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Paper 59
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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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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 IPR2017-02132
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."). Patent Owner filed a Patent Owner Response to the Petition (Paper 19) ("PO Response") and a Motion to Amend. Paper 21 ("Mot. Amend."). Petitioner filed an Opposition to the Motion to Amend (Paper 31) ("Pet. Opp."), followed by a Reply to the Patent Owner 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 50. Petitioner filed an Opposition to Motion to Exclude Evidence. Paper 53. Patent Owner filed a Reply in Support of the Motion to Exclude. Paper 55.

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 addressed below in Section IV and the Motion to Amend has been addressed below in Section III.

B. Related Proceedings

We have instituted three additional *inter partes* reviews of claims of the '559 patent in IPR2017-02131, 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. Pet. 4.

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® (a decavalent vaccine) and PREVNAR 13® (tridecavalent vaccine)." *Id*. at 1:59–65.

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] Pfizer 2012[6]	§ 103(a)	1, 5–10, 16–19, 39, 41, 42, 45
Merck 2011, Pfizer 2012, PVP 2013[7]	§ 103(a)	2, 40, 43
Merck 2011, Pfizer 2012, GSK 2008[8]	§ 103(a)	3, 4, 39, 45
Merck 2011, Pfizer 2012, Hsieh 2000[9]	§ 103(a)	38, 44

Petitioner relies on Declarations of Dennis L. Kasper, M.D. Ex. 1005 and Ex. 1097. Patent Owner relies on Declarations of Geert-Jan Boons, Ph.D. Ex. 2041 and Peter Paradiso, Ph.D., Ex. 2045 and Ex. 2064.

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.[10] 37 C.F.R.

[5] Caulfield et al., WO 2011/100151 A1, published Aug. 18, 2011 ("Merck 2011," Ex. 1006).
[6] Brown et al., *Characterization of Complex Prophylactic Vaccines with Protein and Glycoconjugate Components*, 9th CASSS Symposium (Sept. 12, 2012) ("Pfizer 2012," Ex. 1008).
[7] "Pneumococcal Vaccine Polyvalent" revision to Japan's "Minimum Requirements for Biological Products" published on the website of Japan's National Institute of Infectious Diseases (as of March 2, 2013) ("PVP 2013," Ex. 1009).
[8] Biemans et al., WO 2009/000825 A2, published Dec. 31, 2008 ("GSK 2008," Ex. 1007).
[9] Hsieh, *Characterization of Saccharide-CRM$_{197}$ Conjugate Vaccines*, 103 DEV. BIOL. 93–104 (2000) ("Hsieh 2000," Ex. 1013).
[10] A recent amendment to this rule does not apply here because the Petition was filed before November 13, 2018. See Changes to the Claim

§ 42.100(b). Under the broadest reasonable interpretation approach, claim 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 which 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. 6–7. 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. 13. 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,

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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).

[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.1106, ¶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, 16:6–14. 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;[11] and, (4) where in evidence, objective indicia of nonobviousness.[12] *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

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[11] 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. 33 (citing Ex. 1005 ¶ 60). 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).

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

course of conduct would have been obvious to a person having ordinary skill:

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

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 Pfizer 2012

Petitioner contends that claims 1, 5–10, 16–19, 39, 41, 42, and 45 are unpatentable under 35 U.S.C. § 103(a) as obvious over Merck 2011, Pfizer 2012, and the general knowledge of an ordinary artisan. Pet. 38–54. The thrust of Patent Owner's position with respect to all the claims challenged on

this ground 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, 15–42. 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, 5–10, 16–19, 39, 41, 42, and 45 would have been obvious over Merck 2011, Pfizer 2012, 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)*

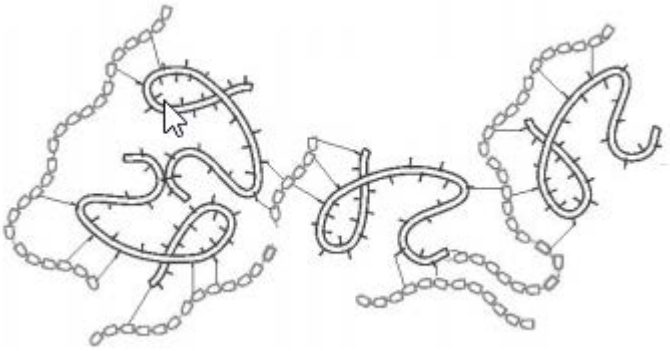
Merck 2011 teaches a pneumococcal conjugate vaccine (PCV) comprising "a multivalent immunogenic composition having 15 distinct polysaccharide-protein conjugates. Each conjugate consists of a capsular polysaccharide prepared from a different serotype of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 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 15–valent pneumococcal conjugate vaccine (PCV–15) "induced high OPA[13] GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine." Ex. 1006, 23:3–4.

[13] Opsonophagocytosis.

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 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. *Pfizer 2012*

Pfizer 2012 depicts examples of glycoconjugate vaccines as reproduced below:



The glycoconjugate vaccine image reproduced above depicts chains of carrier proteins represented by the solid lines conjugated to polysaccharide antigens represented by the connected cylinders. Ex. 1008, 4.
Pfizer 2012 teaches glycoconjugate vaccines with a typical mass range of 500 to 5000 kDa. Ex. 1008, 6. Pfizer 2012 teaches conjugation of polysaccharide to proteins such as CRM_{197}. Ex. 1008, 20. Pfizer 2012

teaches measurement of the size (i.e. mass) of the polysaccharide and conjugate using techniques such as SEC/MALLS. Ex. 1008, 6–7, 21.

3. *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.

4. *Analysis*

Petitioner asserts "Merck 2011 is directed to immunogenic multivalent pneumococcal conjugate compositions that include a serotype 22F conjugate" and that "Merck 2011 demonstrates immunogenicity against serotype 22F by the generation of functional antibody against that serotype." Pet. 40 (citing Ex. 1005 ¶ 105, Ex. 1006, 23:2–4). Petitioner asserts: "Based on Pfizer 2012's disclosure of conjugates between 1,000-5,000 kDa, a POSITA would have been motivated with a reasonable expectation of success to construct a serotype 22F CRM_{197} conjugate in that molecular weight range. . . ." Pet. 40 (citing Ex. 1005 ¶ 106). Petitioner also asserts "Merck 2011 discloses pre-conjugation ratios between 0.2 and 2, which a

POSITA would have considered indicative of a final conjugate ratio in that same range." Pet. 44 (citing Ex. 1006, 17:24–25). Petitioner points out "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." Pet 44–45 (citing Ex. 1006, 19:3–8).

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. 1005 ¶ 111 (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. 1005 ¶ 111 (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. 1005 ¶¶ 112–113 (citing Ex., 1085, 20–24).

Dr. Kasper states a "POSITA easily could have constructed a cross-linked serotype 22F CRM_{197} conjugate in Pfizer 2012's molecular weight range, using the well-known reductive amination or CDAP conjugation chemistries disclosed in Merck 2011." Ex. 1005 ¶ 107, citing Ex. 1006

6:15–7:6. Dr. Kasper states "cross-linked conjugates of 5,000 kDa were well-known" as were pneumococcal conjugate molecular weights of 1,303-9,572 kDa. Ex. 1005 ¶ 107 (citing Ex. 1026, 7, Ex. 1007, 54:27–55:1). 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 Pfizer 2012, *e.g.*, by increasing or decreasing the amount of cross-linking in the conjugate.

Ex. 1005 ¶ 108 (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 Pfizer 2012. We adopt these stated facts as our own. *See* Pet. 19–54. 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, Pfizer 2012, 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. 20 (citing Ex. 2041 ¶ 61).

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. 21 (citing Ex. 2041 ¶ 62). 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. 22 (citing Ex. 1007, Table 2).

Patent Owner asserts:

> 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, Pfizer 2012 would not have provided a POSA with any meaningful guidance or suggestion to generate an immunogenic serotype 22F glycoconjugate within the claimed molecular weight.

PO Reply 18.

Patent Owner asserts "[t]here is no overlap between the molecular weights in GSK 2008 and the '559 claims." PO Resp. 23. 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. 24. 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. 24.

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. 27.

Patent Owner reiterates these arguments in the Patent Owner's Reply and also asserts Petitioner'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 8.

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.

Pfizer 2012, in the context of characterizing vaccines, expressly discloses that the "[t]ypical mass (kDa)" for glycoconjugate vaccines is "500 to 5000." Ex. 1008, 6. As Dr. Kasper notes:

> The disclosed molecular weight range in Pfizer 2012 largely overlaps the claimed range of 1,000-12,500 kDa, and therefore expressly teaches conjugates of 1,000-5,000 kDa that fall within the claimed range. It would have been obvious to a POSITA to apply the teachings of Pfizer 2012 to the pneumococcal CRM_{197} conjugate vaccine of Merck 2011; a POSITA would have been aware of Patent Owner's licensed Prevnar® pneumococcal CRM_{197} conjugate vaccines.

Ex. 1005 ¶ 106.

While GSK 2008 was not expressly relied upon in the statement of the rejection, GSK 2008 evidences typical conjugation methods, polysaccharide sizes, and conjugate sizes of which the ordinary artisan would have been aware. *See, e.g.*, Pet. 30–31.

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 recognized a range of conjugated polysaccharide sizes overlapping those 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. 1005 ¶ 87 (citing Ex. 1007, 17:28–35). Dr. Kasper states "a POSITA would have required only routine

experimentation to obtain a conjugate molecular weight within the desirable range disclosed in Pfizer 2012, *e.g.*, by increasing or decreasing the amount of cross-linking in the conjugate." Ex 1005 ¶ 108 (citing Ex. 1030, 4:56–59). 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' 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 postconjugation 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. 2041 ¶ 62.

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' 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. 1106 ¶ 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. 1106 ¶ 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 Pfizer 2012 of a particular size range for glycoconjugate vaccines, and with the 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 29:22–24.

