a result the molecular weight of the serotype 22F polysaccharide in the final glycoconjugates would be expected to be levels lower than the pre-conjugation weight of 22F (159-167 kDa).

PO Resp. 20. Patent Owner asserts "[t]he polysaccharide size in a final glycoconjugate of GSK 2008 would be unpredictable and as a result, and GSK 2008 cannot render the '559 claims obvious." PO Resp. 20.

Patent Owner asserts that a "POSA would not have determined the molecular weight of serotype 22F glycoconjugates based on GSK 2008 Table 2" because the "table does not provide the molecular weight for the two serotype 22F glycoconjugates" and the "serotype 22F glycoconjugates also differ from the other listed glycoconjugates in that they were associated with dramatically lower antigenicity, and with some of the highest protein to polysaccharide ratios as compared to all of the other serotype glycoconjugates." PO Resp. 23–24.

Patent Owner reiterates these arguments in the Patent Owner's Reply and also asserts "Merck's asserted 'desirable range' is fabricated from the lower and upper molecular weight limits for two non-serotype 22F glycoconjugates (*i.e.*, PS4-PD and PS9V-PD) referenced in Table 2 of GSK-2008." PO Sur-Reply 6.

We agree with Petitioner that these arguments are not persuasive because they are not supported by a preponderance of the evidence (*see* Pet. Reply 3–16).

Merck 2011 teaches that "[c]apsular polysaccharides from *Streptococcus pneumoniae* can be prepared by standard techniques known to those skilled in the art. For example, polysaccharides can be isolated from bacteria and may be sized to some degree by known methods (see, e.g., European Patent Nos. EP497524 and EP497525) and preferably by microfluidisation." Ex. 1006, 4:12–15. Merck 2011 teaches "[p]olysaccharides can be sized in order to reduce viscosity in

polysaccharide samples and/or to improve filterability for conjugated products. In the present invention, capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F of *S. pneumoniae*." Ex. 1006, 4:15–18 (emphasis added). Merck 2011 teaches that:

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

Ex. 1006, 16:27–31.

Thus, Merck 2011 disclosed methods to optimize the size of the polysaccharides using known techniques, including the serotype 22F polysaccharide, and taught to couple to known carrier proteins such as CRM_{197}, while limiting the upper size range using membrane filtration. Ex. 1006, 4:12–18, 16:27–31. Thus, rather than fabricating desired sizes, Merck 2011 specifically provides methods to constrain polysaccharide sizes within a particular size range. Ex. 1006, 16:27–31.

Table 2 in GSK 2008 shows a range of conjugate sizes where the lowest reported value is 1303 kDa and the highest reported value is 9572 kDa, both values falling within the range of 1000 kDa to 12,500 kDa required by claim 1. Ex. 1007, 54–55. GSK 2008 prefers that "saccharide conjugates of the invention should have an average size of saccharide pre-conjugation of 50-1600" kDa but notes that the "present inventors have found that saccharide conjugate vaccines retaining a larger size of saccharide

can provide a good immune response against pneumococcal disease." Ex. 1007, 14:23–25. GSK 2008 teaches that "[f]ull length polysaccharides may be 'sized' i.e. their size may be reduced by various methods such as acid hydrolysis treatment, hydrogen peroxide treatment, sizing by emulsiflex® followed by a hydrogen peroxide treatment to generate oligosaccharide fragments or microfluidization." Ex. 1007, 14:6–10.

GSK 2008 teaches the "saccharide conjugates present in the immunogenic compositions of the invention may be prepared by any known coupling technique" including "direct reductive amination methods as described in US 4365170 (Jennings) and US 4673574 (Anderson). Other methods are described in EP-0-161-188, EP-208375 and EP-0-477508." Ex. 1007, 17:28–30. GSK 2008 is replete with suggestions to conjugate pneumococcal polysaccharides of various serotypes to CRM_{197}. *See, e.g.*, Ex. 1007, 13.

GSK 2008 also provides more specific reasons to optimize the saccharide conjugates for larger sizes by teaching "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, 14:18–21. GSK 2008 teaches "that saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease." Ex. 1007, 14:23–25. GSK 2008 recognizes optimization for larger size saccharide-protein conjugates, limited only by a requirement to be "filterable through a 0.2 micron filter." Ex. 1007, 14:34.

Thus, GSK 2008 demonstrates that the artisan preferred a range of conjugated polysaccharide sizes overlapping that recited by the '559 claims, disclosed methods to optimize the size of the polysaccharides as well as to couple to known conjugates such as CRM_{197}. Ex. 1007, 13–15, 54–55.

Dr. Kasper, relying on GSK 2008, states "[c]onjugation of each polysaccharide to a carrier protein may be performed 'by any known coupling technique,' including conjugation chemistries based on CDAP and/or reductive amination." Ex. 1004 ¶ 82 (citing Ex. 1007, 17:28–35). Dr. Kasper states "[g]iven that routine conjugation techniques and conditions readily achieved those disclosed molecular weights (as well as polysaccharide to protein ratios falling within the claimed range), a POSITA would have understood such molecular weights to be typical of immunogenic conjugates." Ex 1004 ¶ 101. Dr. Kasper also stated, in response to the question "[s]o would you agree that developing pneumococcal glycoconjugates is very much a serotype-specific process?" that "I think there is a common process that you follow. This is routine optimization, as far as I'm concerned. There's nothing unusual about doing that. That's typical." Ex. 2013, 29:21–24.

In rebuttal to Dr. Kasper's position that the molecular weight of the serotype 22F glycoconjugate would have been an optimizable variable, Patent Owner relies on Dr. Boons's statement that:

> The determination of an appropriate molecular weight for a specific serotype glycoconjugate was not, in my opinion, a matter of "routine optimization" of existing reductive amination procedures. A number of variables affect the postconjugate molecular weight and/or immunogenicity of a specific serotype glycoconjugate. Because numerous variables affect the post-conjugation molecular weight and/or immunogenicity of a

> specific serotype glycoconjugate . . . a POSA would not have inferred that 22F glycoconjugates fall within a particular molecular weight based on the molecular weight of other serotype glycoconjugates (e.g., those serotypes listed in Table 2 of GSK 2008). For example, as noted in Jones 2005 (a document cited by Merck), some glycoconjugates were considerably smaller than the range recited in the '559 patent.

Ex. 2040 ¶ 55.

Under deposition, Dr. Boons stated that "something that the person skilled in the art would know, is that multiple parameters are important and can be critical for generating an immunogenic glycoconjugate composition, including degree of oxidation, saccharide to protein ratio, and molecular weights." Ex. 1109, 65:2–8. Dr. Boons stated that "it is well known that glycoconjugate vaccine development is difficult, that multiple parameters need to be optimized, and that success cannot be predicted beforehand." Ex. 1109, 66:21–24.

However, in response to a question as to whether he could "identify a passage in the '559 patent where the inventors describe issues that they had constructing a serotype 22F conjugate that elicits functional antibody," Dr. Boons stated "I can't identify a specific section mentioning specifically 22F." Ex. 1109, 69:7–12. In this discussion, Dr. Boons did not identify any specific teaching in the '559 patent or other prior art that demonstrated that the optimization of the size of the serotype 22F conjugate, known to be desirable by the skilled artisan, would have had any specific issues or concerns. *See* Ex. 1109, 67:2 to 69:25.

Dr. Kasper responded to Dr. Boons's concerns, noting that "[i]t would have been trivial for a POSITA to construct a conjugate with sufficient cross-linking to produce a serotype 22F conjugate over 1,000 kDa; the

serotype 22F polysaccharides and CRM_{197} carrier proteins each have multiple conjugation points." Ex. 1105 ¶ 46. Dr. Kasper noted that "because the disclosed neoglycoconjugates in Jones 2005 contained on average six saccharides . . ., such neo-glycoconjugates would have been over 1,000 kDa with six serotype 22F polysaccharides (and also within the claimed range), even if the polysaccharides were as small as 167 kDa." Ex. 1105 ¶ 48.

Patent Owner's declarant, Dr. Paradiso, was asked during deposition whether a "person of . . . skill in the art . . . would have understood how to vary the conjugation reaction conditions to achieve those different ten conjugates of Table 16?" Ex. 1104, 103:13–17. Dr. Paradiso answered that a "person of skill in the art would, based on the information given in [columns 15 and 16 and Table 16 of the '559 patent] . . . , probably have a good idea on how to vary these parameters." Ex. 1104, 103:19–22. In a follow-up question, Dr. Paradiso agreed that "there is no disclosure of a particular molecular weight of the serotype 22F conjugate that is used in the 16-valent composition [in the '559 patent] . . . ." Ex. 1104, 106:6–9.

The evidence of record, therefore, shows that optimization of polysaccharide conjugate size was well known to the person of ordinary skill in the art, as even Patent Owner's expert Dr. Boons acknowledged. Ex. 1109, 66:21–24. Dr. Boons further acknowledged that the '559 patent did not rely on any specific disclosure explaining issues in generating a serotype 22F conjugate (Ex. 1109, 69:7–12), thereby supporting the reasonable position of Dr. Paradiso that the ordinary artisan would "probably have a good idea on how to vary these parameters." Ex. 1104, 103:19–22. This evidence supports a determination that routine optimization would have been

obvious, particularly when combined with the teachings of Merck 2011 to optimize the size of the polysaccharides using known techniques, including the serotype 22F polysaccharide; with teachings of GSK 2008 of methods to optimize the size of the polysaccharides as well as to couple to known conjugates such as CRM_{197}; and with Dr. Kasper's statement that "[t]his is routine optimization, as far as I'm concerned. There's nothing unusual about doing that. That's typical." Ex. 2013 ¶ 82.

We recognize, but find unpersuasive, Patent Owner's assertion that "it is unreasonable to conclude that the molecular weight of a serotype 22F glycoconjugate would necessarily be over 1,000 kDa" (PO Resp. 22), because the issue is the obviousness of routine optimization of conjugate sizes, not inherent anticipation by GSK 2008. Instead, we agree with Petitioner that "a POSITA would have found GSK 2008's molecular weight range (1,303-9,572 kDa) desirable and would have had a reasonable expectation of achieving an immunogenic serotype 22F conjugate in that range." Pet. Reply 12–13.

We find that a preponderance of the evidence of record demonstrates that conjugate size is a resultseffective 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." *In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

We, therefore, conclude that a preponderance of the evidence of record supports Petitioner's position that the 1,000 to 12,500 kDa size range

in claim 1 of the '559 patent, which overlaps with the 1303 and 9572 kDa in GSK 2008, would have been consistent with the ranges optimized and used to generate multivalent vaccines. Pet. 39; Ex. 1007, 55:2–10. "In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

ii. General Knowledge and Other Prior Art

Patent Owner criticizes Petitioner's reliance on Pfizer 2012 (Ex. 1008),[13] Jones 2005 (Ex. 1026),[14] Lees 2008 (Ex. 1035),[15] and Wyeth 2007 (Ex. 1027)[16] as evidence that the person of ordinary skill in the art would

[13] Pfizer 2012, a slide presentation at a symposium, teaches general kDa mass ranges for glycoconjugates of 50 to 200 for the polysaccharide and 500 to 5,000 for the conjugate. Ex. 1008, 6.

[14] Jones 2005 reviews polysaccharide vaccines including *Streptococcus pneumoniae vaccines*. Ex. 1026, 2. Jones 2005 discusses both glycoconjugate vaccines and a 23-serotype specific pneumococcal polysaccharide vaccine. Ex. 1026, 6. Jones 2005 teaches CRM_{197} as a carrier protein and 5,000 kDa glycoconjugates. Ex. 1026, 7. Jones 2005 also shows a cartoon representation that depicts different structural types of glycoconjugate vaccines. Ex. 1026, 8, Fig. 2.

[15] Lees 2008 reviews conjugation chemistry, and particularly, polysaccharides and carrier proteins used in pneumococcal vaccines. Ex. 1035, 23. Lees 2008 identifies factors including the ratio of protein and polysaccharide as variables that may be controlled during the conjugation process. Ex. 1035, 5. Lees 2008 teaches sizing of the conjugates by purification using size exclusion chromatography or filtering through membranes with particular molecular weight cutoffs. Ex. 1035, 5.

[16] Wyeth 2007, a slide presentation at a colloquium, teaches the process of polysaccharide manufacture for pneumococcus vaccines. Ex. 1027, 4. Wyeth 2007 teaches a method of characterizing polysaccharides in a vaccine by size. Ex. 1027, 10–16. Wyeth 2007 teaches a serotype 7F

have understood that "the claimed ranges of the '559 Patent were known as typical and desirable." PO Resp. 26–31; Pet. Reply 6.

Patent Owner asserts that Petitioner "relies on a mass spectrometry slide in Pfizer 2012 for the statement that a 'typical' mass for a glycoconjugate could be within the range of 500-5,000 kDa," but Patent Owner asserts that a "POSA would not have interpreted the statement to mean that all glycoconjugates are within the range of 500-5,000 kDa. EX2040, ¶69. Pfizer 2012 does not provide any guidance to a POSA on how to generate a *S. pneumoniae* serotype 22F glycoconjugate or what the resulting molecular weight should be." PO Resp. 26. Patent Owner asserts that "Dr. Kasper's testimony illustrates the lack of any guidance, teaching or suggestion on conjugation chemistry or procedures in Pfizer 2012." PO Resp. 27 (citing Ex. 2013, 59:25 to 60:14). Patent Owner asserts that "Pfizer 2012 does not refer to serotype 22F glycoconjugates and only refers to general molecular weights well outside the range in the '559 patent claims." PO Resp. 27.

We find these arguments unpersuasive because we understand the citation to Pfizer 2012 as evidencing that 500 to 5000 kDa was a known size range for glycoconjugates consistent with the disclosure of a range up to 1600 kDA disclosed by GSK 2008. *See* Prelim. Resp. 27–28; Ex. 1008, 6; Ex. 1007, 94 (*cf*. Pet. 19, 39).

Moreover, while we agree with Patent Owner that Pfizer 2012 does detail the procedures used for conjugation, Dr. Kasper stated in his testimony that in Pfizer 2012 "if you look at page 4, they describe two

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polysaccharide conjugated to CRM_{197} that falls within a range of 9,202 to 11,950 kDa. Ex. 1027, 21.

different technologies for conjugation, one for cross-linking and one for single-end conjugation." Ex. 2013, 60:5–8 (citing Ex. 1008, 4). Dr. Kasper also stated that "[a]s of January 21, 2014, both reductive amination and CDAP had been used to construct immunogenic conjugates, including in licensed pneumococcal vaccines." Ex. 2035 ¶ 35. Dr. Kasper states that "Pfizer 2012 discloses that such conjugates are typically 500-5,000 kDa, with the vast majority of the disclosed range (1,000-5,000 kDa) overlapping the claimed range of 1,000-12,500 kDa." Ex. 2035 ¶ 103. Dr. Kasper asserts that "a POSITA would have been motivated with a reasonable expectation of success to apply Pfizer 2012's disclosed 1,000 to 5,000 kDa range (within the claimed range of 1,000 to 12,500 kDa) to the serotype 22F conjugates of Merck 2011's pneumococcal CRM_{197} conjugate composition." Ex. 2035 ¶ 103.

Patent Owner asserts that: "Jones 2005 does not mention any serotype 22F glycoconjugates, much less how to make these glycoconjugates"; that "Wyeth 2007 does not mention serotype 22F or provide any guidance as to how to make a serotype 22F glycoconjugate"; and that "Lees 2008 does not refer to any serotype 22F glycoconjugates, much less how to make an immunogenic serotype 22F glycoconjugate having the specific molecular weight and ratio parameters recited in the '559 patent claims." PO Resp. 27–30 (citing Ex. 2040 ¶¶ 70, 72, 74).

We are unpersuaded by Patent Owner's general allegations because each of these references provides specific teachings regarding vaccine glycoconjugates that establish the knowledge of the ordinary artisan. As Dr.

Lees[17] stated, "immunogenic 22F glycoconjugates already existed before 2014. Specifically, the 22F glycoconjugates taught in both GSK-711 and Merck-086 were shown to be immunogenic." Ex. 2039 ¶ 124. Dr. Lees noted that "GSK-711 shows that both 22F conjugates (22F-PhtD and 22F-AH-PhtD) are immunogenic measured by both IgG and OPA antibodies." Ex. 2039

¶ 128 (citing Ex. 1007, 93). Petitioner cites Jones 2005, Wyeth 2007, and Lees 2008 in order to demonstrate that the specific conditions used for making glycoconjugate in general were well known.

Patent Owner then makes specific assertions identifying deficiencies in Jones 2005, Wyeth 2007, and Lees 2008. For Jones 2005, Patent Owner asserts that "Jones 2005 refers to a (non-pneumococcal) glycoconjugate having a molecular weight (5,000 kDa) within the recited range of the '559 patent claims, and one that does not (90 kDa)" and asserts a "POSA likely would have initially focused on the smaller neo-glycoconjugate, because it would be expected to be simpler to generate and easier to characterize." PO Resp. 28. For Wyeth 2007, Patent Owner asserts that:

> Wyeth 2007 and GSK 2008 viewed together demonstrate that different conjugation chemistries can result in glycoconjugates with different molecular weights. Wyeth 2007 recites 7F glycoconjugates of 9,202-11,950 kDa, while GSK 2008 recites 7F glycoconjugates of 3907-4452 kDa. *Id.*, ¶73 (citing EX1027 at 21; EX1007 at Table 2). The differences between the molecular weights for 7F glycoconjugates disclosed in Wyeth 2007 and GSK 2008 highlight the need to

[17] Ex. 2039 is a Declaration by Dr. Lees submitted by the Petitioner in IPR 2018-00187 in support of a petitioner asserting the unpatentability of claims 1–45 of the '559 patent. Ex. 2039 ¶ 1.

> determine the appropriate molecular weight of a given serotype glycoconjugate on a case-by-case basis. *Id.*

PO Resp. 29. For Lees 2008, Patent Owner asserts that "Lees 2008 cautions that 'careful control' over numerous factors (e.g., pH, temperature, ratio of protein and polysaccharide and concentration of each) is 'key to successful conjugation.'" PO Resp. 30. Patent Owner further asserts, as to Lees 2008, that a "POSA would have known that more than routine experimentation would be needed to determine the appropriate molecular weight (or polysaccharide to protein ratio) of any given serotype glycoconjugate, and that appropriate conjugation conditions for each serotype glycoconjugate needed to be carefully determined on a case-by-case basis." PO Resp. 31 (citing Ex. 2040 ¶ 74).

We find these specific arguments unpersuasive. Jones 2005 teaches the repeating unit structure of types 1, 2, 3, 4, 5, 6B, 9N, 9V, 12F, 14, 18C, 19F, and 23F of *S. pneumoniae*. *See* Ex. 1026, 5. Jones 2005 does teach structurally variant conjugate vaccines comprising either neoglycoconjugate or crosslinked oligosaccharides with CRM_{197} (*see* Ex. 1026, 8, Fig. 2), but Jones 2005 explains that the "immune responses elicited by these different structural variants are generally similar." Ex. 1026, 7. Jones 2005 teaches, for *Haemophilus influenzae* type b glycoconjugate vaccines, that different methods result in different sizes, with a reductive amination approach resulting in a glycoconjugate that "is approximately 90 kDa in size, is approximately 30% carbohydrate and contains an average of six glycan chains per carrier protein" while cyanogen bromide activation approach results in a conjugate that "is a crosslinked network of polysaccharide and protein with a molecular weight of, on average, 5×10^6 Da [(5,000 kDa)]."

Ex. 1026, 7. Jones 2005 teaches "[s]tudies of the crosslinked conjugate vaccines have focused principally on the molecular size" (Ex. 1026, 12) and explains that "[m]olecular sizing of the conjugates is a simple and effective means to ensure consistency of the final conjugate." Ex. 1026, 13–14.

Thus, Jones 2005 demonstrates that the ordinary artisan was aware that different conjugation methods yielded different size glycoconjugates, that size was an important parameter, and that size was controllable using molecular sizing techniques.

Wyeth 2007 provides an example where glycoconjugates of serotype 7F of *S. pneumoniae* with CRM_{197} have a molecular weight between 9,200 kDa and 11,950 kDa. *See* Ex. 1027, 21. While Patent Owner correctly notes that these values differ from those for serotype 7F in GSK 2008 (*see* Ex. 1007, 56), we note that the two vaccines are conjugated to different carriers, CRM_{197} in Wyeth 2007 and *Haemophilus influenzae* protein D in GSK 2008. Ex. 1027, 21; Ex. 1007, 44, 55. Wyeth 2007 emphasizes that size is a central parameter for vaccine production. Ex. 1027, 7. Wyeth 2007 teaches a size assay for size measurement of glycoconjugate vaccines. *See, e.g.*, Ex. 1027, 12, 14.

Thus, Wyeth 2007 also demonstrates that size of glycoconjugates was an important concern for the ordinary artisan, provides a method for determining that size, and demonstrates that a particular glycoconjugate could be generated in the claimed size range using a different carrier protein.

Lees 2008 notably teaches that serotype 22F vaccines are used in formulations, teaching "the currently available licensed 23-valent pneumococcal PS vaccine is formulated with PSs from the 23 most prevalent strains: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C,

19F, 19A, 20, 22F, 23F, and 33F." Ex. 1035, 2. Lees 2008 teaches that "[s]ize fractionation is usually necessary" (Ex. 1035, 4) and that "[c]areful control over the factors relevant to the particular chemistry is key to successful conjugation. These factors include pH, temperature, the ratio of the protein and PS, and the concentration of each." Ex. 1035, 5. Thus, Lees 2008 demonstrates that the factors necessary to obtain particular glycoconjugates are results-optimizable variables, noting "[s]ince each capsular serotype has a different structure, reaction conditions, including concentrations, molar ratios of periodate, oxidation times, and pH, must be optimized." Ex. 1035, 6. Lees 2008 explains that after the reaction has been completed, particular desired sizes of glycoconjugates can be obtained because "purification of the conjugate is usually performed by size exclusion, by using either size exclusion chromatography or membranes with appropriate molecular weight cutoffs." Ex. 1035, 5.

Thus, Lees 2008 demonstrates not only that serotype 22F pneumococcal vaccines are desirable, but provides detailed discussion regarding the known parameters necessary to obtain particular glycoconjugates as well as methods to limit those glycoconjugates to the desired size.

Considered as a whole, we conclude that the disclosures in Jones 2005 of a 5000 kDa glycoconjugate, in Wyeth 2007 of pneumococcal serotype 7F glycoconjugates with sizes between 9202 and 11950 kDa, and in Lees 2008 of a multiple conjugate formation provide evidence that glycoconjugate size was a known optimizable variable. *See* Pet. 37, 39–40; Ex. 1026, 7; Ex. 1027, 21; Ex. 1035, 7. That is, these additional references underline the basic teachings in Merck 2011 and GSK 2008 discussed above and further

demonstrate that at the time of invention, a person of ordinary skill in the art would have recognized how to generate glycoconjugates of varying sizes using known techniques and recognized that size was a known, optimizable variable.