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. 26), because the issue is the obviousness of routine optimization of conjugate sizes, not inherent anticipation by Pfizer 2012 or GSK 2008. Instead, we agree with Petitioner that "a POSITA would have found the 1,000-5,000 kDa molecular weight range disclosed in Pfizer 2012 to be 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 results-effective variable associated with improved stability of conjugates and good immune response, limited only by filter size, thereby rendering "optimization within the grasp of one of ordinary skill in the art." *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 1,000 to 5,000 kDa range of Pfizer 2012, would have been consistent with the ranges optimized and used to generate multivalent vaccines. Pet. 39; Ex. 1008, 6. "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 Jones 2005 (Ex. 1026)[14] and Lees 2008 (Ex. 1035)[15] as evidence that the person of ordinary skill in the art would have understood that "the claimed ranges of the '559 Patent were known as typical and desirable." PO Resp. 28–30; Pet. Reply 15.

Patent Owner asserts that: "Jones 2005 does not mention any serotype 22F glycoconjugates, much less how to make these glycoconjugates" 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. 28–30 (citing Ex. 2041 ¶¶ 73, 75).

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.

[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.

Lees[16] 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 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 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. 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. 29–30. 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

[16] 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.

glycoconjugate, and that appropriate conjugation conditions for each serotype glycoconjugate needed to be carefully determined on a case-by-case basis." PO Resp. 30 (citing Ex. 2041 ¶ 75).

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.

Lees 2008 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 and in Lees 2008 of a multiple conjugate formation provide evidence that glycoconjugate size was a known

optimizable variable. *See* Pet. 42; Ex. 1026, 7; 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. 2041 ¶ 76). Patent Owner further asserts "Pfizer 2012 does not refer to any polysaccharide to protein ratios for any serotype glycoconjugates." PO Resp. 31.

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. 31–32. 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. 2041 ¶ 80). Patent Owner asserts "a POSA would not have had any idea how to determine the appropriate ranges for this undefined parameter." PO Resp. 33. 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. 33–34.

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. 1106 ¶ 32.

Dr. Boons states that a "POSA in January 2014 would not have been familiar with this term." Ex. 2041 ¶ 79. 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. 2041 ¶ 79.

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' 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' 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. 2041 ¶ 81). 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 (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. EX2041, ¶85. 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. 37–38.

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. 1005 ¶ 111. 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. 1005 ¶ 111.

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. 2041 ¶ 81. 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. 2037 ¶ 84. 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. 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 (cited by Merck in Ground 3), 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. 38 (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. 39–40 (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, 77:7–20. 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. 2041 ¶ 86 (citing Ex. 1026, 13).

A preponderance of the evidence does not support Patent Owner's position. 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, 20:26–28. 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[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.

iv. 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. 40 (citing Ex.

[17] We note that Ex. 2039 ¶ 58 inadvertently cites the WHO guidelines with an "*Id*." referring to Ex. 1019, rather than the correct citation to Ex. 2060, 17.

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. 40–41 (citing Ex. 2041 ¶ 88). 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. 41.

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. 2037 ¶ 119.

We therefore conclude that with respect to all the claims challenged on this ground that the cited prior art does suggests compositions with 22F

glycoconjugates that are immunogenic, within the claimed molecular weight ranges, and within the claimed polysaccharide to carrier protein conjugate ratios.

D. Obviousness over Merck 2011, Pfizer 2012, 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. 55, 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/Pfizer 2012." Pet. 54–55. 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 isolated polysaccharide" would have been at least 0.625-1.875; that entire specified range meets the claim limitation of "at least 0.6."

Pet. 58–59, citing Ex. 1005 ¶ 138.

Patent Owner asserts "Merck 2011 and Pfizer 2012 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. 43. 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. 43–44 (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. 44.

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., vi). 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. 1005 ¶ 132 (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. 1005 ¶ 133 (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, Pfizer 2012, 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, Pfizer 2012, and GSK 2008

Petitioner asserts that "GSK 2008 discloses compositions with conjugates of serotypes 22F, 15B and 33F." Pet. 61. Petitioner asserts that a "POSITA would have understood that 'serotype 15' in GSK 2008 includes all serotypes within serogroup 15, including serotype 15B as claimed." Pet. 61 (citing Ex. 1005 ¶ 143). Petitioner further asserts that "GSK 2008 discloses compositions with conjugates of serotypes 22F, 15B, 33F, 12F, 10A, 11A and 8." Pet. 62. Petitioner asserts that "the claimed serotypes were well-known to be prevalent and had already been included in the Pneumovax® 23 polysaccharide vaccine." Pet. 62 (citing Ex. 1031, 2; Ex. 1054, 4).

Patent Owner asserts a "POSA reading claims 3 or 4 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. 45. Patent Owner asserts that "[n]one of Merck 2011, Pfizer 2012 or GSK 2008 exemplifies immunogenic compositions that include a conjugate of pneumococcal serotype 15B, as required by claims 3 and 4." PO Resp. 47. 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. 47 (citing Ex. 2041 ¶ 95 and Ex. 1035, 1–2).

1. *GSK 2008 (Exhibit 1007)*

GSK 2008 was already discussed substantively above. 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 (emphases added).

GSK 2008 teaches: "Preferably the ratio of carrier protein to *S. pneumoniae* saccharide is between 1:5 and 5:1 . . . (w/w)." Ex. 1007, 20:24–26. GSK 2008 claims a conjugate where "the average size (e.g. Mw) of the 22F saccharide is between 50 and 800 kDa. . . ." Ex. 1007, 93 (claim 56).

2. *Analysis*

i. Reasons to include serotypes of claims 3 and 4

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, Pfizer 2012, 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]one of Merck 2011, Pfizer 2012, or GSK 2008 exemplifies immunogenic compositions that include a conjugate of pneumococcal serotype 15B." Ex. 2041 ¶ 95. 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, it would have been obvious to a POSITA to additionally include a serotype 15B conjugate." Ex. 1005 ¶ 142. 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. Lee's 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.

ii. *GSK 2008 teaching about serotype 22F polysaccharide to protein ratio*

Patent Owner asserts that "Table 2 of GSK 2008 refers to a 22F conjugate (referred to as 'PS22F-PhtD') having a protein to polysaccharide ratio of 2.17, which [Petitioner] translates to a polysaccharide to protein ratio of 1/2.17, or 0.46." PO Resp. 48 (citing Ex. 1005 ¶ 89). Patent Owner asserts that "[t]able 2 also provides data for a second glycoconjugate referred to as 'PS22F-AHPhtD'" that "has a protein to polysaccharide ratio of 3.66-4.34." PO Resp. 48 (citing Ex. 1007, Table 2).

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. 50 (citing Ex. 1007, 108). Patent Owner asserts that "Figure 6 clearly teaches that the PS22F-AH-PhtD glycoconjugate was functionally superior to the PS22F-PhtD glycoconjugate." PO Resp. 50.

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. EX2041, ¶99.

PO Resp. 52.

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. 1106 ¶ 52. Dr. Lees' stated 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. 10, 48.

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. 1005 ¶ 89; Ex. 1106 ¶ 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. 2041 ¶ 99.

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. Ex. 1007, table 2. 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.

In addition, two 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, Merck 2011 and GSK 2008 both 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, the prior art provides a reasonable expectation of success 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.

We therefore conclude that incorporation of known immunogenic serotypes such as 10A, 11A, 15B, and 33F into the vaccine suggested by Merck 2011, Pfizer 2012, GSK 2008, and the knowledge of the ordinary

artisan would have been obvious in order to increase the coverage of serotypes of pneumococcal vaccines.

F. Obviousness over Merck 2011, Pfizer 2012, 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. 64. 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. 64, citing Ex. 1005 ¶ 148.

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. 53. Patent Owner also 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. 53.

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. 32–33. 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. 1005 ¶ 148 (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 Pfizer 2012. *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. 1005 ¶ 149. 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. "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, Pfizer 2012, 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). *See also Lectrosonics, Inc. v. Zaxcom, Inc.*, Case IPR 2018-01129, slip op. 4–7 (PTAB Feb. 25, 2019)(Paper 15) (Clarifying motion to amend requirements, including clarification of requirements regarding scope of proposed substitute claims.)

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 or strikethrough and additions are underlined.

> Claim 46 (substitute for original claim 1, if found unpatentable): An immunogenic composition comprising:
>
> a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the 22F glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a CRM_{197} carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2;
>
> glycoconjugates from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F all individually conjugated to CRM_{197};
>
> an aluminum salt adjuvant; and
>
> wherein the composition exhibits more than a 2-log increase above baseline in serum IgG levels in New Zealand White Rabbits across all serotypes in the composition following administration of two equal doses of the composition in the form of an initial dose and a booster dose.
>
> Claim 47 (Substitute for original claim 2): 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. 2045 ¶¶ 16–38.

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.1097, ¶¶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 asserts that proposed substitute claims 46–52 are unpatentable as obvious over the combination of Hausdorff, Merck 2011, Pfizer 2012, and the knowledge of the ordinary artisan. Pet. Opp. 2–19; *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. 1097; 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. 2045; Ex. 2064).

We determine that claims 46 and 48–52 would have been obvious over the combination of Merck 2011, Pfizer 2012, Hausdorff, and the knowledge of the skilled artisan. We also 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, Pfizer 2012, 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, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F." Ex. 2027 ¶ 230. Hausdorff teaches:

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

> measured by ELISA and functional activity was assessed by OPA.

Ex. 2027 ¶ 230.

Table 3 of Hausdorff, 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. Pfizer 2012 (Ex. 1008)

As discussed above in Section II.C.2, Pfizer 2012 teaches glycoconjugate vaccines with a typical mass range of 500 to 5000 kDa. Ex. 1008, 6. Pfizer 2012 additionally teaches conjugation of polysaccharide to proteins such as CRM_{197}.

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. 1097 ¶ 23). Petitioner asserts "serotype 22F was well-known as an emerging and clinically relevant pneumococcal serotype not in Prevnar 13®. *See, e.g.*, Ex.1097, ¶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. 1097 ¶¶ 29–31; 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. 1097 ¶ 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. 1097 ¶ 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. 1097 ¶¶ 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. 2064 ¶ 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. 2064 ¶ 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. 2064 ¶ 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. 2064 ¶ 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 (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. 2064 ¶ 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 Pfizer 2012." PO Reply 4 (citing Ex. 2064 ¶ 14). Patent Owner asserts Petitioner'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 Petitioner'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 7–8 (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 Pfizer 2012—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. Thus, Merck 2011 provides specific reasons to incorporate serotype 22F into a pneumococcal vaccine to provide robust antibody responses that will provide immunity and reduce disease in human populations. As discussed extensively regarding claim 1 above, Merck 2011 and Pfizer 2012 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. 1097 ¶ 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. 1097 ¶ 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" is 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* EX2045 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, 4–6. Because claim 46 recites the 2-fold increase in IgG levels, not in opsonophagocytic killing 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

[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.