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

Patent Owner asserts "Merck 2011, GSK 2008 and the general knowledge would not have motivated a POSA to generate a 22F glycoconjugate with the recited polysaccharide to carrier protein ratio." PO Resp. 31 (citing Ex. 2040 ¶¶ 75–76).

i. Merck 2011's "charge ratio"

Patent Owner asserts that "the referenced ratio in Merck 2011 is presented in terms of 'charge', not weight to weight, as required by the '559 patent claims." PO Resp. 32. Patent Owner asserts "[a]t deposition, Dr. Kasper was unable to define what is meant by the term 'charge ratio'" and, therefore, "Merck's basis for the assertion that a general relationship exists between this term and weight-to-weight ratio is unclear." PO Resp. 33 (citing Ex. 2040 ¶ 79). Patent Owner asserts "a POSA would not have had any idea how to determine the appropriate ranges for this undefined parameter." PO Resp. 34. Patent Owner asserts "Merck 2011 also does not teach or suggest that any pre-conjugation polysaccharide to protein ratio (much less a w/w ratio) would be a 'result-effective variable' or have any impact on the resulting properties, *e.g.*, immunogenicity, of its serotype 22F glycoconjugates." PO Resp. 34.

While we agree with Patent Owner that the meaning of the term "charge ratio" is not intrinsically clear from Merck 2011, Patent Owner's

assertion that Dr. Kasper was unable to define the term is incorrect, as Dr. Kasper stated that "[c]harge ratio refers to the preconjugation ratio of your two components." Ex. 2013, 78:20–21. Dr. Kasper supports this interpretation based on "45 years of experience in the field, that's how it's commonly used." Ex. 2013, 79:2–3. Dr. Kasper explains, in response to the question of "[h]ow is charge ratio determined?" that "[t]he common usage would be the ratio of the weight of one that you put into the reaction to the weight of the other, the amount of one -- it's a stoichiometric ratio based on the amount of material that goes in." Ex. 2013, 80:12–17. Dr. Kasper also notes that "Merck 2011 specifically discloses that serotype 22F did not require unusual conjugation conditions. In particular, Merck 2011 discloses common activation and conjugation conditions, as well as any serotypes for which the conditions that deviate from those common conditions. Common conditions are not modified for serotype 22F." Ex. 1105 ¶ 32.

Dr. Boons states that a "POSA in January 2014 would not have been familiar with this term." Ex. 2040 ¶ 78. Dr. Boons responds to Dr. Kasper's statements by noting that Weber 2009 is an example where "the term 'charge ratio' means exactly what one would expect from the words recited in this term, i.e., the ratio of charges (not weights) between two different elements." Ex. 2040 ¶ 78.

Although we agree with Patent Owner that Merck's teaching of a 0.2–2 to 1 charge ratio for polysaccharide and carrier protein does not necessarily equate to the 0.4 to 2 w/w ratio required by claim 1, Merck's teaching nevertheless suggests that the ratio (i.e., proportional relationship) between the amount of polysaccharide to carrier protein represents an optimizable variable. Even Dr. Boons, after disagreeing with the question

"[d]o you agree that based on the Oxford Dictionary of Chemical Engineering for 'charge' the term 'charge ratio' in Merck 2011 refers to the ratio of the quantities of polysaccharide and protein that are fed into the conjugation reaction?" acknowledges that "I look at molar equivalents, not at weight equivalents. Actually I teach my students when you perform reactions weights are far less important than molar equivalents." Ex. 1109, 171:15–20, 173:14–18. Dr. Boons's statements indicate that the relative amount of the components, whether measured in moles or molecular weight, is a known parameter for optimization.

Therefore, even if Dr. Boons's interpretation of "charge ratio" as referring to molar equivalents of the polysaccharide and carrier protein is correct, and even if these ratios represent pre-conjugation amounts rather than post-conjugation amounts, the evidence still supports an understanding of Merck 2011 as suggesting that the relative amounts of these two components are results optimizable for the conjugation reaction and resultant vaccine.

ii. Merck 2011's pre- and post-conjugate ratios

Patent Owner asserts the "ratio values in Merck 2011 are pre-conjugation ratios that do not necessarily indicate post-conjugation characteristics of the glycoconjugate." PO Resp. 34 (citing Ex. 2040 ¶ 80). Patent Owner asserts "Tables 1 and 2 of GSK 2008 disclose pre-conjugation ratios that are 28% higher (2.5/1 up to 3.2/1 for serotype 19A) or 50% lower (1/1 down to 0.5/1 for serotype 23F) compared to the final conjugation ratios." PO Resp. 34–35 (citing Ex. 1007, 53–56). Patent Owner asserts that based on these tables in GSK 2008, "a POSA would have understood that one could not reasonably predict a post-conjugation polysaccharide to

protein ratio based on pre-conjugation polysaccharide to protein ratios." PO Resp. 35. Patent Owner asserts that "[i]n Table 2 of GSK 2008, some glycoconjugates comprised up to 11.2% free polysaccharide and up to 4.9% free carrier protein" and that "Merck 2011 considered its first formulation comprised unconjugated polysaccharide at levels high enough to be problematic, and that the levels of these conjugated polysaccharides and carrier protein were allegedly reduced to an unknown level in the second formulation." PO Resp. 36–37 (citing Ex. 1007, Table 2 and Ex. 1006, 24:1–28).

Patent Owner also asserts:

> [t]here is no evidence that the polysaccharides and carrier proteins listed in Merck 2011 Table 1 exist in the composition in a 1:1 ratio for each serotype. EX2040, ¶84. Table 1 lists the total amount of the fifteen different polysaccharides and the total amount of the carrier protein, it does not assess polysaccharide/protein ratio by serotype.

PO Resp. 38.

We are not persuaded by Patent Owner's arguments that Table 1 in Merck 2011 does not suggest a weight/weight ratio of polysaccharide to carrier protein within the range of 0.4 and 2 as required by claim 1 of the '559 patent because Table 1 of Merck 2011 discloses an example that would reasonably have been expected to result in a 1:1 w/w ratio of the 22F polysaccharide to the CRM_{197} carrier protein. Ex. 1006, 19:5–9; Ex. 1087 ¶ 120. This expectation is supported by Dr. Kasper's statement that the ratios "resulted in an average polysaccharide to protein ratio in the conjugates of approximately 1." Ex. 1004 ¶ 115.

Even comparing the pre- and post-conjugation evidence in Tables 1 and 2 of GSK 2008 that relate to serotypes other than serotype 22F,

we note that either a 50% reduction or a 28% increase in the 1:1 starting pre-conjugation ratio for serotype 22F disclosed in Merck 2011 would still result in a final conjugation composition that falls within the 0.4 and 2 w/w ratio range required by claim 1. Therefore, even fully accepting Patent Owner's position, the final conjugated composition of serotype 22F in Merck 2011 would have been expected to render claim 1 obvious. *See, e.g.*, *Ineos USA LLC v. Berry Plastics Corp*., 783 F.3d 865, 869 (Fed. Cir. 2015) ("When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range.")

We recognize that Dr. Boons states that "[g]iven the variation between pre- and post-conjugation ratios in Tables 1 and 2 of GSK 2008, a POSA would have understood that pre-conjugation ratios do not indicate post-conjugation ratios and that the appropriate ratio of each serotype glycoconjugate must be determined on a case-by-case basis." Ex. 2040 ¶ 80. However, Dr. Boons has not established that the post-conjugation ratios for any serotype shown in the Merck 2011 Table 2 fall outside the range recited in claim 1, while Dr. Kasper states "[f]or the PS22F-PhtD conjugate, the carrier protein to polysaccharide ratio is 2.17 (which translates to a polysaccharide to carrier protein ratio of 1/2.17 or 0.46), with only 5.8% free (unconjugated) polysaccharide." Ex. 2035 ¶ 89. Thus, the evidence of record in Merck 2011 suggests that the polysaccharide to carrier protein ratio of a serotype 22F conjugate falls within the claimed ratio range of 0.4 to 2.

Moreover, Dr. Lees supports the obviousness of the claimed range, noting that:

> It is desirable to avoid very low or very high polysaccharide-to-carrier protein ratios. Glycoconjugates having a very low polysaccharide-to-carrier protein ratio would

> require administration of large amounts of the conjugates in order to provide an effective amount of the polysaccharide. Ex. 1054 at 13. By contrast, glycoconjugates with a very high polysaccharide-to-carrier protein ratio may interfere with the immunogenic role of the carrier protein.

Ex. 2039 ¶ 57. Dr. Lees further notes that "[a]ccording to the WHO guidelines, the ratio of polysaccharide to carrier protein should be within the range approved . . . . For pneumococcal conjugate vaccines, while the particulars may differ for a specific serotype, the WHO guidelines specifically recommend a ratio 'in the range of 0.3–3.0.'" Ex. 2039 ¶ 58 (internal citation omitted). We note that Dr. Lees appears to be referring to a 2009 statement in *Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines* published by the Expert Committee on Biological Standardization of the World Health Organization that teaches "[t]ypically for pneumococcal conjugate vaccines the ratio is in the range of 0.3 to 3.0 but varies with the serotype. The ratio can be determined either by independent measurement of the amounts of protein and polysaccharide present, or by methods which give a direct measure of the ratio." Ex. 2060, 17.

Therefore, a preponderance of the evidence of record supports the obviousness of selecting polysaccharide to carrier protein ratio values for the serotype 22F polysaccharides within the 0.4 and 2 range recited in claim 1 of the '559 patent based on the disclosures of Merck 2011, GSK 2008, and the knowledge of the ordinary artisan, including the WHO guidelines.

iii. GSK teaching about serotype 22F polysaccharide to protein ratio

Patent Owner asserts "none of the ratio ranges in GSK 2008 are serotype specific and other ratio ranges in this same paragraph cited by Merck have values falling outside of the claimed range." PO Resp. 39. Patent Owner asserts "other portions of GSK 2008 refer to a variety of carrier protein to polysaccharide ratio ranges (*e.g.*, 6:1 to 3:1, and 6:1 to 3.5:1) that, when converted to polysaccharide to protein ratio ranges as in the '559 patent, fall entirely outside of the claimed range (*e.g.*, 0.17 to 0.33 and 0.17 to 0.28)" and, therefore, "a POSA would not have had any motivation to select the specific ratio range cited by Merck over any of the other ratio ranges disclosed in GSK 2008." PO Resp. 39–40.

Patent Owner asserts that based on Figure 6 of GSK 2008, "there is a striking difference (what appears to be a 12-fold difference) between the OPA results from the two different 22F glycoconjugates." PO Resp. 43. Patent Owner asserts that "a POSA trying to make an immunogenic serotype 22F glycoconjugate would have turned to PS22F-AHPhtD rather than PS22F-PhtD" because of "clear and unambiguous statements and data provided in GSK 2008 regarding the superiority of the PS22F-AH-PhtD glycoconjugate." PO Resp. 42.

Patent Owner asserts that:

> Due to the significant inferiority of the PS22F-PhtD glycoconjugate, a POSA would have been "discouraged" from generating this glycoconjugate and "would be led in a direction divergent from the path" adopted by Pfizer, *i.e.*, a POSA would have been directed to prepare a serotype 22F glycoconjugate having a polysaccharide to protein ratio outside the claimed range. EX2040, ¶88.

PO Resp. 45.

Patent Owner compares these facts to *Insite Vision Inc. v. Sandoz, Inc*., 783 F.3d 853 (Fed. Cir. 2015), and asserts, "[s]imilar to the facts of *Insite*, the challenged patent claims recite a combination of features (*e.g*., polysaccharide to protein ratios and molecular weights), and the cited prior art reference does not disclose one of the recited claim features (*i.e*., molecular weight) in that combination." PO Resp. 41.

We do not find these arguments persuasive. As already noted, GSK 2008 discloses a range of ratios of polysaccharide to carrier protein that includes and fully overlaps the range claimed. Ex. 1007, 20:24–28. *Peterson*, 315 F.3d at 1329. Dr. Kasper states that the "narrowest range in claim 48 [of GSK 2008] is a protein to polysaccharide ratio of 2:1 to 1:1, which translates to a polysaccharide to protein ratio of 0.5 to 1." Ex. 1105 ¶ 52. Also, we have already discussed Dr. Lees' statement that "[f]or pneumococcal conjugate vaccines, while the particulars may differ for a specific serotype, the WHO guidelines specifically recommend a ratio 'in the range of 0.3–3.0.'" Ex. 2039 ¶ 58 (citing Ex. 2060, 17 ("Typically for pneumococcal conjugate vaccines the ratio is in the range of 0.3 to 3.0 but varies with the serotype.")). Patent Owner also acknowledges that GSK 2008 teaches a final conjugate of serotype 22F that has a polysaccharide to protein ratio of 0.46, within the range required by claim 1. *See* PO Resp. 41.

The exemplary serotype 22F-PhtD conjugate with a 0.46 ratio, along with the overlapping ranges disclosed and claimed by GSK 2008, the overlapping Merck 2011 0.2–2 to 1 charge ratio, and the statement by Dr. Lees that this range substantially overlaps the World Health Organization's recommended ratios for pneumococcal conjugate vaccines, all provide

reasonable motivation for the ordinary artisan to select ratios for the serotype 22F conjugate within the range required by claim 1 of the '559 patent. Ex. 1004 ¶ 84; Ex. 1105 ¶ 52; Ex. 1006, 19:24–25; Ex. 2039 ¶ 58; Ex. 2060, 17.

We recognize that Figure 6 of GSK 2008 shows what Patent Owner states to be a 12-fold lower level of antibody titer for serotype 22F-PhtD with a 0.46 ratio relative to serotype 22F-AH-PhtD with a 3.66 to 4.34 ratio. *See* Ex. 1007, 108. We also recognize that Dr. Boons states that a "POSA would have avoided the glycoconjugate that was associated with the significantly worse immunogenicity (*i.e.*, PS22F-PhtD), not the glycoconjugate that required a little more effort to make (*i.e.*, PS22F-AH-PhtD)." Ex. 2040 ¶ 88.

However, GSK 2008 teaches that either conjugate may be used, noting a "13 valent vaccine was made by further adding the serotypes 19A and 22F conjugates above (with 22F either directly linked to PhtD, or alternatively through an ADH linker)." Ex. 1007, 55:5–7. Thus, the plain text of GSK 2008 teaches that either conjugate may be used. Therefore, even if the GSK 2008 teaching were interpreted as a preference for the higher polysaccharide to protein ratio rather than simply a preference for the ADH linker, it is well settled that disclosed examples, and even preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971). "[A] given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). *See also In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) ("The prior art's mere disclosure of more than one alternative does not constitute a teaching

away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the [claimed] solution.").

We also note that GSK 2008 shows the immunogenicity for the two serotype 22F conjugates as either 37% or 28–31%, demonstrating similar results for both conjugates. Patent Owner points to no teaching in GSK 2008 that criticizes, discredits, or discourages the use of a ratio within the range required by claim 1.

Patent Owner points to *Insite* as indicating that one of ordinary skill in the art would not have been motivated to select the claimed conjugate because the claims require "a combination of features (*e.g.*, polysaccharide to protein ratios and molecular weights), and the cited prior art reference does not disclose one of the recited claim features (*i.e.*, molecular weight)." PO Resp. 41 (*citing Insite*, 783 F.3d at 861).

In *Insite*, the Federal Circuit relied on District Court findings that "it would not have been obvious to a person of ordinary skill in the art to formulate a topical azithromycin formulation for ophthalmic treatment of any infection" because "there were 'innumerable' options for ophthalmic treatments" and concerns that azithromycin "might not penetrate ocular tissue based on its high molecular weight, charge and insolubility in water." *Insite*, 783 F.3d at 861.

In contrast, here, both of the cited prior art references, Merck 2011 and GSK 2008, specifically direct the ordinary artisan to incorporate serotype 22F conjugates into pneumococcal vaccines. *See* Ex. 1006, 6:1–4 ("[T]he addition of new polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses demonstrates the feasibility of expanding coverage of pneumococcal serotypes not covered by

existing pneumococcal vaccines."). *See also* Ex. 1007, 5:32 to 6:1 ("The present invention provides an immunogenic composition . . . [that] comprises a 22F saccharide conjugate.").

Moreover, as discussed above, the Merck 2011 and GSK 2008 references together suggest molecular weights and polysaccharide to carrier protein ratios that overlap and fall within the ranges recited in claim 1 of the '559 patent. *See, e.g.*, Ex. 1007, 55–56; Ex. 1004 ¶ 84; Ex. 1105 ¶ 52; Ex. 1006, 19:24–25. In addition, the ordinary artisan was aware of desirable ranges of polysaccharide to carrier protein. *See* Ex. 2039 ¶ 58; Ex. 2060, 17.

Therefore, unlike *Insite*, we conclude that the evidence of record directly suggests incorporation of a serotype 22F glycoconjugate into a pneumococcal vaccine and suggests selection of molecular weight and polysaccharide to carrier protein ratio from a limited series of optimizable ranges disclosed in the prior art.

We also conclude that the prior art provides a reasonable expectation of success in doing so, particularly in light of the disclosure in the prior art of functional glycoconjugates. Specifically, GSK 2008 demonstrates an immunogenic serotype 22F glycoconjugate with an overlapping polysaccharide to carrier protein ratio and Merck 2011 demonstrates an immunogenic serotype 22F glycoconjugate in a 1:1 polysaccharide to carrier protein ratio. Ex. 1007, 55–56; Ex. 1006, 21. Patent Owner provides no evidence showing that any serotype 22F glycoconjugate fails to result in an immunogenic response.

iv. Optimization of 1:1 polysaccharide to protein ratio

Patent Owner asserts a "POSA would disagree with Dr. Kasper's assertion that one would be 'shooting for' a polysaccharide to protein ratio of 1:1. . . . GSK 2008, in fact, teaches the opposite. For example, Table 1 of GSK 2008 provides pre-conjugation protein/polysaccharide ratios ranging from 1:1 to 3:1." PO Resp. 46 (citing Ex. 1008, Table 1). Patent Owner asserts that Example 2 of GSK 2008 "targets a ratio well below 1:1 and outside the claimed ranges" where the "conjugate had a final protein to polysaccharide ratio of 4.1 (w/w), which translates to a polysaccharide to protein ratio of 1:4.1, or 0.24." PO Resp. 47 (citing Ex. 1007, 52:38).

We are not persuaded that the range recited in claim 1 of polysaccharide to the carrier protein, between 0.4 and 2, is unobvious. We note that while Dr. Kasper responded to a question about a 1:1 saccharide to protein ratio as "[t]hat's what you're shooting for most often," Dr. Kasper continued to state regarding the ratio that "[b]ut they fall within a range. And the Pfizer patent and the GSK patent define a range of .4 to 2." Ex. 2013, 77:7–23. Thus, Dr. Kasper states that the range recited in claim 1 would have been obvious based on the ranges disclosed in the prior art.

We recognize Patent Owner's reliance on Dr. Boons' statement that "[p]rior to generating a glycoconjugate, a POSA would not have assumed that any particular post-conjugation polysaccharide to protein ratio would necessarily be appropriate for generating that given glycoconjugate." Ex. 2040 ¶ 90 (citing Ex. 1026, 13).

A preponderance of the evidence does not support Patent Owner's position. As already noted, GSK 2008 specifically suggests a range of carrier protein that overlaps the range recited in claim 1 of the '559 patent,

and GSK 2008 specifically teaches "the majority of the conjugates, for example 6, 7, 8, 9 or more of the conjugates have a ratio of carrier protein to saccharide that is greater than 1:1, for example 1.1:1." Ex. 1007, 20:24–28. Of equal significance, Merck 2011 teaches conjugations in which equal amounts of polysaccharide and carrier protein are present, including equal amounts of serotype 22F, suggesting a 1:1 ratio of these components. Ex. 1006, Table 1. Dr. Lees also supports the obviousness of the claimed range, stating that "[f]or pneumococcal conjugate vaccines, while the particulars may differ for a specific serotype, the WHO guidelines specifically recommend a ratio 'in the range of 0.3–3.0.'" Ex. 2039 ¶ 58 (citing Ex. 2060, 17 ("Typically for pneumococcal conjugate vaccines the ratio is in the range of 0.3 to 3.0 but varies with the serotype.")). Dr. Lees further notes that the "desired ratios of polysaccharide to carrier protein can be achieved typically by varying the relative amounts of starting polysaccharide materials and carrier proteins in the reaction mixture, optimizing the reaction conditions and monitoring the conjugation chemistry." Ex. 2039 ¶ 60.

v. JNIDD and polysaccharide to protein ratio

Patent Owner asserts that "the English portion of JNIID does not refer to any serotype 22F glycoconjugates, much less a polysaccharide to protein ratio range for a serotype 22F glycoconjugate." PO Resp. 48 (citing Ex. 2013, 103:14–23). Patent Owner asserts "a POSA understood that appropriate parameters for each serotype glycoconjugate needed to be determined on a case-by-case basis, and a POSA would not have assumed that a polysaccharide to protein ratio for one serotype glycoconjugate would be appropriate for a different polysaccharide to protein glycoconjugate." PO Resp. 48 (citing Ex. 2040 ¶ 92). Patent Owner also asserts:

> This understanding is also made clear in another document cited by Merck, Jones 2005 (EX1026). Jones 2005 states that: "[t]he optimal [polysaccharide-protein] ratio has to be determined by experiment in preclinical studies or clinical trials." *Id.* (quoting EX1026 at 13). Lees 2008 further notes that "[t]he unique structures of each serotype mean that the precise activation and conjugation conditions ***must be carefully controlled and optimized***. . . ." EX1035 at 7-8.

PO Resp. 48–49.

We agree with Patent Owner that the prior art recognized that conjugate size and polysaccharide to protein ratio were known results optimizable variables, and we agree that JNIID does not specifically discuss serotype 22F. However, JNIID does identify saccharide to protein ratios for seven serotypes, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, that range from a low of 0.3 to a high of 2.6, with the vast majority falling within the range of 0.4 and 2 recited by claim 1 of the '559 patent. Ex. 1085, 23. Thus, we agree with Dr. Kasper's statement that "[e]ach disclosed ratio [in JNIID] overlaps to a large extent with the claimed ratio of 0.4 to 2, consistent with the general understanding in the art as of January 21, 2014 that such ratios are typical for immunogenic conjugates." Ex. 2035 ¶ 113.

c. serotype 15B in claim 3 and 10A and 11A in claim 4

Patent Owner asserts a "POSA reading claims 3 or 4 (or claims 5–8) would understand that all of the serotype glycoconjugates recited in these claims would be required to be immunogenic, not just serotype 22F glycoconjugates." PO Resp. 51. Patent Owner asserts that "[n]either Merck 2011 nor GSK 2008 exemplifies immunogenic compositions that include a conjugate of pneumococcal serotype 15B, as required by claims 3 and 4." PO Resp. 52. Patent Owner asserts Lees 2008 "teaches that multivalent

pneumococcal glycoconjugate compositions 'present additional complexities' due to each serotype being chemically distinct, requiring optimization of each glycoconjugate within the compositions." PO Resp. 52 (internal citation omitted).