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*, 437 F.3d at 1167. Here, Merck 2011 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. 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. Moreover, 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, Pfizer 2012, 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. 1097 ¶ 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. 1097 ¶ 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. 1097 ¶ 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. 1005 ¶ 132 (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 in "further view of 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. 1097 ¶¶ 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. 1097 ¶¶ 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 CRM_{197} 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. 1097 ¶ 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, Pfizer 2012, 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 1005 ¶ 22, Exhibit 1090, Exhibit 1094, Exhibit 1095, Exhibit 1101, Exhibit 1103, Exhibit 1110, Exhibit 1111, Exhibit 1112, and Exhibit 1114. Paper 50 ("Patent Owner Mot. to Exclude").

As to Exhibit 1005 ¶ 22, 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 Petitioner "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 50, 9.

Patent Owner also asserts that "Exhibit 1110 should be excluded as legally irrelevant under Fed. R. Evid. 401 and 402." Paper 50, 9. Patent Owner asserts Petitioner "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 50, 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.2045, ¶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* Paper 53, 10. 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, Pfizer 2012 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, 5–10, 16–19, 39, 41, 42, 45 of the '559 patent are unpatentable over the combination of Merck 2011 and Pfizer 2012; (2) claims 2, 40, and 43 of the '559 patent are unpatentable over the combination of Merck 2011, Pfizer 2012, and PVP 2013; (3) that claims 3, 4, 39, and 45 of the '559 patent are unpatentable over the combination of Merck 2011, Pfizer 2012, and GSK 2008; and (4) that claims 38 and 44 are unpatentable over the combination of Merck 2011, Pfizer 2012, 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 1005 ¶ 22, 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 1005 ¶ 22, 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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Paper 43
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 IPR2017-02136
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 11–15 and 20–37 Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Dismissing 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 11–15 and 20–37 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 Preliminary Response. Paper 6 ("Prelim. Resp.").

On March 22, 2018, we instituted an *inter partes* review of all challenged claims. Paper 7 ("Dec. Inst."). Patent Owner filed a Patent Owner Response to the Petition (Paper 19) ("PO Response"). Petitioner filed a Reply to the Patent Owner Response. Paper 26 ("Pet. Reply"). Patent Owner filed a Sur-Reply. Paper 33 ("PO Sur-Reply"). Patent Owner filed a Motion to Exclude Evidence. Paper 35. Petitioner filed an Opposition to Motion to Exclude Evidence. Paper 38. Patent Owner filed a Reply in Support of the Motion to Exclude. Paper 39.

On November 13, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 42 ("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 11–15 and 20–37 of the '559 patent are unpatentable. See 35 U.S.C. § 316(e). Additionally, the Motion to Exclude Evidence by Patent Owner has been addressed 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]

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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.

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® (a 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.

D. Illustrative Claims

All of the challenged claims 11–15 and 20–37 depend either directly or indirectly from independent claim 1 of the '559 patent.[4] Claims 1, 11, and 31 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. pneumo*niae 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 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).
[4] Claims 1–10, 16–19, and 38–45 were not challenged in this proceeding, but were challenged in the related proceedings in IPR 2017-02131 and 2017-02132.

> 11. The immunogenic composition of claim 1, wherein said immunogenic composition further comprises a buffer, a salt, a divalent cation, a non-ionic detergent, a cryoprotectant, an anti-oxidant, or a combination thereof.
>
> 31. A method of preventing an infection caused by *S. pneumoniae* in a subject comprising administering to the subject an effective amount of the immunogenic composition of claim 1.

Ex. 1001, 141:27–33, 142:26–29, 143:27–30.

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):

Reference	Basis	Claims Challenged
Merck 2011,[5] GSK 2008[6]	§ 103(a)	11–14, 23–33, 35–37
Merck 2011, GSK 2008, '787 Patent[7]	§ 103(a)	15
Merck 2011, GSK 2008, Obaro 2002[8]	§ 103(a)	20, 21
Merck 2011, GSK 2008, Sigurdardottir 2008[9]	§ 103(a)	22

[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] Khandke et al., US 7,935,787 B2, issued May 3, 2011 ("'787 Patent," Ex. 1010).
[8] Obaro et al., *Safety and immunogenicity of pneumococcal conjugate vaccine in combination with diphtheria, tetanus toxoid, pertussis and Haemophilus influenzae type b conjugate vaccine*, 21 PEDIATRIC INFECTIOUS DISEASE J. 940–6 (2002) ("Obaro 2002," Ex. 1040).
[9] Sigurdardottir et al., *Safety and immunogenicity of CRM197-conjugated pneumococcal–meningococcal C combination vaccine (9vPnC–MnCC)*

Merck 2011, GSK 2008, MMWR 2012[10]	§ 103(a)	34

Petitioner relies on the Declaration of Dennis L. Kasper, M.D. Ex. 1087. Patent Owner relies on the Declaration of Dr. Geert-Jan Boons, Ph.D. Ex. 2042.

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.[11] 37 C.F.R. § 42.100(b) (2017). Under the broadest reasonable interpretation approach, claim 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).

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whether given in two or three primary doses, 26 VACCINE 4178–86 (2008) ("Sigurdardottir 2008," Ex. 1011).

[10] Bennett et al., *Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, 61 MMWR 816–9 (2012) ("MMWR 2012," Ex. 1012).

[11] 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).

We determine that the following claim term need 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 Response, Patent Owner contends "the context within the claim requires that the *composition* is immunogenic, not merely serotype 22F glycoconjugate in isolation." PO Resp. 14. 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 15.

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.1107, ¶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, 16:6–14. 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;[12] and, (4) where in evidence,

[12] 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.

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

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

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

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).

Pet. 29 (citing Ex. 1087 ¶ 62). 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).

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

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 11–14, 23–33, and 35–37 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. 34. The thrust of Patent Owner's position with respect to all the claims challenged on this ground 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, 16–57. 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 11–14, 23–33, and 35–37 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 pneumococcal conjugate vaccine (PCV) comprising "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 15-valent pneumococcal conjugate vaccine (PCV-15) "induced high OPA[14] 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 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

[14] Opsonophagocytosis.

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 (claim 61).

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. 36 (citing Ex. 1087 ¶ 108; 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. 37 (citing Ex. 1087 ¶ 111). 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. 43 (citing Ex. 1087 ¶ 119).

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. 1087 ¶ 120 (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. 1087 ¶ 120 (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. 1087 ¶¶ 123–124 (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. 1087 ¶ 121, (citing 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. 1087 ¶ 121 (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. 1087 ¶¶ 123–124 (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. 1087 ¶ 111. 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. 1087 ¶ 112 (citing 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. 1087 ¶ 113 (citing 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. 1087 ¶ 113 (citing Ex. 1006 16:30–31, 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. 1087 ¶ 114 (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. 1087 ¶ 114 (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. 1087 ¶ 115 (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. 34–55. 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, 11-14, 23-33, 35-37. Merck 2011, GSK 2008, and the general knowledge do not alone or in combination teach or suggest this limitation.

PO Resp. 16.

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. 17–18 (citing Ex. 2042 ¶ 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. 18 (citing Ex. 2042 ¶ 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. 19 (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. 21. 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. 21–22. 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. 22.

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. 25.

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. 1087 ¶ 85 (citing Ex. 1007, 17:1–30). 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 1087 ¶ 106. 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, 29:12–14, 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 postconjugation 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. 2042 ¶ 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. 1107 ¶ 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. 1107 ¶ 48.

Patent Owner's declarant, Dr. Paradiso, was asked during deposition whether a "person of ordinary 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, 29:21–24.

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. 24), 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 (emphasis omitted).

We find that a preponderance of the evidence of record demonstrates that conjugate size is a results-effective variable associated with improved stability of conjugates and good immune response, limited only by filter size, thereby rendering "optimization within the grasp of one of ordinary skill in the art." *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. 41; 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),[15] Jones 2005 (Ex. 1026),[16] Lees 2008 (Ex. 1035),[17] and Wyeth 2007 (Ex. 1027)[18] as evidence that the person of ordinary skill in the art would have understood that "the claimed ranges of the '559 Patent were known as typical and desirable." PO Resp. 26–32; Pet. Reply 6.

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[15] 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.

[16] 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.

[17] 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.

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

Patent Owner asserts that Petitioner "relies on a statement 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. EX2042, ¶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. 27–28. 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. 28 (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. 28.

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. 28–29; Ex. 1008, 6; Ex. 1007, 94 (*cf*. Pet. 19, 39).

Moreover, while we agree with Patent Owner that Pfizer 2012 does not 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 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. 1107 ¶ 36. Dr. Kasper states, in

response to a question, that Pfizer 2012 "shows a typical mass for glycoconjugate of 500-5,000 kDa" that the "teaching includes pneumococcus. And, in fact, the example [Pfizer 2012] give[s] on page 7 is a pneumococcal polysaccharide." Ex. 2013, 59:2–12.

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. 29–31 (citing Ex. 2042 ¶¶ 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. Kasper stated, prior art including GSK 2008 exemplified "[p]reparation of multivalent pneumococcal vaccines containing serotype 22F conjugates." Ex. 1087 ¶ 86. Dr. Kasper noted that GSK 2008 disclosed that "22F-PhtD administered within the 13-valent conjugate vaccine formulation were shown immunogenic and induced opsonophagocytic titers in young Balb/c mice." Ex. 1087 ¶ 88 (citing Ex. 1007, 75). 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. 29–30. 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. EX2042, ¶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 determine the appropriate molecular weight of a given serotype glycoconjugate on a case-by-case basis. *Id.*

PO Resp. 30–31. 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. 31–32. 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. 32 (citing Ex. 2042 ¶ 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, 39–41; 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. 33 (citing Ex. 2042 ¶¶ 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. 34. 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. 35 (citing Ex. 2042 ¶ 79). Patent Owner asserts "a POSA would not have had any idea how to determine the appropriate ranges for this undefined parameter." PO Resp. 35. 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. 35–36.

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. 1107 ¶ 32.