While we agree, as noted above, that Patent Owner correctly construes the claims to require the term "immunogenic" to apply to all of the serotypes present in the composition, we are not persuaded that claims 3 and 4 are unobvious over the disclosures in Merck 2011, GSK 2008, and the knowledge of the person of ordinary skill in the art.

GSK 2008 teaches a "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, 8:29–31. Thus, GSK 2008 expressly suggests a vaccine containing serotypes 10A, 11A, and 15. Just as we agreed with Patent Owner that the construction of the word "immunogenic" in claim 1 reasonably requires each serotype contained in a vaccine to induce an immune response, we also find that the disclosure of a vaccine by GSK 2008 containing multiple serotypes also requires induction of an immune response to each serotype. Otherwise there would be no need to include a serotype unable to induce such a response. And indeed, GSK 2008 uses the same term, immunogenic, to describe the pneumococcal vaccine composition. *See* Ex. 1007, 5:27.

We recognize that Dr. Boons correctly notes that "[n]either Merck 2011 nor GSK 2008 exemplifies immunogenic compositions that include a conjugate of pneumococcal serotype 15B." Ex. 2040 ¶ 96. However, "[a]ll the disclosures in a reference must be evaluated . . . and a reference is not

limited to the disclosure of specific working examples." *In re Mills*, 470 F.2d 649, 651 (CCPA 1972).

We note that Dr. Kasper stated that at the time of invention, the ordinary artisan was aware of serotype 15B, that PVP 2013 discloses inclusion of serotype 15B in a pneumococcal vaccine, and that "[b]ased on GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to additionally include a serotype 15B conjugate." Ex. 1004 ¶¶ 44, 88, 120 (citing Ex. 1009, 1). Dr. Kasper also noted that "serotypes 15B and 33F had already been included in the Pneumovax® 23 polysaccharide vaccine." Ex. 1096 ¶ 60 (citing Ex. 1054, 4). Dr. Kasper stated for serotypes 22F, 33F, and 15B that "each one had to be optimized structurally, and then they could be combined. And they would induce an immune response." Ex. 2013, 43:10–13.

This is consistent with Dr. Lees statement that "[c]laims 3–8 [of the '559 patent] collectively recite 20 additional serotypes. However, . . . all 20 of the recited serotypes were already included in multivalent pneumococcal vaccines on the market in 2014" and, therefore, "[o]ne would also have reasonably expected success because, as shown in GSK-711 and Merck-086, 22F and other new serotypes were successfully included in multivalent PCV compositions while maintaining the immunogenicity to all serotypes in the compositions." Ex. 2039 ¶¶ 158–59.

We, therefore, conclude that incorporation of known immunogenic serotypes such as 10A, 11A, 15B, and 33F into the vaccine suggested by Merck 2011, GSK 2008, and the knowledge of the ordinary artisan would have been obvious in order to increase the coverage of serotypes of pneumococcal vaccines.

D. Obviousness over Merck 2011, GSK 2008, and PVP 2013

Petitioner asserts that "PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an 'O-acetyl/polysaccharide unit molar ratio' of '0.5 - 1.5'; that entire specified range meets the claimed ratio of 'at least 0.1.'" Pet. 57, citing Ex. 1009, 4. Petitioner asserts that "[b]ecause the immunogenicity of a conjugate depends in large part on the immunogenicity of the included polysaccharide, a POSITA would have considered the teachings of PVP 2013 when designing the pneumococcal conjugate compositions of Merck 2011/GSK 2008." Pet. 56. Petitioner asserts:

> [g]iven that the O-acetyl content of native 22F capsular polysaccharide was known to be approximately 0.8 (Ex. 1029 at 1), it would have been obvious to a POSITA that the "ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM polysaccharide in the activated polysaccharide" would have been at least 0.625-1.875; that entire specified range meets the claim limitation of "at least 0.6."

Pet. 61–62, citing Ex. 1004 ¶ 150.

Patent Owner asserts "Merck 2011 and GSK 2008 do not refer to the minimum acetate levels required by claims 2, 40, and 43" and asserts that Petitioner "relies on PVP 2013 (EX1009) to allege that the acetate contents specified in these claims would have been obvious." PO Resp. 54. Patent Owner asserts the "23-valent free unconjugated polysaccharide vaccine referred to in PVP 2013, is not the same as the glycoconjugate compositions that are claimed in the '559 patent" because "the polysaccharides in a free polysaccharide-based vaccine composition are not conjugated to any carrier protein." PO Resp. 54 (citing Ex. 2013, 109:8–23 and Ex. 1071, 5). Patent

Owner asserts "[b]ecause carrier proteins or glycoconjugates are not mentioned in PVP 2013, this document would not have taught a POSA how to arrive at the specific polysaccharide to protein ratio (w/w) recited in the '559 patent claims." PO Resp. 54.

1. *PVP 2013 (Exhibit 1009)*

PVP 2013 is titled "Pneumococcal Vaccine Polyvalent" and was published on the website of Japan's National Institute of Infectious Diseases (*see* Pet., v). PVP 2013 discusses starting materials used to make vaccines including 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. *See* Ex. 1009, 1. PVP 2013 teaches various tests used to analyze polysaccharides used in the vaccines including, among others, an *O*-acetate content test. Ex. 1009, 3, 4. PVP 2013 provides a range of *O*-acetate for a variety of serotypes including a range of 0.5 – 1.5 for serotype 22F. Ex. 1009, 4.

2. *Analysis*

We find these arguments unpersuasive. Claim 2 requires "at least 0.1 mM acetate per mM polysaccharide" and claims 40 and 43 require a mM ratio that "is at least 0.6." Ex. 1001, 141:35–37, 144:15–18, 27–30. Dr. Kasper stated "PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an 'O-acetyl/ polysaccharide unit molar ratio' of '0.5 - 1.5'; that entire specified range meets the claimed ratio of 'at least 0.1.'" Ex. 1004 ¶ 142 (citing Ex. 1009, 4). Consistent with Dr. Kasper's statement, PVP 2013 states the "*O*-acetate content (*O*-acetyl/polysaccharide unit molar ratio) shall be within the range

of the following specification" where the range for serotype 22F is given as "0.5–1.5." Ex. 1009, 3, 4.

Dr. Kasper explained that Rajam 2007[18] evidences "that O-acetyl groups can contribute to the immunogenicity of pneumococcal polysaccharides." Ex. 1004 ¶ 143 (citing Ex. 1086). Rajam 2007 states "the primary functional epitope of 15B-Ps is linked to the O acetylation of the monosaccharide residues. Removal of this O-acetyl group results in loss of the functional antibody activity." Ex. 1086, 4. This teaching, in combination with the teaching of PVP 2013 to incorporate acetate into serotype 22F in particular, demonstrates that the evidence of record better supports Petitioner's position that use of acetate in the molar ratios suggested by PVP 2013 would have been expected to improve vaccine activity.

Consequently, PVP 2013 and the knowledge of the ordinary artisan reasonably suggest to utilize a molar ratio of acetate to polysaccharide for serotype 22F that falls within the requirements of claims 2, 40, and 43.

As to Patent Owner's assertions regarding polysaccharide to protein ratios and molecular weight ranges, we have already found the ratio of polysaccharide to protein and molecular weight ranges obvious for claim 1 as discussed above and claims 2, 40, and 43 are drawn to further ratios of acetate to polysaccharide suggested by PVP 2013.

[18]Gowrisankar Rajam et al., *Functional Antibodies to the O-Acetylated Pneumococcal Serotype 15B Capsular Polysaccharide Have Low Cross-Reactivities with Serotype 15C*, 14 CLINICAL & VAC. IMMUNOL. 1223–27 (2007) ("Rajam 2007," Ex. 1086).

We therefore conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by Merck 2011, GSK 2008, and the knowledge of the ordinary artisan with the acetate ratios suggested by PVP 2013 in order to retain immunogenic activity as disclosed by PVP 2013.

E. Obviousness over Merck 2011, GSK 2008, and Hsieh 2000

Petitioner asserts that Hsieh 2000 "discloses methods for characterizing CRM_{197} conjugate vaccines, including multivalent pneumococcal conjugate vaccines prepared by reductive amination." Pet. 62. Petitioner asserts that "[b]ased on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to obtain at least 30% of the conjugates of claim 1 with a K_d below or equal to 0.3 in a CL-4B column." Pet. 62, citing Ex. 1004 ¶ 152.

Patent Owner asserts "[n]either Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, GSK 2008, Hsieh 2000 and the 'general knowledge.' Therefore, Merck has likewise not met its burden in showing that claims 38 and 44 are obvious." PO Resp. 55. Patent Owner asserts "Hsieh 2000 does not refer to serotype 22F glycoconjugates. Hsieh 2000 also does not contain any guidance about targeting any particular molecular weight or polysaccharide to protein ratio for a serotype 22F glycoconjugate." PO Resp. 56 (citing Ex. 2040 ¶ 102).

1. *Hsieh 2000 (Exhibit 1013)*

Hsieh 2000 discusses the characterization of vaccines composed of polysaccharides conjugated to CRM_{197}, including a 7-valent pneumococcal saccharide-CRM_{197} conjugate vaccine. Ex. 1013, 1. Hsieh 2000 teaches that "CRM_{197} is a mutant of diphtheria toxin" and "lists the methods that have

been used to characterize CRM_{197}" including "High Performance Size-exclusion Liquid Chromatography . . . [that] is adequate to control the consistency and purity of the product." Ex. 1013, 2. Hsieh 2000 teaches that important parameters for conjugate vaccines include molecular size and polysaccharide to protein ratio among others. *See* Ex. 1013, 6. Hsieh explains that "[i]t is essential to demonstrate the covalent linkage of the saccharide to the carrier protein." Ex. 1013, 8

2. *Analysis*

We agree with Petitioner that "Hsieh 2000 discloses that '[s]ize exclusion chromatography (SEC) with either CL-2B or CL-4B sepharose is used' to assess molecular size" and Hsieh 2000 "discloses the typical extent of conjugation for CRM_{197} conjugates, and how to measure it." Pet. 26–27. Claim 38 requires the glycoconjugates to "have a K_d below or equal to 0.3 in a CL-4B column." Ex 1001, 144:7–9. Dr. Kasper stated "Hsieh 2000 discloses that pneumococcal conjugates should generally have a K_d below or equal to 0.3 in a CL-4B column." Ex. 1004 ¶ 152 (citing Ex. 1013, 6). Hsieh 2000 analyzed saccharide-CRM_{197} conjugates and stated:

> For pneumococcal conjugate, the molecular structure is more complicated than Hib or meningococcal conjugates. The molecular weight distribution can spread over a much wider range in the CL-4B profile, as shown in Figure 3. Therefore, a single value of 50% K_d or similar expression may not be indicative of the complex nature of the conjugate. As a qualitative measurement, a percent value of less than 0.3 K_d can be used to indicate the quantity of high molecular fraction in the conjugate.

Ex. 1013, 6. Thus, Hsieh 2000 directly suggests that for pneumococcal saccharide-CRM_{197} conjugates a 0.3 value K_d value obtained from a CL-4B column is desirable. Ex. 1013, 6. Patent Owner provides no evidence that

there would be any difficulty or unpredictability in performing Hsieh's assay on the conjugates suggested by Merck 2011 and GSK 2008. *See In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) ("Attorney's argument in a brief cannot take the place of evidence.").

Claim 44 requires the "degree of conjugation of said glycoconjugate is between 2 and 15." Ex. 1001, 144:32–34. Dr. Kasper stated "[b]ased on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to construct the conjugate of claim 1 with a 'degree of conjugation' between 2 and 15." Ex. 1004 ¶ 153 (citing Ex. 1013, 8). Hsieh 2000 teaches "[f]or saccharide-CRM_{197} conjugates, there is a limited number of exposed lysines on surface CRM_{197}, which can participate in the conjugation reaction. The loss of lysine has been relatively consistent in the range of 6-9." Ex. 1013, 8. Thus, the only evidence of record, Hsieh 2000, teaches a degree of conjugation between 6 and 9. Ex. 1013, 8. Patent Owner raises general concerns about variation in glycoconjugates, without providing specific evidence of unpredictability for 22F, but the requirement is not an absolute expectation of success, but rather a reasonable expectation of success based on the teachings of the prior art. "Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *Kubin*, 561 F.3d at 1360 (internal quotation marks and citation omitted).

We, therefore, conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by Merck 2011, GSK 2008, and the knowledge of the ordinary artisan with purification and conjugation techniques of Hsieh 2000 to obtain quality conjugates.

III. PATENT OWNER'S MOTION TO AMEND

Patent Owner's motion to amend is contingent on a finding of unpatentability of claims 1, 2, 3, 4, 9, 41, and 42 by the Board. Mot. Amend 1. Because we conclude that Petitioner has demonstrated that these claims are unpatentable (among other claims), we proceed to consider Patent Owner's motion to substitute claims 46–52 for claims 1, 2, 3, 4, 9, 41, and 42. For the reasons discussed below, Patent Owner's motion to amend is denied.

A. Threshold Requirements

In an *inter partes* review, claims may be added as part of a proposed motion to amend. 35 U.S.C. § 316(d).

The Board must assess the patentability of the proposed substitute claims "without placing the burden of persuasion on the patent owner." *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1328 (Fed. Cir. 2017) (en banc). Patent Owner's proposed substitute claims, however, must still meet the statutory requirements of 35 U.S.C. § 316(d) and the procedural requirements of 37 C.F.R. § 42.121 as a threshold matter. *See* USPTO's Memorandum, GUIDANCE ON MOTIONS TO AMEND IN VIEW OF AQUA PRODUCTS (Nov. 2017), available at https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf. Accordingly, Patent Owner must demonstrate: (1) the amendment proposes a reasonable number of substitute claims; (2) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter; (3) the amendment responds to a ground of unpatentability involved in the trial; and (4) the original disclosure sets forth written description support for each proposed claim. *See* 35 U.S.C.

§ 316(d)(1)(B),(3); 37 C.F.R. § 42.121; *Hospira, Inc. v. Genentech, Inc.*, Case IPR2017-00737, slip op. at 47 (PTAB Oct. 3, 2018) (Paper 108).

B. Proposed Substitute Claims

Proposed substitute claims 46 and 47 are reproduced below with markings showing proposed changes from claims 1 and 2, respectively. Deletions are shown in brackets and additions are underlined.

> Claim 46 (substitute for original claim 1): 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): The immunogenic composition of claim ~~1~~ 46, wherein the glycoconjugate comprises at least ~~0.1~~ 0.8 mM acetate per mM polysaccharide.

Mot. Amend App'x i, ii; Ex. 2044 ¶¶ 16–37.

C. Broadening, Definiteness, and Written Description

We construe only those terms that are in controversy, and only to the extent necessary to resolve the controversy. *See Vivid Techs.*, 200 F.3d at 803. None of the newly added claim terms are in controversy, so no claim construction is required.

In particular, we determine that the substitute claims do not broaden the invention and that substitute claim 47 is definite and has adequate written description support.

1. Claims do not improperly broaden the term "immunogenic"

Petitioner asserts "Patent Owner's proposed claims should be rejected because they impermissibly incorporate a broadened 'immunogenic' term." Pet. Opp. 24. Petitioner asserts that "Patent Owner's proposed claims would cover compositions that would not have infringed the original claims, *i.e.*, compositions that elicit the recited 2-log increase in serum IgG levels **without eliciting functional antibody against serotype 22F**." Pet. Opp. 25.

Patent Owner asserts:

> The substitute claim was not meant to broaden the scope beyond the original claims. Should the Board deem it necessary to construe the term "immunogenic" in the context of the substitute claims, Pfizer's position is that the term should be construed consistently with the manner in which the parties construed the term in the context of the original claims.

PO Reply 10.

We agree with Patent Owner that the term "immunogenic" does not impermissibly broaden the claims. As discussed in our claim interpretation section above, we agree with Patent Owner that the term "immunogenic" requires functional antibody be elicited against each immunogen contained

in the composition. Because every original claim and every newly proposed claim requires an immunogenic composition that comprises serotype 22F, the newly added claims require functional antibody against serotype 22F. Therefore, the inclusion of other serotypes serves to narrow the claims, because the claims must include an "immunogenic" serotype 22F glycoconjugate, along with additional "immunogenic" glycoconjugates of other serotypes.

2. Claim 47 is not indefinite

Petitioner asserts that "[p]roposed claim 47 should also be rejected as indefinite under 35 U.S.C. § 112(b) because the meaning of the claim term 'the glycoconjugate' is unclear." Pet. Opp. 22. Petitioner asserts that "proposed claim 46 recites 14 distinct 'glycoconjugates' - and there is no indication which one is 'the glycoconjugate' of proposed claim 47. Ex.1096, ¶¶82-84." Pet. Opp. 22.

Patent Owner asserts "claim 47 is readily interpreted as directed to the 22F conjugate as it is a proposed substitute to claim 2 and is supported by disclosures relating to a 22F conjugate." PO Reply 10–11.

We agree with Patent Owner that the reasonable reading of "the glycoconjugate" in claim 47 refers to the serotype 22F glycoconjugate referenced in independent claim 46. However, even if we agreed with Petitioner's interpretation and "the glycoconjugate" would then refer to all of the glycoconjugates in claim 46, this interpretation would simply further narrow claim 47 to require all of the glycoconjugates to satisfy the 0.8 mM acetate per mM polysaccharide limitation.

3. Claim 47 has written description support

Petitioner asserts a "POSITA would have understood that this paragraph does not disclose that the amount of acetate relative to polysaccharide in the serotype 22F conjugate can be 'at least 0.8 mM acetate per mM polysaccharide.'" Pet. Opp. 23 (internal citation omitted).

Patent Owner asserts "[c]laim 47 is directly supported by the disclosure: 'at least . . . about 0.8 mM acetate per mM serotype 22F polysaccharide' in both the application issuing as the '559 patent and the provisional to which it claims priority." PO Reply 12.

We agree with Patent Owner. The '559 patent states "the serotype 22F glycoconjugate of the invention comprises at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 or 0.7 or about 0.8 mM acetate per mM serotype 22F polysaccharide." Ex. 1001, 26:1–4. We determine that the ordinary artisan, confronted with the phrase "at least . . . or about 0.8 mM acetate" would understand this to encompass "at least about" 0.8 mM acetate, thus, allowing for either "at least" or "about" that amount of acetate.

D. Unpatentability

Petitioner assets that proposed substitute claims 46–52 are unpatentable as obvious over the combination of Hausdorff, Merck 2011, GSK 2008, and the knowledge of the ordinary artisan. Pet. Opp. 2–18; *see also* Pet. Sur-Reply 3–8. To support its Opposition, Petitioner proffers the declaration of Dr. Kasper and the deposition of Dr. Paradiso. Ex. 1096; Ex. 1104. Patent Owner disagrees. PO Reply 1–9; *see also* PO Sur-Sur-Reply 1–5. To

support its Motion Reply, Patent Owner proffers the declarations of Dr. Paradiso (Ex. 2044; Ex. 2063).

We determine that claims 46 and 48–52 would have been obvious over the combination of Merck 2011, GSK 2008, Hausdorff, and the knowledge of the skilled artisan. We determine that claim 47 would have been obvious with the further addition of PVP 2013.

1. Claims 46–52 are obvious over Hausdorff, Merck 2011, GSK 2008, and the knowledge of the ordinary artisan

a. Hausdorff (Ex. 2027)

Hausdorff 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." (Hausdorff ¶ 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 68) 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, reproduced below, 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.

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 the geometric mean titer "achieved in pooled serum samples, following two doses of the 13vPnC vaccine." Ex. 2027 ¶ 231.

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

b. Merck 2011 (Ex. 1006)

As discussed above in Section II.C.1, Merck 2011 teaches an immunogenic composition composed of serotypes "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. 1006, 1:9–11. Table 1 of Merck 2011 shows a vaccine formulation with a 1:1 ratio for 14 serotypes including serotype 22F and a 2:1 ratio for serotype 6B, specifically showing the formulation comprises 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. 1006, 19:5–9.

Merck 2011 teaches 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. 1006, 23:15–17.

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.

In Table 4, Merck 2011 teaches the "fold-rise in antibody levels to the non-Prevnar® serotypes from Day 0 to Day 28 (Post-dose 2, PD-2)." Ex. 1006, 24:14–15.

In the NZWR-3 and NZWR-4 studies in Table 4 of Merck 2011, 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. 1006, Table 4.

c. GSK 2008 (Ex. 1007)

As discussed above in Section II.C.2, GSK 2008 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, 8:29–31. GSK 2008 teaches conjugation of polysaccharides to the carrier protein CRM_{197} (*see* Ex. 1007, 10:12–14) and teaches "[p]referably the ratio of carrier

protein to *S. pneumoniae* saccharide is between 1:5 and 5:1." Ex. 1007, 20:24–26. GSK 2008 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, 94.

d. Analysis

i. Claim 46

Petitioner asserts a "POSITA as of January 21, 2014 would have been motivated with a reasonable expectation of success to add the immunogenic serotype 22F conjugate of Merck 2011 to the immunogenic 13-valent composition of Hausdorff." Pet. Opp. 4 (citing Ex. 1096 ¶ 23). Petitioner asserts "serotype 22F was well-known as an emerging and clinically relevant pneumococcal serotype not in Prevnar 13®. *See, e.g.*, Ex.1096, ¶26; Ex.1098, 1; Ex.1099, 7; Ex.1100, 1." Pet. Opp. 4. Petitioner asserts that the ordinary artisan would have had reason to use CRM_{197} as the protein conjugate and an aluminum salt as the adjuvant. Pet. Opp. 5 (citing Ex. 1096 ¶¶ 29–30; Ex. 2027 ¶ 59; Ex. 1006, 11:31–33).

Petitioner asserts that a "POSITA would have had a reasonable expectation that combining such conjugates would yield a 14-valent composition with the claimed 2-log increase in serum IgG levels." Pet. Opp. 8. Petitioner asserts that Hausdorff "reports that the 13-valent composition, with or without adjuvant, exhibits the claimed 2-log increase in serum IgG levels." Pet. Opp. 6 (citing Ex. 2027 ¶ 231). Petitioner also asserts that "for serotype 22F, Merck 2011 discloses more than a 2-log increase in IgG levels (*i.e.*, 243.0- and 135.0-fold increases) above baseline in 2 studies." Pet. Opp. 8 (citing Ex.1006, 24:17–25:1 (Table 4)).

Petitioner asserts that a "POSITA would not have been concerned that adding one more conjugate to the 13-valent composition of Hausdorff would negatively impact immunogenicity of the composition." Pet. Opp. 8 (citing Ex. 1096 ¶ 43). Petitioner asserts that

> Patent Owner's expert in a related proceeding, Dr. Fattom, confirmed that immune interference "is not something that will prevent you from developing any vaccine with any valency. It's a risk management and risk evaluation." Ex.1102, 77:25-78:21. It was well-known that Patent Owner had successfully added 6 more CRM_{197} conjugates to its 7-valent pneumococcal CRM_{197} conjugate vaccine.