Dr. Boons states that a "POSA in January 2014 would not have been familiar with this term." Ex. 2042 ¶ 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. 2042 ¶ 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-conjugation 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. 36 (citing Ex. 2042 ¶ 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. 36 (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. 37. 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. 38–39 (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. EX2042, ¶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. 39–40.

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. Rather, 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. 1087 ¶ 120.

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. 2042 ¶ 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. 1087 ¶ 87. 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, Lees 2008 supports the obviousness of optimizing the claimed range, noting that "[r]egulatory authorities have considered the potency assay for conjugate vaccines to be a combination of the determination of the PS-to-protein ratio and the estimation of the amount of residual free saccharide. Ex. 1035, 9.

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.

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. 40. 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. 40–41.

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. 44. 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. 43–44.

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. EX2042, ¶89.

PO Resp. 46–47.

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. 42.

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. 1107 ¶ 52. 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. 42.

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, provides 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. 1107 ¶ 52; Ex. 1006, 19:24–25.

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. 2042 ¶ 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. 42 (*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 [and] 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. 1107 ¶ 52; Ex. 1006, 19:24–25. In addition, the ordinary artisan was aware of desirable ranges of polysaccharide to carrier protein. *See* Ex. 1107 ¶ 18, 52.

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. 47 (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. 48 (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 "[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. 2042 ¶ 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 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.

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. 49 (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. 49–50 (citing Ex. 2042 ¶ 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. 50.

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 "as of January 21, 2014 [JNIID] demonstrates that the claimed molecular weight and polysaccharide to protein ratio ranges of the '559 Patent were known to be typical and desirable." Ex. 1107 ¶ 18 (citing Ex. 1085, 23).

We therefore conclude that with respect to all the claims challenged on this ground that the cited prior art does suggests compositions with 22F glycoconjugates that are immunogenic, within the claimed molecular weight ranges, and within the claimed polysaccharide to carrier protein conjugate ratios.

D. Obviousness over Merck 2011, GSK 2008, and '787 patent

Petitioner asserts that based on the "'787 Patent (Ex. 1010), a POSITA would have been motivated with a reasonable expectation of

success to include the immunogenic composition of claim 1 in a syringe that is siliconized and/or made of glass." Pet. 56 (citing Ex. 1087 ¶ 143). Petitioner asserts that "'787 Patent discloses pneumococcal polysaccharide-protein conjugate formulations in siliconized containers, including glass syringes; the formulations inhibit protein aggregation caused by the silicone oil." Pet. 56 (citing Ex. 1010 13:34 to 14:23).

Patent Owner asserts

> Neither Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, GSK 2008, the '787 patent, and the "general knowledge," because Merck has not identified any reasons as to why the '787 patent remedies the deficiencies of Merck 2011 or GSK 2008. Merck has not met its burden in showing that claim 15 is obvious.

PO Resp. 52.

1. *'787 patent (Exhibit 1010)*

The '787 patent discusses "an ongoing need in the art to improve the stability of immunogenic compositions such as polysaccharide-protein conjugates." Ex. 1010, 9:57–59. The '787 patent discusses "the polysaccharide-protein conjugate formulation is a 13-valent pneumococcal conjugate (13vPnC) formulation comprising a *S. pneumoniae* serotype . . . polysaccharide conjugated to a CRM_{197} polypeptide." Ex. 1010, 6:39–43. The '787 patent explains the "formulations of the present invention are particularly useful in stabilizing the immunogen (i.e., a polysaccharide-protein conjugate . . . in the presence silicon oil found on container means such syringes, glass vials, rubbers stoppers and the like." Ex. 1010, 14:12–21.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to modify the multivalent pneumococcal vaccine containing the 22F serotype rendered obvious by Merck 2011 and GSK 2008 with a siliconized syringe as disclosed by the '787 patent for use with a 13 valent pneumococcal conjugate vaccine because these formulations function to stabilize the antigen.

We therefore conclude that a preponderance of the evidence supports the obviousness of modifying the conjugate vaccine suggested by Merck 2011, GSK 2008, and the knowledge of the ordinary artisan with the siliconized and glass syringes disclosed by the '787 patent in order to stabilize the vaccine as disclosed by the '787 patent.

E. Obviousness over Merck 2011, GSK 2008, and Obaro 2002

Petitioner asserts that based on Obaro 2002, "a POSITA would have been motivated with a reasonable expectation of success to include an antigen from a pathogen other than pneumococcus in the immunogenic composition of claim 1." Pet. 57 (citing Ex. 1087 ¶ 146). Petitioner asserts that "Obaro 2002 reports the safety and immunogenicity of Patent Owner's 9-valent pneumococcal CRM197-conjugate vaccine ('PnCV') when given in combination with a vaccine ('TETRAMUNE') containing diphtheria toxoid, tetanus toxoid, whole cell pertussis, and CRM_{197}-conjugated *Haemophilus influenzae* type B oligosaccharide." Pet. 57 (citing Ex. 1040, 2). Petitioner asserts "a POSITA would have understood that combining distinct individual vaccines (e.g., pneumococcal and non-pneumococcal

vaccinations) into a single composition is desirable, to enhance protection against disease and minimize the number of injections to a patient, particularly for infants." Pet. 57 (citing Ex. 1087 ¶ 146).

Patent Owner asserts "[n]either Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, GSK 2008, Obaro 2002, and the 'general knowledge.' Therefore, Merck has likewise not met its burden in showing that claims 20 and 21 are obvious." PO Resp. 53. Patent Owner asserts:

> Obaro 2002 does not disclose the molecular weight or polysaccharide to protein ratio for any of its glycoconjugates. As such, a POSA would not have had any motivation from Obaro 2002 to generate an immunogenic composition comprising a serotype 22F glycoconjugate having a molecular weight or polysaccharide to protein ratio falling within the specific ranges recited in any of the '559 patent claims (including claims 20 and 21).

PO Resp. 53–54 (citing Ex. 2042 ¶ 94).

1. *Obaro 2002 (Exhibit 1040)*

Obaro 2002 states "we evaluated the safety and immunogenicity of a 9-valent pneumococcal conjugate vaccine given in combination with TETRAMUNE [*Haemophilus influenzae* type b vaccine] administered simultaneously at different sites or mixed and administered as a single injection." Ex. 1040, 2. Obaro 2002 teaches the pneumococcal vaccine "was prepared in a lyophilized form and contained 2 µg of types 1, 4, 5, 9V, 14, 19F and 23F pneumococcal polysaccharides; 2 µg of type 18C oligosaccharide; and 4 µg of type 6B polysaccharide. Each polysaccharide or oligosaccharide was coupled independently to CRM_{197}, a nontoxic mutant of diphtheria toxoid, to give 20 µg of CRM_{197} per dose." Ex. 1040, 2.

Obaro 2002 states the "combination of TETRAMUNE and PnCV is safe and immunogenic." Ex. 1040, 1; emphasis omitted. Obaro 2002 teaches "[c]ombination of vaccines should make administration easier, less expensive and more acceptable to parents." Ex. 1040, 2.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to combine the pneumococcal vaccine including the 22F serotype with other vaccines including a *Haemophilus influenzae* type b vaccine because Obaro 2002 explains that combination of these vaccines makes administration easier and less expensive. While Patent Owner is correct that Obaro 2002 is silent on the molecular weights for the pneumococcus conjugate vaccine, both Merck 2011 and GSK 2008 disclose reasons to select the molecular weights required by claim 1 as discussed above. As to the polysaccharide to protein ratios, these are also disclosed in Merck 2011 and GSK 2008 as already discussed. In addition, Obaro 2002 teaches a 1:1 ratio for serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F because Obaro 2002 teaches 2 µg of polysaccharide for 8 serotypes and 4 µg for serotype 6B combined with 20 µg of CRM_{197}. Ex. 1040, 2.

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 by combining it with the *Haemophilus influenzae* type b vaccine of Obaro 2002 to simplify and reduce the expense of vaccine administration.

F. Obviousness over Merck 2011, GSK 2008, and Sigurdardottir 2008

Petitioner asserts that based on Sigurdardottir 2008, "a POSITA would have been motivated with a reasonable expectation of success to include a meningococcal serogroup C conjugate in the immunogenic composition of claim 1." Pet. 60 (citing Ex. 1087 ¶ 148). Petitioner asserts that "Sigurdardottir 2008 'evaluated safety and immunogenicity of a combined 9-valent pneumococcal and meningococcal C conjugate vaccine ['9vPnC-MnCC']" and Sigurdardottir 2008 concludes "9vPnC-MnCC is safe and immunogenic" Pet. 60 (citing Ex. 1011, 2, 8). Petitioner asserts "that combining distinct individual vaccines (e.g., pneumococcal and non-pneumococcal vaccinations) into a single composition is desirable, to enhance protection against disease and minimize the number of injections to a patient." Pet. 57 (citing Ex. 1087 ¶ 146).

Patent Owner asserts "[n]either Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, GSK 2008, Sigurdardottir 2008, and the 'general knowledge.' Therefore, Merck has likewise not met its burden in showing that claim 22 is obvious." PO Resp. 54. Patent Owner asserts:

> The pneumococcal glycoconjugates of Sigurdardottir 2008 comprise nine different serotype glycoconjugates (i.e., serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F), none of which is serotype 22F. EX1011 at 2. Sigurdardottir 2008 also does not refer to the molecular weight or polysaccharide to protein ratio for any of the glycoconjugates present in its vaccine.

PO Resp. 54–55 (citing Ex. 2042 ¶ 96). Patent Owner acknowledges that "Sigurdardottir 2008 does refer to serotype 22F." PO Resp. 55. Patent

Owner asserts, however, that a "POSA would not have had any motivation from Sigurdardottir 2008 to generate an immunogenic composition comprising a serotype 22F glycoconjugate having a molecular weight or polysaccharide to protein ratio falling within the specific ranges recited in any of the '559 patent claims." PO Resp. 55 (citing Ex. 2042 ¶ 97).

1. *Sigurdardottir (Exhibit 1011)*

Sigurdardottir states "we investigated the safety and immunogenicity of a 9-valent CRM197-conjugated pneumococcal-polysaccharide vaccine combined with a CRM197-conjugated *Meningococcus C* polysaccharide." Ex. 1011, 2. Sigurdardottir teaches the

> trial vaccine contained nine pneumococcal serotype polysaccharides, 2 µg of saccharide per pneumococcal serotypes 1, 4, 5, 9V, 14, 18C, 19F and 23F, 4 µg of pneumococcal serotype 6B and 10 µg of meningococcal group C oligosaccharide (same concentration as in monovalent Meningococcus C CRM197 conjugate, Meningitec®) coupled to 18.5 µg of CRM197 carrier protein.