Pet. Opp. 8 (citing Ex. 1096 ¶ 43). Petitioner also asserts that Dr. Paradiso held the position in a published paper that "'[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**.'" Pet. Opp. 9 (citing Ex. 1091, 3 (emphasis added in Pet. Opp.)). Petitioner asserts that Dr. Paradiso "testified that a POSITA would not have been concerned about immune interference with a 21-valent composition 'based on the data with the 16- and the 20-valent vaccine, which achieved the two-log increase.'" Pet. Opp. 9 (citing Ex.1104, 110:22–111:10).

Petitioner asserts that "Merck 2011 describes its 15-valent composition as 'highly immunogenic' (in both infant rhesus monkeys ('IRMs') and NZWRs) against all 15 serotypes in the composition, and 'comparable to' Prevnar® with respect to the 7 overlapping serotypes." Pet. Opp. 10 (citing Ex. 1006, 30:3–14 and Ex. 1096 ¶¶ 45, 51). Petitioner asserts that "Patent Owner's expert, Dr. Paradiso, conceded that Merck 2011 discloses data in Figure 1 (IRM assay) establishing that 'after three doses the

responses for the 15-valent composition of Merck 2011 and that of Prevnar[®] were comparable.'" Pet. Opp. 10 (citing Ex. 1104, 138:4–9).

Patent Owner acknowledges that "Merck 2011 discloses a fifteen-valent composition ('PCV-15') that includes thirteen conjugates of the same serotypes and carrier disclosed in Hausdorff and two additional conjugates, one of which is a 22F-CRM_{197} conjugate." PO Reply 1 (citing Ex. 2063 ¶ 6). Patent Owner asserts, however, that "the data in Merck 2011 show that such a combination would not have achieved the 2-log IgG Increase required by substitute claim 46." PO Reply 1 (citing Ex. 2063 ¶ 5).

Patent Owner asserts "[i]n Merck 2011 Table 3, responses for PCV-15 are compared to those of Prevnar® for the 7 common serotypes covered by Prevnar®." PO Reply 1 (citing Ex. 1006, 25:15– 26:15; Ex. 2063 ¶ 7). Patent Owner asserts the "results in Table 3 show that the PCV-15 composition elicited poorer responses (i.e., < 1.0) than Prevnar® to several serotypes and in several arms of the study." PO Reply 2 (citing Ex. 2063 ¶ 9). Patent Owner relies on Dr. Paradiso to assert that "[f]ar from showing that PCV-15 is 'comparable' to Prevnar® (*see* Opp. at 12), these results show that PCV-15 elicited poorer responses than Prevnar® and suffers from immune interference." PO Reply 2–3 (citing Ex. 1104, 147:13–25).

Patent Owner asserts the results of Table 4 of Merck 2011 "show that PCV-15 failed to exhibit the 2-log IgG Increase to all serotypes as required by the substitute claim." PO Reply 3 (citing Ex. 2063 ¶ 13). Patent Owner asserts that "[g]iven the poor responses to numerous serotypes of the Merck 2011 formulations containing the undefined 22F conjugate, a POSA would have no reasonable expectation of making a composition that meets the 2-log IgG Increase of the substitute claims based on Hausdorff in view of

Merck 2011 and GSK 2008." PO Reply 4 (citing Ex. 2063 ¶ 14). Patent Owner asserts "Merck's argument that a POSA would dismiss the poor responses shown by Table 3 as variances generally associated with the rabbit immunogenicity test (*see* Opp. 11) rings hollow since Merck 2011 and Dr. Kasper relied on rabbit immunogenicity tests." PO Reply 5 (citing Ex. 1006, 25:15–26:1; Ex. 2062, 15:24–16:5).

Patent Owner asserts that Petitioner "argues that a POSA would not have been concerned with the immune interference demonstrated by Tables 3 and 4 because 13-valent conjugate vaccines had avoided immune interference in the past." PO Reply 6. Patent Owner asserts that "Merck 2011 itself reflected such concerns: '[o]ther PCVs have covered 7, 10, 11, or 13 of the serotypes contained in PCV-15, but immune interference has been observed for some serotypes.'" PO Reply 6 (citing Ex. 1006, 4:13–15). Patent Owner asserts that Petitioner's

> argument is also contradicted by its own statement to the USPTO in prosecuting U.S. Application 13/020,402, related to Merck 2011, that it was well known as of the priority date of Merck 2011 that "carrier induced epitopic suppression (CIES) was a problem when increasing the number of polysaccharides in pneumococcal conjugate vaccines."

PO Reply 6 (citing Ex. 2061, 4).

Patent Owner also asserts "Merck's assertion that serotype 22F was a known emerging serotype merely identifies a problem, not a motivation to combine particular references." PO Reply 7. Patent Owner also asserts that Petitioner's "opposition ignores the critical limitations that the claimed 'immunogenic composition compris[es]' a '22F glycoconjugate [that] has a molecular weight of between 1000 kDa and 12,500 kDa,' 'wherein a ratio

(w/w) of the [22F] polysaccharide to the [CRM_{197}] carrier protein is between 0.4 and 2.'" PO Reply 8 (internal citation omitted).

Viewing the evidence as a whole, we determine that a preponderance of the evidence demonstrates that it would have been obvious to incorporate a serotype 22F polysaccharide—conjugated to CRM_{197}, with molecular weights and saccharide to protein ratios falling in the claimed ranges as rendered obvious by Merck 2011 and GSK 2008—into a pneumococcal vaccine with the 13 serotypes and aluminum salt adjuvant disclosed by Hausdorff with a reasonable expectation of success in obtaining a 2-log increase above baseline in serum IgG levels as required by claim 46.

As to reasons to include serotype 22F into such a composition, Merck 2011 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. 1006, 4:1–4. GSK 2008 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, 5:5–9. Thus, both Merck 2011 and GSK 2008 provide specific reasons to incorporate serotype 22F into a pneumococcal vaccine to provide robust antibody responses that will provide herd immunity and reduce disease in human populations. As discussed extensively regarding claim 1

above, these two references also render the specific molecular weight and saccharide to protein ratios obvious and we incorporate that reasoning here.

As to the issue of immune interference and a reasonable expectation of success in obtaining a 2-log increase, Table 3 of Hausdorff shows that a composition with thirteen of the fourteen serotypes that were required by 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, the issue resolves to whether there would have been a reasonable expectation of success in the inclusion of serotype 22F in Hausdorff's pneumococcal vaccine composition while retaining the 2-log increased immune response of the thirteen serotypes and also allowing a 2-log increase in serotype 22F response.

Dr. Kasper states that

> Because the increases in serum IgG levels reported in Hausdorff were all well-above the 2-log threshold, as was also the case for the serotype 22F conjugate of Merck 2011, a POSITA would have had a reasonable expectation that the addition of the serotype 22F conjugate of Merck 2011 to the 13-valent composition of Hausdorff would yield the claimed 14-valent composition with the recited 2-log increase in serum IgG levels.

Ex. 1096 ¶ 34. This position is supported by Merck 2011, 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. 1006, 2:24–30, Ex.

1006, 24, Table 4. While Merck 2011 mentions immune interference in the background section relating to prior art formulations, Patent Owner does not identify a statement in Merck 2011 that immune interference occurred in PCV-15. Ex. 1006, 4:13–15.

We recognize Patent Owner correctly notes that Merck 2011 only obtained a 2-log increase of serum IgG levels in serotype 22F conjugates in two of the four arms, and annotates Figures 3 and 4 in Merck 2011 to identify particular experimental results that did not satisfy the 2-log increase. PO Reply 3–4. However, "'[o]bviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*.'" *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 2011 experiments showed a greater than 1-log increase in serum IgG levels and half of the experiments shows a greater than 2-log increase supports the determination that there was a reasonable expectation of success in achieving the claimed combination at a greater than 2-log increase. *See* Ex. 1006, 2:24–30, 24, Table 4.

Dr. Kasper cites Paradiso 2009 to support his position that immune interference would not have been expected with the addition of a serotype 22F-CRM_{197} conjugate to the thirteen serotype composition of Hausdorff because Paradiso 2009 states "[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. 1091, 3; Ex. 1096, 43. Dr. Paradiso, Patent Owner's expert, stated in deposition that "I would agree that what I said was that up to a 13-valent pneumococcal conjugate vaccine that it's been possible to induce good immunity to new serotypes without

negatively affecting the components already in the vaccine." Ex. 1104, 85:16–20. Dr. Paradiso also stated "I didn't" in response to a question of whether he made "any qualifications in the statement where the 13-valent composition was the upper threshold." Ex. 1104, 86:9–13.

We recognize Patent Owner's argument that the Merck 2011 "results show that PCV-15 elicited poorer responses than Prevnar® and suffers from immune interference" based on a statement by Dr. Paradiso that the Merck 2011 "formulation as a whole raises concern about potential interference" PO Reply 2–3; Ex. 1104, 147:24–25. Patent Owner also asserts:

> Table 2 of Skinner[19] (and Table 2 of Merck 2011), shows that PCV-15 elicited a variety of poorer responses when compared to Prevnar®. *See* EX1113 at 24:3-23; EX1110 at 6. Based on this data, a POSA would have understood that PCV-15 exhibited immune interference and would not have had a reasonable expectation that Merck's asserted combination would achieve the 2-log IgG Increase across all serotypes as required by every substitute claim. *See* EX2044 at ¶ 72.

PO Sur-Sur-Reply 2.

We are not persuaded by Patent Owner's arguments because Skinner 2011 shows IgG levels in Figure 3, while showing serotype-specific opsonophagocytic killing activity in Table 2. Ex. 1110, 6. Because claim 46 recites the 2-fold increase in IgG levels, not in opsonophagocytic killing

[19] Skinner 2011 is a prior art reference that teaches evaluation of a 15-valent pneumococcal CRM_{197} conjugate vaccine in a monkey model. Ex. 1110, 1. Skinner 2011 teaches increasing amounts of serotype specific antibodies after each immunization with the vaccine in monkeys for each of the 15 serotypes in the vaccine. Ex. 1110, 5, Figure 4. Skinner 2011 teaches that there was no serotype interference as the number of serotypes used was increased. Ex. 1110, 6.

activity, Figure 3 of Skinner 2011 is more relevant to the claim. Moreover, in a Reply Deposition, Dr. Paradiso was asked about results in Figure 3 of Skinner 2011 showing that "the IgG responses for PCV-15 were comparable to or higher than that for PCV-13 for all of the serotypes" and answered "So I agree that in this figure that is true, yes." Ex. 1113, 26:3–8 (referring to Ex. 1110, 4, Fig. 3). We note that Skinner 2011 teaches that "IRMs [(infant rhesus monkeys)] immunized with PCV-15 did not appear to demonstrate serotype interference as the antibody responses to the seven Prevnar® serotypes were not diminished by inclusion of additional polysaccharide conjugates as the vaccine was expanded to include either 13 or 15 types." Ex. 1110, 6. Indeed, Figure 3 of Skinner shows increased levels of IgG for every serotype in PCV-15 relative to all other pneumococcal vaccine compositions. Ex. 1110, Fig. 3.

Patent Owner also addresses deficiencies in Petitioner's reliance on Exhibit 1111, Exhibit 1112, and Exhibit 1114. PO Sur-Sur-Reply 4–5. We do not rely upon these Exhibits to demonstrate a reasonable expectation of success nor does our review of them find any evidence persuasively rebutting a reasonable expectation of success in generating a pneumococcal vaccine with serotype 22F with a 2-fold increase in IgG responses in New Zealand White Rabbits.

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 2011 and GSK 2008 specifically suggested incorporation of a serotype 22F conjugate linked to CRM_{197} into a pneumococcal vaccine that was already composed of other known serotypes, including all of the thirteen serotypes disclosed by Hausdorff. Ex. 1006, 1:9–11; Ex. 1007, 8:29–31; Ex. 2027 ¶ 230.