Ex. 1011, 2. Sigurdardottir states a booster comprising the 23-valent pneumococcal-polysaccharide vaccine containing serotype 22F was used. Ex. 1011, 2. Sigurdardottir teaches "decreas[ing] the number of infant vaccinations by combining pneumococcal and Meningococcus C CRM197 conjugates." Ex. 1011, 7.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to combine the pneumococcal vaccine including the 22F serotype with other vaccines including a Meningococcus C vaccine because Sigurdardottir explains that

combination of these vaccines permits a decreased number of vaccinations. While Patent Owner is correct that Sigurdardottir is silent on the molecular weights for the pneumococcus conjugate vaccine, both Merck 2011 and GSK 2008 disclose reasons to select the molecular weights required by claim 1 as discussed above. Sigurdardottir also recognizes that serotype 22F is a vaccine target. Ex. 1011, 2. As to the polysaccharide to protein ratios, these are also disclosed in Merck 2011 and GSK 2008 as already discussed. In addition, Sigurdardottir teaches an approximately 1:1 ratio for serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F because Sigurdardottir teaches 2 µg of polysaccharide for 8 serotypes and 4 µg for serotype 6B combined with 18.5 µg of CRM_{197}. Ex. 1011, 2.

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 by combining it with the Meningococcus C vaccine of Sigurdardottir to simplify and reduce the expense of vaccine administration.

G. Obviousness over Merck 2011, GSK 2008, and MMWR 2012

Petitioner asserts that based on MMWR 2012, "a POSITA would have been motivated with a reasonable expectation of success to practice the method of claim 30 (taught by the combination of Merck 2011 and GSK 2008) in an immunocompromised human." Pet. 61 (citing Ex. 1087 ¶ 149). Petitioner asserts that "MMWR 2012 discloses the 'recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ≥19 years with immunocompromising conditions." Pet. 61 (citing Ex. 1012, 12).

Patent Owner asserts "[n]either Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, GSK 2008, MMWR 2012, and the 'general knowledge.' Therefore, Merck has likewise not met its burden in showing that claim 34 is obvious." PO Resp. 56. Patent Owner asserts "Prevnar13® does not include a serotype 22F glycoconjugate, and MMWR 2012 also does not disclose the molecular weight or polysaccharide to protein ratio for any of the glycoconjugates present in Prevnar13®." PO Resp. 56 (citing Ex. 2042 ¶ 99). Patent Owner asserts "a POSA would not have had any motivation from MMWR 2012 to generate and utilize an immunogenic composition comprising a serotype 22F glycoconjugate having a molecular weight or polysaccharide to protein ratio falling within the specific ranges recited in any of the '559 patent claims." PO Resp. 56–57.

1. *MMWR 2012 (Exhibit 1012)*

MMWR 2012 states

> the Advisory Committee on Immunization Practices (ACIP) recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, or cochlear implants (Table). PCV13 should be administered to eligible adults in addition to the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax 23, Merck & Co. Inc.), the vaccine currently recommended for these groups of adults.

Ex. 1012, 12. MMWR 2012 teaches "[a]dults with specified immunocompromising conditions who are eligible for pneumococcal vaccine should be vaccinated with PCV13 during their next pneumococcal

vaccination opportunity." Ex. 1012, 14.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to vaccinate immunocompromised individuals with the pneumococcal vaccine including the 22F serotype with other vaccines including a *Haemophilus influenzae* type b vaccine because MMWR 2012 suggests that such individuals should be vaccinated with pneumococcal vaccines, including the 23-valent vaccine that includes the 22F serotype. Ex. 1012, 12; Ex. 1087 ¶ 41. While Patent Owner is correct that MMWR 2012 is silent on the molecular weights for the pneumococcus conjugate vaccine, both Merck 2011 and GSK 2008 disclose reasons to select the molecular weights required by claim 1 as discussed above. As to the polysaccharide to protein ratios, these are also disclosed in Merck 2011 and GSK 2008 as already discussed.

We, therefore, conclude that a preponderance of the evidence supports the obviousness of treating immunocompromised patients with the vaccine suggested by Merck 2011, GSK 2008, and the knowledge of the ordinary artisan because MMWR 2012 suggests the desirability of treating this patient population with a pneumococcal vaccine. Ex. 1012, 12, 14.

III. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude the following Exhibits, or portions thereof: Exhibit 1087 ¶ 23, Exhibit 1094, and Exhibit 1095, Paper 35 ("Patent Owner Mot. to Exclude").

We do not rely on any of this evidence in making our ultimate determination on the patentability of the challenged claims. Accordingly,

we need not decide Patent Owner's motion and we therefore dismiss Patent Owner's motion as moot.

V. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that (1) claims 11–14, 23–33, and 35–37 of the '559 patent are unpatentable over the combination of Merck 2011 and GSK 2008, (2) claim 15 of the '559 patent is unpatentable over the combination of Merck 2011, GSK 2008, and '787 patent; (3) claims 20 and 21 of the '559 patent are unpatentable over Merck 2011, GSK 2008, and Obaro 2002; (4) claim 22 of the '559 patent is unpatentable over Merck 2011, GSK 2008, and Sigurdardottir 2008; and (5) claim 34 of the '559 patent is unpatentable over the combination of Merck 2011, GSK 2008, and MMWR 2012.

We dismiss Patent Owner's Motion to exclude Exhibit 1087 ¶ 23, Exhibit 1094, and Exhibit 1095 as moot.

VI. ORDER

For the reasons given, it is

ORDERED, based on a preponderance of the evidence, that claims 11–15 and 20–37 are unpatentable;

FURTHER ORDERED, Patent Owner's Motion to Exclude Exhibit 1087 ¶ 23, Exhibit 1094, and Exhibit 1095 is dismissed as moot;

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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Paper 45
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

PFIZER INC.,
Patent Owner.

Case IPR2017-02138
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 11–15 and 20–37 Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Dismissing 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 11–15 and 20–37 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 Preliminary Response. Paper 6 ("Prelim. Resp.").

On March 22, 2018, we instituted an *inter partes* review of all challenged claims. Paper 7 ("Dec. Inst."). Patent Owner filed a Request for Rehearing (Paper 11) that was denied (Paper 16). Patent Owner then filed Patent Owner Response to the Petition. Paper 22 ("PO Resp."). Petitioner filed a Reply to the Patent Owner Response. Paper 28 ("Pet. Reply"). Patent Owner filed a Sur-Reply. Paper 35 ("PO Sur-Reply").

Patent Owner filed a Motion to Exclude Evidence. Paper 37. Petitioner filed an Opposition to Motion to Exclude Evidence. Paper 40. Patent Owner filed a Reply in Support of the Motion to Exclude. Paper 41.

On November 13, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 44 ("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 11–15 and 20–37 of the '559 patent are unpatentable. *See* 35 U.S.C. §316(e). Additionally, the Motion to Exclude Evidence by Patent Owner has been addressed below in Section III.

B. Related Proceedings

We have instituted three additional *inter partes* reviews of claims of the '559 patent in IPR2017-02131, IPR2017-02132, and IPR2017-02136. We also note that IPR2017-00378, IPR2017-00380, and IPR2017-00390 were instituted with respect to U.S. 8,562,999, and that several PGR and IPR petitions were also filed with respect to U.S. 9,399,060 B2 and 8,895,024 B2. Pet. 4.

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

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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.

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.

D. Illustrative Claims

All of the challenged claims 11–15 and 20–37 depend either directly or indirectly from independent claim 1 of the '559 patent.[4] Claims 1, 11, and 31 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.

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[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).

[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.

> 11. The immunogenic composition of claim 1, wherein said immunogenic composition further comprises a buffer, a salt, a divalent cation, a non-ionic detergent, a cryoprotectant, an anti-oxidant, or a combination thereof.
>
> 31. A method of preventing an infection caused by *S. pneumoniae* in a subject comprising administering to the subject an effective amount of the immunogenic composition of claim 1.

Ex. 1001, 141:28–34, 142:26–29, and 143:27–30.

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):

Reference	Basis	Claims Challenged
Merck 2011,[5] Pfizer 2012[6]	§ 103(a)	11–14, 23–27, 29–33, 35–37
Merck 2011, Pfizer 2012, GSK 2008[7]	§ 103(a)	28
Merck 2011, Pfizer 2012, '787 Patent[8]	§ 103(a)	15
Merck 2011, Pfizer 2012, Obaro 2002[9]	§ 103(a)	20, 21

[5] Caulfield et al., WO 2011/100151 A1, published Aug. 18, 2011 ("Merck 2011," Ex. 1006).

[6] Brown et al., *Characterization of Complex Prophylactic Vaccines with Protein and Glycoconjugate Components*, 9th CASSS Symposium (Sept. 12, 2012) ("Pfizer 2012," Ex. 1008).

[7] Biemans et al., WO 2009/000825 A2, published Dec. 31, 2008 ("GSK 2008," Ex. 1007).

[8] Khandke et al., US 7,935,787 B2, issued May 3, 2011 ("'787 Patent," Ex. 1010).

[9] Obaro et al., *Safety and immunogenicity of pneumococcal conjugate vaccine in combination with diphtheria, tetanus toxoid, pertussis and*

Merck 2011, Pfizer 2012, Sigurdardottir 2008[10]	§ 103(a)	22
Merck 2011, Pfizer 2012, MMWR 2012[11]	§ 103(a)	34

Petitioner relies on Declarations of Dennis L. Kasper, M.D. Ex. 1088 and Ex. 1108. Patent Owner relies on a Declaration of Geert-Jan Boons, Ph.D. Ex. 2043.

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.[12] 37 C.F.R. § 42.100(b). Under the broadest reasonable interpretation approach, claim 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

Haemophilus influenzae type b conjugate vaccine, 21 PEDIATRIC INFECTIOUS DISEASE J. 940–6 (2002) ("Obaro 2002," Ex. 1040).