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 fourteen serotype pneumococcal vaccine composition as required by claim 46 with 2-fold increases in IgG responses in New Zealand White Rabbits because Merck 2011 itself exemplifies 2-fold increases in IgG responses in New Zealand White Rabbits for serotype 22F conjugates and because both Paradiso 2009 and Skinner 2011 support the position that inclusion of an additional serotype 22F-CRM_{197} conjugate into the thirteen serotype composition of Hausdorff would not have been expected to result in immune interference. Ex. 1006, 24.

We conclude that claim 46 would have been obvious over Hausdorff, Merck 2011, GSK 2008, and the knowledge of the ordinary artisan.

ii. Claim 47

Petitioner asserts that "PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an 'O-acetyl/polysaccharide unit molar ratio' of '0.5 - 1.5'; that specified range overlaps largely with the claimed ratio of 'at least 0.8.'" Pet. Opp. 14, (citing Ex. 1009, 3–4). Petitioner asserts that "[b]ecause immunogenicity of a conjugate depends in large part on immunogenicity of the included polysaccharide, a POSITA would have considered the teachings of PVP 2013 for the composition of claim 47; that composition incorporates many of

the same polysaccharides as PVP 2013, including serotype 22F." Pet. Opp. 13 (citing Ex. 1096 ¶ 53). Petitioner asserts that a "POSITA would have understood that O-acetyl groups can contribute to the immunogenicity of pneumococcal polysaccharides." Pet. Opp. 14 (citing Ex. 1096 ¶ 55). Petitioner asserts that a "POSITA as of January 21, 2014 would have been motivated to maintain at least 0.8 mM acetate per mM polysaccharide, *i.e.*, approximately native levels of acetate in the serotype 22F polysaccharide." Pet. Opp. 13–14 (citing Ex. 1096 ¶ 54, Ex. 1001, 15:67 to 16:2).

Patent Owner does not separately argue that Petitioner failed to meet its burden for dependent claim 47.

Dr. Kasper stated "PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an 'O-acetyl/ polysaccharide unit molar ratio' of '0.5 - 1.5'; that entire specified range meets the claimed ratio of 'at least 0.1.'" Ex. 1004 ¶ 142 (citing Ex. 1009, 4). Consistent with Dr. Kasper's statement, PVP 2013 states the "*O*-acetate content (*O*-acetyl/polysaccharide unit molar ratio) shall be within the range of the following specification" where the range for serotype 22F is given as "0.5–1.5." Ex. 1009, 3, 4.

Viewing the evidence as a whole, we determine that a preponderance of the evidence demonstrates that it would have been obvious that use of acetate in the molar ratios suggested by PVP 2013 would have been expected to improve vaccine activity.

iii. Claims 48 and 49

Petitioner asserts "[b]ased on GSK 2008, a POSITA would have been motivated with a reasonable expectation of success to include CRM_{197} conjugates of those 6 additional serotypes - well-known as emerging and

clinically relevant pneumococcal serotypes." Pet. Opp. 15 (citing Ex. 1096 ¶¶ 59–60). Petitioner asserts "the fact that Pneumovax® 23 polysaccharide vaccine featured serotypes 15B, 33F, 12F, 10A, 11A and 8 underscores that they were well-known to be prevalent." Pet. Opp. 16 (citing Ex. 1096 ¶¶ 60, 67; Ex. 1054, 4).

Patent Owner asserts:

> Merck fails to show that claims 48 and 49, which require additional conjugates, are not patentable. Merck fails to show any disclosure of serotype 15B in the art, and identifies no motivation for a POSA to conjugate serotypes 15B, 12F, 10A, 11A, and 8 to CRM197 or for those conjugates to be immunogenic or achieve the 2-log IgG Increase.

PO Reply 9.

Viewing the evidence as a whole, we determine that a preponderance of the evidence demonstrates that it would have been obvious to incorporate additional known *S. pneumoniae* serotypes into a pneumococcal vaccine. Claims 48 and 49 recite the additional inclusion of serotypes 15B, 33F, 12F, 10A, 11A, and 8, all conjugated to CRM_{197}. GSK 2008 specifically suggests inclusion of serotypes 33F, 12F, 10A, 11A, 8, along with serotype 15. *See* Ex. 1007, 8:29–31. Dr. Kasper states that a "POSITA would have understood that there is no individual 'serotype 15' and that 'serotype 15' in GSK 2008 includes all serotypes within serogroup 15, including serotype 15B as claimed." Ex. 1096 ¶ 60. Patent Owner provides no evidence that the ordinary artisan would not have understood the term "serotype 15" to include serotype 15B. We also note that the 1990 Physicians' Desk Reference disclosed that Pneumovax 23 contained serotype 15B, establishing that the prior art recognized this serotype as desirable in a pneumococcal vaccine. Ex. 1054, 4.

We conclude that claims 48 and 49 would have been obvious over Hausdorff, Merck 2011, GSK 2008, and the knowledge of the ordinary artisan.

IV. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude the following Exhibits, or portions thereof: Exhibit 1004 ¶ 21, Exhibit 1090, Exhibit 1094, Exhibit 1095, Exhibit 1101, Exhibit 1103, Exhibit 1110, Exhibit 1111, Exhibit 1112, and Exhibit 1114. Paper 49 ("Patent Owner Mot. to Exclude").

As to Exhibit 1004 ¶ 21, 1090, 1094, 1095, 1101, 1103, 1111, 1112, and 1114, we do not rely on any of that evidence in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to those exhibits and paragraphs, and we dismiss that portion of Patent Owner's motion as moot.

Patent Owner asserts that we should exclude Exhibit 1110 because "Merck is offering Exhibit 1110 to prove the truth of the matter asserted in the document, the exhibit is hearsay under Fed. R. Evid. 801. Since Exhibit 1110 does not fall within an exception to the rule against hearsay, Exhibit 1110 should be excluded under Fed. R. Evid. 802." Paper 49, 9.

Patent Owner also asserts that "Exhibit 1110 should be excluded as legally irrelevant under Fed. R. Evid. 401 and 402." Paper 49, 9. Patent Owner asserts "Merck also fails to identify how information on testing in infant rhesus monkeys is relevant to addressing deficiencies in its burden to prove unpatentability of the substitute claims." Paper 49, 10.

Petitioner asserts that "Exs.1110–1112 are admissible scientific papers published in the timeframe between Merck 2011's (Ex.1006) priority date (February 9, 2010) and January 21, 2014, and represent the state of the art

during that period." Paper 53, 10. Petitioner asserts that these papers "directly contradict Patent Owner's contention with respect to its Motion to Amend: that a POSITA would have interpreted the data of Merck 2011 as demonstrating immune interference for Merck's PCV-15 (pneumococcal CRM_{197} conjugate vaccine)." Paper 53, 10.

Petitioner asserts that "Skinner 2011 [(Ex. 1110)][is] . . . not being relied upon for the truth of the matters asserted therein," but rather that "Skinner 2011 [is] . . . cited for what [it] . . . indisputably disclosed to a POSITA as of January 21, 2014." Paper 53, 13. Petitioner also asserts regarding the relevance of Exhibit 1110 that "Patent Owner's argument is a red herring. The entire premise of the Motion to Amend is that '[t]he response to the vaccine in claim 46 suggests efficacy levels comparable to the original Prevnar® for which efficacy [*i.e.*, in humans] was demonstrated.' Ex.2044, ¶59." Paper 53, 12.

With few exceptions, the Federal Rules of Evidence apply to *inter partes* proceedings. 37 C.F.R. § 42.62. The moving party has the burden of proof to establish that it is entitled to the requested relief. 37 C.F.R. §§ 42.20(c), 42.62(a).

As to hearsay, Exhibit 1110 is a scientific journal article submitted as rebuttal evidence regarding the knowledge of an ordinary artisan regarding immune interference. *See* Pet. Reply, 1. Exhibit 1110 was offered simply as evidence of what it described, not for proving the truth of the matters addressed in the document, and, thus, is not hearsay. *EMC Corp. v. Personal Web Techns., LLC*, Case IPR2013-00085, slip op. at 66 (PTAB May 15, 2014) (Paper 73); *see also* Fed. R. Evid. § 801(c) (1997 Adv. Comm. Note) ("If the significance of an offered statement lies solely in the

fact that it was made, no issue is raised as to the truth of anything asserted, and the statement is not hearsay.").

As to relevance, evidence is relevant if it has any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence. *See* Fed. R. Evid. § 401. The Federal Circuit recognizes that there is a "low threshold for relevancy." *OddzOn Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1407 (Fed. Cir. 1997). The issue of immune interference is relevant to the issue of reasonable expectation of success for Hausdorff, Merck 2011, and GSK 2008 in rendering obvious the compositions claimed in Patent Owner's Motion to Amend. *See, e.g.*, PO Reply 2, Pet. Opp. 9. Exhibit 1110 provides an exemplary model system where immune interference did not occur based on the inclusion of additional *S. pneumoniae* serotype glycoconjugates. Ex. 1110, 6. We determine that Exhibit 1110 is relevant and are not persuaded by Patent Owner's argument, which goes to the weight of the evidence rather than its admissibility.

We deny Patent Owner's request to exclude Exhibit 1110.

V. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that (1) claims 1, 3–10, 16–19, 39, 41, 42, and 45 of the '559 patent are unpatentable over the combination of Merck 2011 and GSK 2008, (2) claims 2, 40, and 43 of the '559 patent are unpatentable over the combination of Merck 2011, GSK 2008, and PVP 2013; and (3) that claims 38 and 44 of the '559 patent are unpatentable over the combination of Merck 2011, GSK 2008, and Hsieh 2000.

We deny Patent Owner's Contingent Motion to Amend to replace claims 1–4, 9, 41, and 42 with substitute claims 46–52, as those claims are unpatentable over the cited art.

We dismiss Patent Owner's Motion to exclude Exhibits 1004 ¶ 21, 1090, 1094, 1095, 1101, 1103, 1111, 1112, and 1114 as moot.

We deny Patent Owner's Motion to exclude Exhibit 1110.

VI. ORDER

For the reasons given, it is

ORDERED, based on a preponderance of the evidence, that claims 1–10, 16–19, and 38–45 are unpatentable;

FURTHER ORDERED, Patent Owner's Motion to Amend is denied as to replacing claims 1–4, 9, 41, and 42 with substitute claims 46–52;

FURTHER ORDERED, Patent Owner's Motion to Exclude Exhibits 1004 ¶ 21, 1090, 1094, 1095, 1101, 1103, 1111, 1112, and 1114 is dismissed as moot;

FURTHER ORDERED, Patent Owner's Motion to Exclude Exhibit 1110 is denied;

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.

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Exhibit B

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Paper 68
Entered: February 4, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE OFFICE OF THE UNDERSECRETARY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

PFIZER INC.,
Patent Owner.

IPR2017-02131
IPR2017-02132
IPR2017-02136
IPR2017-02138
Patent 9,492,559 B2

Before ANDREW HIRSHFELD, *Commissioner for Patents, Performing the Functions and Duties of the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office.*

ORDER

The Office has received a request for Director review of the Final Written Decision in each of the above-captioned cases. *See, e.g.*, IPR2017-02131, Ex. 3100. The requests were referred to Mr. Hirshfeld, Commissioner for Patents, Performing the Functions and Duties of the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office.

It is ORDERED that the request for Director review in each case is denied; and

FURTHER ORDERED that the Patent Trial and Appeal Board's Final Written Decision in each case is the final decision of the agency.

IPR2017-02131
IPR2017-02132
IPR2017-02136
IPR2017-02138
Patent 9,492,559 B2

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