[10] Sigurdardottir et al., *Safety and immunogenicity of CRM_{197}-conjugated pneumococcal–meningococcal C combination vaccine (9vPnC–MnCC) whether given in two or three primary doses*, 26 VACCINE 4178–86 (2008) ("Sigurdardottir 2008," Ex. 1011).

[11] Bennett et al., *Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, 61 MMWR 816–9 (2012) ("MMWR 2012," Ex. 1012).

[12] 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).

disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms which 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." Dec. Inst. 6–7. 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. 14. 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 [S]pecification, [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 16.

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.1108, ¶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;[13] and, (4) where in evidence,

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

objective indicia of nonobviousness.[14] *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

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

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

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> 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. 33 (citing Ex. 1005 ¶ 60). 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. *See 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).

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

> instance the fact that a combination was obvious to try might show that it was obvious under [35 U.S.C.] §103.

KSR, 550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that [35 U.S.C.] § 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 Pfizer 2012

Petitioner contends that claims 11–14, 23–27, 29–33, and 35–37 are unpatentable under 35 U.S.C. § 103(a) as obvious over Merck 2011, Pfizer 2012, and the general knowledge of an ordinary artisan. Pet. 39–62. The thrust of Patent Owner's position with respect to all the claims challenged on this ground 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, 17–52. 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 11–14, 23–27, 29–33, and 35–37 would have been obvious over Merck 2011, Pfizer 2012, 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 pneumococcal conjugate vaccine (PCV) comprising "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 15-valent pneumococcal conjugate vaccine (PCV-15) "induced high OPA[15] GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine." Ex. 1006, 23:3–4.

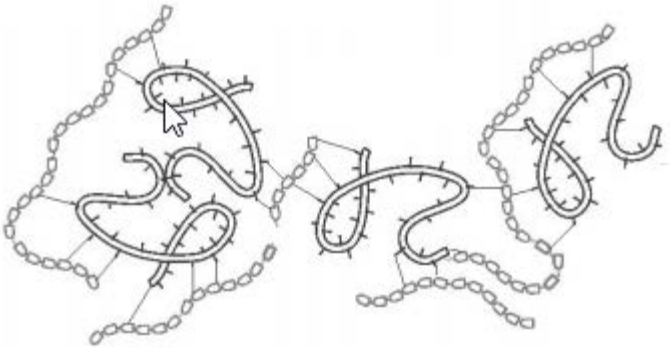
Merck 2011 teaches "purified polysaccharides are chemically activated to make the saccharides capable of reacting with the carrier protein. . . . Coupling to the protein carrier (e.g., CRM_{197}) can be by reductive amination via direct amination to the lysyl groups of the protein." Ex. 1006, 6:11–23. 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."

[15] Opsonophagocytosis.

Ex. 1006, 17:24–25. Table 1 of Merck 2011 shows a vaccine formulation comprising 32 µg of total polysaccharide and 32 µg of CRM_{197} carrier protein with the total polysaccharide being composed of 2 µg of 14 serotypes including 22F and 4 µg of serotype 6B. Ex. 1006, 19:5–9.

2. *Pfizer 2012*

Pfizer 2012 depicts examples of glycoconjugate vaccines as reproduced below:



The glycoconjugate vaccine image reproduced above depicts chains of carrier proteins represented by the solid lines conjugated to polysaccharide antigens represented by the connected cylinders. Ex. 1008, 4.
Pfizer 2012 teaches glycoconjugate vaccines with a typical mass range of 500 to 5000 kDa. Ex. 1008, 6. Pfizer 2012 teaches conjugation of polysaccharide to proteins such as CRM_{197}. Ex. 1008, 20. Pfizer 2012 teaches measurement of the size (i.e. mass) of the polysaccharide and conjugate using techniques such as SEC/MALLS. Ex. 1008, 6–7, and 21.

3. *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.

4. *Analysis*

Petitioner asserts "Merck 2011 is directed to immunogenic multivalent pneumococcal conjugate compositions that include a serotype 22F conjugate" and that "Merck 2011 demonstrates immunogenicity against serotype 22F by the generation of functional antibody against that serotype." Pet. 41 (citing Ex. 1088 ¶ 110, Ex. 1006, 23:2–4). Petitioner asserts: "Based on Pfizer 2012's disclosure of conjugates between 1,000-5,000 kDa, a POSITA would have been motivated with a reasonable expectation of success to construct the serotype 22F CRM_{197} conjugate of Merck 2011 in that molecular weight range." Pet. 41 (citing Ex. 1088 ¶ 111, Ex.1008, 6). Petitioner also asserts "Merck 2011 discloses pre-conjugation ratios between 0.2 and 2, which a POSITA would have considered indicative of a final conjugate ratio in that same range." Pet. 45 (citing Ex. 1006, 17:24–25). Petitioner points out "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." Pet 45–46 (citing Ex. 1006, 19:3–8).

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. 1088 ¶ 116 (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. 1088 ¶ 116 (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. 1088 ¶¶ 117–118 (citing Ex. 1085, 20–24).

Dr. Kasper states a "POSITA easily could have constructed a cross-linked serotype 22F CRM_{197} conjugate in Pfizer 2012's molecular weight range, using the well-known reductive amination or CDAP conjugation chemistries disclosed in Merck 2011." Ex. 1088 ¶ 112 (citing Ex. 1006, 6:15–7:6). Dr. Kasper states "cross-linked conjugates of 5,000 kDa were well-known" as were "pneumococcal conjugate molecular weights of 1,303-9,572 kDa." Ex. 1088 ¶ 112 (citing Ex. 1026, 7; Ex. 1007, 54:27–55:1). 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 Pfiser 2012, *e.g*., by increasing or decreasing the amount of cross-linking in the conjugate.

Ex. 1088 ¶ 113, (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 Pfizer 2012. We adopt these stated facts as our own. *See* Pet. 19–54. 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." [Ex.]1001 at claim 1, 11-14, 23-27, 29-33, and 35-37. Merck 2011, Pfizer 2012, and the general knowledge do not alone or in combination teach or suggest this limitation.

PO Resp. 17.

i. Merck 2011, Pfizer 2012, and the knowledge of the ordinary artisan suggest the claimed molecular weight

Patent Owner asserts a "POSA would have given little or no weight to Pfizer 2012 when designing a pneumococcal glycoconjugate, much less a serotype 22F glycoconjugate." PO Resp. 17. Patent Owner asserts "Pfizer 2012 does not provide any information about how to make any of these

diverse types of vaccines." PO Resp. 18. Patent Owner asserts "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. 19.

We agree with Petitioner that these arguments are not persuasive because they are not supported by a preponderance of the evidence (*see* Pet. Reply 3–7).

We find that Patent Owner has not persuasively demonstrated that the teachings of Merck 2011 regarding polysaccharide sizing and conjugation would require undue experimentation to obtain serotype 22F polysaccharide conjugates within the range suggested by Pfizer 2012. Merck 2011 teaches "polysaccharides can be isolated from bacteria and may be sized to some degree by known methods;" "sized in order to reduce viscosity in polysaccharide samples and/or to improve filterability for conjugated products;" and "prepared from serotypes . . . 22F . . . of *S. pneumoniae*." Ex. 1006, 4:14–18. Merck 2011 teaches the "polysaccharide conjugates may be prepared by known coupling techniques." Ex. 1006, 6:13–14.

Pfizer 2012 teaches the range of 500 to 5000 for glycoconjugates (Ex. 1008, 6), and GSK 2008 also evidences that "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.

Thus, a preponderance of the evidence of record suggests that the ordinary artisan would have recognized the desirable range for glycoconjugates disclosed by Pfizer 2012 and would have been able to generate serotype 22F glycoconjugates within that range as evidenced by

Merck 2011 and GSK 2008.

ii. 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. 21 (citing Ex. 2043 ¶ 61; Ex. 1035 7–8).

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. 22 (citing Ex. 2043 ¶ 62). 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. 23 (citing Ex. 1007, Table 2).

As already noted, Patent Owner asserts:

> 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, Pfizer 2012 would not have provided a POSA with any meaningful guidance or suggestion to generate an immunogenic serotype 22F glycoconjugate within the claimed molecular weight.

PO Reply 18.

Patent Owner asserts "[t]here is no overlap between the molecular weights in GSK 2008 and the '559 claims." PO Resp. 25. 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. 25–26. 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. 26.

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. 28.

Patent Owner reiterates these arguments in the Patent Owner's Reply and also asserts Petitioner'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 7.

We agree with Petitioner that these arguments are not persuasive because they are not supported by a preponderance of the evidence. *See* Pet. Reply 7–15.

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.

Pfizer 2012, in the context of characterizing vaccines, expressly discloses that the "[t]ypical mass (kDa)" for glycoconjugate vaccines is "500 to 5000." Ex. 1008, 6. As Dr. Kasper notes:

> The disclosed molecular weight range in Pfizer 2012 largely overlaps the claimed range of 1,000-12,500 kDa, and therefore expressly teaches conjugates of 1,000-5,000 kDa that fall within the claimed range. It would have been obvious to a POSITA to apply the teachings of Pfizer 2012 to the pneumococcal CRM_{197} conjugate vaccine of Merck 2011; a POSITA would have been aware of Patent Owner's licensed Prevnar® pneumococcal CRM_{197} conjugate vaccines.

Ex. 1005 ¶ 106.

While GSK 2008 was not expressly relied upon in the statement of the rejection, GSK 2008 evidences typical conjugation methods, polysaccharide sizes, and conjugate sizes of which the ordinary artisan would have been aware. *See, e.g.*, Pet. 29–30.

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 recognized 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, and 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. 1088 ¶ 88 (citing Ex. 1007, 17:1–30). Dr. Kasper states "a POSITA would have required only routine experimentation to obtain a conjugate molecular weight within the desirable range disclosed in Pfizer 2012, *e.g.*, by increasing or decreasing the amount of cross-linking in the conjugate." Ex 1088 ¶ 113 (citing Ex. 1030, 4:56–59). 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' 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. 2043 ¶ 62.

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' 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. 1108 ¶ 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. 1108 ¶ 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 Pfizer 2012 of a particular size range for glycoconjugate vaccines, and with the 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." *See* 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. 27), because the issue is the obviousness of routine optimization of conjugate sizes, not inherent anticipation by Pfizer 2012 or GSK 2008. Instead, we agree with Petitioner that "a POSITA would have found the 1,000-5,000 kDa molecular weight range disclosed in Pfizer 2012 to be 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 results-effective variable associated with improved stability of conjugates and good immune response, limited only by filter size, thereby rendering "optimization within the grasp of one of ordinary skill in the art." *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 1,000 to 5,000 kDa range of Pfizer 2012, would have been consistent with the ranges optimized and used to generate multivalent vaccines. Pet. 39; Ex. 1008, 6. "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).

iii. General Knowledge and Other Prior Art

Patent Owner criticizes Petitioner's reliance on Jones 2005 (Ex. 1026)[16] and Lees 2008 (Ex. 1035)[17] as evidence that the person of ordinary skill in the art would have understood that "the claimed ranges of the '559 Patent were known as typical and desirable." *See* PO Resp. 29–31; Pet. Reply 15–16.

Patent Owner asserts that: "Jones 2005 does not mention any serotype 22F glycoconjugates, much less how to make these glycoconjugates" 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

[16] 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.

[17] 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.

recited in the '559 patent claims." PO Resp. 30–31 (citing Ex. 2043 ¶¶ 73, 75).

Patent Owner then makes specific assertions identifying deficiencies in Jones 2005 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. 30.

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. 31. 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. 32 (citing Ex. 2043 ¶ 75).

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. Petitioner cites Jones 2005 and Lees 2008 in order to demonstrate that the specific conditions used for making glycoconjugate in general were well known. Pet. 43 (citing Ex. 1026, 7; Ex. 1035, 6–8).

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.

Lees 2008 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 and in Lees 2008 of a multiple conjugate formulation provide evidence that glycoconjugate size was a known optimizable variable. *See* Pet. 42; Ex. 1026, 7; and 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. 32 (citing Ex. 2043 ¶ 76). Patent Owner further asserts "Pfizer 2012 does not refer to any polysaccharide to protein ratios for any serotype glycoconjugates." PO Resp. 33.

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. 33 (citing Ex. 2043 ¶ 78; Ex. 1006, 19:24–25). 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. 34 (citing Ex. 2043 ¶ 80). Patent Owner asserts "a POSA would not have had any idea how to determine the appropriate ranges for this undefined parameter." PO Resp. 35. 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. 35 (citing Ex. 2043 ¶ 77; *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977)).

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. 1108 ¶ 32.

Dr. Boons states that a "POSA in January 2014 would not have been familiar with this term." Ex. 2043 ¶ 79. 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. 2043 ¶ 79.

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?" Acknowledged this by stating: "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' 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' 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. 35 (citing Ex. 2043 ¶ 81). 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. 35 (citing Ex. 1007, 53–56, Tables 1–2). 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. 36. 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. 37–38 (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. EX2043, ¶85. 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. 39.

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. 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. 1088 ¶ 116.

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. 2043 ¶ 81. 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. 1088 ¶ 90. 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, Lees 2008 supports the obviousness of optimizing the claimed range, noting that "[r]egulatory authorities have considered the

potency assay for conjugate vaccines to be a combination of the determination of the PS-to-protein ratio and the estimation of the amount of residual free saccharide. Ex. 1035, 9.

Additionally, JNIID identifies 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. 1088 ¶ 118.

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. 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 (cited by Merck in Ground 3), 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. 39–40 (citing Ex. 2019, 71:16–72:6, 44:7–16; 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. 40–41 (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. 2043 ¶ 86 (citing Ex. 1026, 13).

A preponderance of the evidence does not support Patent Owner's position. 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.

D. Obviousness over Merck 2011, Pfizer 2012, and GSK 2008

Petitioner asserts "[b]ased on GSK 2008 and the general knowledge of a POSITA, a POSITA would have been motivated with a reasonable expectation of success to formulate the immunogenic composition of claim 1 in lyophilized form to improve stability." Pet. 56 (citing Ex. 1088 ¶ 136).

Patent Owner asserts "GSK 2008 does not teach or suggest the molecular weights recited in the '559 patent claims and teaches away from the polysaccharide to protein ratio recited in the '559 patent claims." PO Resp. 43 (citing Ex. 2043 ¶ 88).

Patent Owner asserts that Petitioner focuses on one of the two serotype 22F glycoconjugates disclosed in GSK 2008, PS22F-PhtD, that Petitioner "translates to a polysaccharide to protein ratio of 1/2.17, or 0.46." PO Resp. 43 (citing Ex. 1005 ¶ 90; Ex. 1007, 55–56, Table 2). Patent Owner asserts "Table 2 also provides data for a second glycoconjugate referred to as 'PS22F-AHPhtD'" that has a "polysaccharide to protein ratio of 1:4.34-1:3.66, or 0.23-0.27" that "clearly falls outside of the '559 patent claimed range." PO Resp. 43–44 (citing Ex. 1007, 55–56, Table 2).

Patent Owner asserts that "PS22F-AH-PhtD (i.e., the glycoconjugate having the ratio outside the claimed range), 'was shown [to be] much more immunogenic' than PS22F-PhtD (the glycoconjugate allegedly having a ratio within the claimed range) in terms of both IgG levels and opsonophagocytic (OPA) titre." PO Resp. 44 (citing Ex. 1007, 85:14–15). 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. 45 (citing Ex. 2043 ¶ 90). Patent Owner asserts that "a POSA would have

avoided making a serotype 22F glycoconjugate similar to the disclosed PS22F-PhtD and instead opted for the PS22F-AH-PhtD glycoconjugate." PO Resp. 45 (citing Ex. 2043 ¶ 91).

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. EX2043, ¶ 91.

PO Resp. 47.

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. 1108 ¶ 52. 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. 43.

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, provides 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. 1088 ¶ 90; Ex. 1108 ¶ 52; and Ex. 1006, 19:24–25.

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. 2043 ¶ 91.

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.

Two 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, 4:1–4 ("[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, 4:32 to 5:1 ("The present invention provides an immunogenic composition [that] comprises a 22F saccharide conjugate.").

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. 1088 ¶ 90; Ex. 1108 ¶ 52; and Ex. 1006, 19:24–25. In addition, the ordinary artisan was aware of desirable ranges of polysaccharide to carrier protein. *See* Ex. 1108 ¶¶ 18, 52.

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.

E. Obviousness over Merck 2011, Pfizer 2012, and '787 patent

Petitioner asserts that based on the "'787 Patent, a POSITA would have been motivated with a reasonable expectation of success to include the immunogenic composition of claim 1 in a syringe that is siliconized and/or made of glass." Pet. 56 (citing Ex. 1088 ¶ 137). Petitioner asserts that "'787 Patent discloses pneumococcal polysaccharide-protein conjugate formulations in siliconized containers, including glass syringes; the formulations inhibit protein aggregation caused by the silicone oil." Pet. 57 (citing Ex. 1010 13:34–4:23).

Patent Owner asserts

> Neither Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, Pfizer 2012, the '787 patent, and the "general knowledge," because Merck has not identified any reasons as to why the '787 patent remedies the deficiencies of Merck 2011 or Pfizer 2012. Merck has not met its burden in showing that claim 15 is obvious.

PO Resp. 48.

1. *'787 patent (Exhibit 1010)*

The '787 patent discusses "an ongoing need in the art to improve the stability of immunogenic compositions such as polysaccharide-protein conjugates." Ex. 1010, 9:57–59. The '787 patent discusses "the polysaccharide-protein conjugate formulation is a 13-valent pneumococcal conjugate (13vPnC) formulation comprising a *S. pneumoniae* serotype . . . polysaccharide conjugated to a CRM_{197} polypeptide." Ex. 1010, 6:39–43.

The ’787 patent explains the “formulations of the present invention are particularly useful in stabilizing the immunogen (i.e., a polysaccharide-protein conjugate . . . in the presence silicon oil found on container means such syringes, glass vials, rubbers stoppers and the like.” Ex. 1010, 14:12–21.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to modify the multivalent pneumococcal vaccine containing the 22F serotype rendered obvious by Merck 2011 and Pfizer 2012 with a siliconized syringe as disclosed by the ’787 patent for use with a 13 valent pneumococcal conjugate vaccine because these formulations function to stabilize the antigen.

We therefore conclude that a preponderance of the evidence supports the obviousness of modifying the conjugate vaccine suggested by Merck 2011, Pfizer 2012, and the knowledge of the ordinary artisan with the siliconized and glass syringes disclosed by the ’787 patent in order to stabilize the vaccine as disclosed by the ’787 patent.

F. Obviousness over Merck 2011, Pfizer 2012, and Obaro 2002

Petitioner asserts that based on Obaro 2002, “a POSITA would have been motivated with a reasonable expectation of success to include an antigen from a pathogen other than pneumococcus in the immunogenic composition of claim 1.” Pet. 58 (citing Ex. 1088 ¶ 140). Petitioner asserts that “Obaro 2002 reports the safety and immunogenicity of Patent Owner’s 9-valent pneumococcal CRM_{197}-conjugate vaccine (‘PnCV’) when given in

combination with a vaccine ('TETRAMUNE') containing diphtheria toxoid, tetanus toxoid, whole cell pertussis, and CRM_{197}-conjugated *Haemophilus influenzae* type B oligosaccharide." Pet. 58 (citing Ex. 1040, 2). Petitioner asserts "a POSITA would have understood that combining distinct individual vaccines (e.g., pneumococcal and non-pneumococcal vaccinations) into a single composition is desirable, to enhance protection against disease and minimize the number of injections to a patient, particularly for infants." Pet. 58 (citing Ex. 1088 ¶ 140).

Patent Owner asserts "[n]either Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, Pfizer 2012, Obaro 2002, and the 'general knowledge.' Therefore, Merck has likewise not met its burden in showing that claims 20 and 21 are obvious." PO Resp. 48–49. Patent Owner asserts:

> Obaro 2002 does not disclose the molecular weight or polysaccharide to protein ratio for any of its glycoconjugates. As such, a POSA would not have had any motivation from Obaro 2002 to generate an immunogenic composition comprising a serotype 22F glycoconjugate having a molecular weight or polysaccharide to protein ratio falling within the specific ranges recited in any of the '559 patent claims (including claims 20 and 21).

PO Resp. 49 (citing Ex. 2043 ¶ 94; Ex. 1040, 2).

1. *Obaro 2002 (Exhibit 1040)*

Obaro 2002 states "we evaluated the safety and immunogenicity of a 9-valent pneumococcal conjugate vaccine given in combination with TETRAMUNE [*Haemophilus influenzae* type b vaccine] administered simultaneously at different sites or mixed and administered as a single injection." Ex. 1040, 2. Obaro 2002 teaches the pneumococcal vaccine

"was prepared in a lyophilized form and contained 2 µg of types 1, 4, 5, 9V, 14, 19F and 23F pneumococcal polysaccharides; 2 µg of type 18C oligosaccharide; and 4 µg of type 6B polysaccharide. Each polysaccharide or oligosaccharide was coupled independently to CRM_{197}, a nontoxic mutant of diphtheria toxoid, to give 20 µg of CRM_{197} per dose." Ex. 1040, 2. Obaro 2002 states the "combination of TETRAMUNE and PnCV is safe and immunogenic." Ex. 1040, 1 (emphasis omitted). Obaro 2002 teaches "[c]ombination of vaccines should make administration easier, less expensive and more acceptable to parents." Ex. 1040, 2.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to combine the pneumococcal vaccine including the 22F serotype with other vaccines including a *Haemophilus influenzae* type b vaccine because Obaro 2002 explains that combination of these vaccines makes administration easier and less expensive. While Patent Owner is correct that Obaro 2002 is silent on the molecular weights for the pneumococcus conjugate vaccine, both Merck 2011 and Pfizer 2012 disclose reasons to select the molecular weights required by claim 1 as discussed above. As to the polysaccharide to protein ratios, these are also disclosed in Merck 2011 and Pfizer 2012 as already discussed. In addition, Obaro 2002 teaches a 1:1 ratio for serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F because Obaro 2002 teaches 2 µg of polysaccharide for 8 serotypes and 4 µg for serotype 6B combined with 20

µg of CRM_{197}. Ex. 1040, 2.

We, therefore, conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by Merck 2011, Pfizer 2012, and the knowledge of the ordinary artisan by combining it with the *Haemophilus influenzae* type b vaccine of Obaro 2002 to simplify and reduce the expense of vaccine administration.

G. Obviousness over Merck 2011, Pfizer 2012, and Sigurdardottir 2008

Petitioner asserts that based on Sigurdardottir 2008, "a POSITA would have been motivated with a reasonable expectation of success to include a meningococcal serogroup C conjugate in the immunogenic composition of claim 1." Pet. 60 (citing Ex. 1088 ¶ 142). Petitioner asserts that "Sigurdardottir 2008 'evaluated safety and immunogenicity of a combined 9-valent pneumococcal and meningococcal C conjugate vaccine ['9vPnC-MnCC']"' and Sigurdardottir 2008 concludes "9vPnC-MnCC is safe and immunogenic." Pet. 61 (citing Ex. 1011, 2, 8). Petitioner asserts "that combining distinct individual vaccines (*e.g.*, pneumococcal and non-pneumococcal vaccinations) into a single composition is desirable, to enhance protection against disease and minimize the number of injections to a patient." Pet. 60–61 (citing Ex. 1007, 43:1–11).

Patent Owner asserts "[n]either Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, Pfizer 2012, Sigurdardottir 2008, and the 'general knowledge.' Therefore, Merck has likewise not met its burden in showing that claim 22 is obvious." PO Resp. 50. Patent Owner asserts:

> The pneumococcal glycoconjugates of Sigurdardottir 2008 comprise nine different serotype glycoconjugates (*i.e.*,

> serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F), none of which is serotype 22F. EX1011 at 2. Sigurdardottir 2008 also does not refer to the molecular weight or polysaccharide to protein ratio for any of the glycoconjugates present in its vaccine.

PO Resp. 50 (citing Ex. 2043 ¶ 96). Patent Owner acknowledges that "Sigurdardottir 2008 does refer to serotype 22F." PO Resp. 50. Patent Owner asserts, however, that a "POSA would not have had any motivation from Sigurdardottir 2008 to generate an immunogenic composition comprising a serotype 22F glycoconjugate having a molecular weight or polysaccharide to protein ratio falling within the specific ranges recited in any of the '559 patent claims." PO Resp. 51 (citing Ex. 2043 ¶ 97).

1. *Sigurdardottir (Exhibit 1011)*

Sigurdardottir states "we investigated the safety and immunogenicity of a 9-valent CRM197-conjugated pneumococcal-polysaccharide vaccine combined with a CRM197-conjugated *Meningococcus C* polysaccharide." Ex. 1011, 2. Sigurdardottir teaches the

> trial vaccine contained nine pneumococcal serotype polysaccharides, 2 µg of saccharide per pneumococcal serotypes 1, 4, 5, 9V, 14, 18C, 19F and 23F, 4 µg of pneumococcal serotype 6B and 10 g of meningococcal group C oligosaccharide (same concentration as in monovalent Meningococcus C CRM197 conjugate, Meningitec®) coupled to 18.5 µg of CRM197 carrier protein.

Ex. 1011, 2. Sigurdardottir states a booster comprising the 23-valent pneumococcal-polysaccharide vaccine containing serotype 22F was used. Ex. 1011, 2. Sigurdardottir teaches "to decrease number of infant

vaccinations by combining pneumococcal and Meningococcus C CRM197 conjugates." Ex. 1011, 7.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to combine the pneumococcal vaccine including the 22F serotype with other vaccines including a Meningococcus C vaccine because Sigurdardottir explains that combination of these vaccines permits a decreased number of vaccinations. Ex. 1011, 7. While Patent Owner is correct that Sigurdardottir is silent on the molecular weights for the pneumococcus conjugate vaccine, both Merck 2011 and Pfizer 2012 disclose reasons to select the molecular weights required by claim 1 as discussed above. Sigurdardottir also recognizes that serotype 22F is a vaccine target. Ex. 1011, 2. As to the polysaccharide to protein ratios, these are also disclosed in Merck 2011 and Pfizer 2012 as already discussed. In addition, Sigurdardottir teaches an approximately 1:1 ratio for serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F because Sigurdardottir teaches 2 µg of polysaccharide for 8 serotypes and 4 µg for serotype 6B combined with 18.5 µg of CRM_{197}. Ex. 1011, 2.

We, therefore, conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by Merck 2011, Pfizer 2012, and the knowledge of the ordinary artisan by combining it with the Meningococcus C vaccine of Sigurdardottir to simplify and reduce the expense of vaccine administration.

H. Obviousness over Merck 2011, Pfizer 2012, and MMWR 2012

Petitioner asserts that based on MMWR 2012, "a POSITA would have been motivated with a reasonable expectation of success to practice the method of claim 30 (taught by the combination of Merck 2011 and Pfizer 2012) in an immunocompromised human." Pet. 61–62 (citing Ex. 1088 ¶ 143). Petitioner asserts that "MMWR 2012 discloses the 'recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ≥19 years with immunocompromising conditions." Pet. 62 (citing Ex. 1012, 12).

Patent Owner asserts "[n]either Merck nor its expert, Dr. Kasper, has demonstrated that claim 1 is obvious over Merck 2011, Pfizer 2012, MMWR 2012, and the 'general knowledge.' Therefore, Merck has likewise not met its burden in showing that claim 34 is obvious." PO Resp. 51. Patent Owner asserts "Prevnar13® does not include a serotype 22F glycoconjugate, and MMWR 2012 also does not disclose the molecular weight or polysaccharide to protein ratio for any of the glycoconjugates present in Prevnar13®." PO Resp. 52 (citing Ex. 2043 ¶ 99). Patent Owner asserts "a POSA would not have had any motivation from MMWR 2012 to generate and utilize an immunogenic composition comprising a serotype 22F glycoconjugate having a molecular weight or polysaccharide to protein ratio falling within the specific ranges recited in any of the '559 patent claims." PO Resp. 52 (citing Ex. 2043 ¶ 100).

1. *MMWR 2012 (Exhibit 1012)*

MMWR 2012 states

> the Advisory Committee on Immunization Practices (ACIP) recommended routine use of 13-valent pneumococcal conjugate

> vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, or cochlear implants (Table). PCV13 should be administered to eligible adults in addition to the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax 23, Merck & Co. Inc.), the vaccine currently recommended for these groups of adults.

Ex. 1012, 12. MMWR 2012 teaches "[a]dults with specified immunocompromising conditions who are eligible for pneumococcal vaccine should be vaccinated with PCV13 during their next pneumococcal vaccination opportunity." Ex. 1012, 14.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to vaccinate immunocompromised individuals with the pneumococcal vaccine including the 22F serotype with other vaccines including a *Haemophilus influenzae* type b vaccine because MMWR 2012 suggests that such individuals should be vaccinated with pneumococcal vaccines, including the 23-valent vaccine that includes the 22F serotype. Ex. 1012, 12; Ex. 1087 ¶ 41. While Patent Owner is correct that MMWR 2012 is silent on the molecular weights for the pneumococcus conjugate vaccine, both Merck 2011 and Pfizer 2012 disclose reasons to select the molecular weights required by claim 1 as discussed above. As to the polysaccharide to protein ratios, these are also disclosed in Merck 2011 and Pfizer 2012 as already discussed.

We, therefore, conclude that a preponderance of the evidence supports the obviousness of treating immunocompromised patients with the vaccine

suggested by Merck 2011, Pfizer 2012, and the knowledge of the ordinary artisan because MMWR 2012 suggests the desirability of treating this patient population with a pneumococcal vaccine. Ex. 1012, 12, and 14.

III. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude the following Exhibits, or portions thereof: Exhibit 1088 ¶ 24, Exhibit 1094, and 1095. Paper 37 ("Patent Owner Mot. to Exclude").

We do not rely on any of this evidence in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion and we therefore dismiss Patent Owner's motion as moot.

V. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that: (1) claims 11–14, 23–27, 29–33, and 35–37 of the '559 patent are unpatentable over the combination of Merck 2011 and GSK 2008; (2) claim 28 of the '559 patent is unpatentable over the combination of Merck 2011, Pfizer 2012, and GSK 2008; (3) claim 15 of the '559 patent is unpatentable over the combination of Merck 2011, Pfizer 2012, and '787 patent; (4) claims 20 and 21 of the '559 patent are unpatentable over Merck 2011, Pfizer 2012, and Obaro 2002; (5) claim 22 of the '559 patent is unpatentable over Merck 2011, Pfizer 2012, and Sigurdardottir 2008; and (6) claim 34 of the '559 patent is unpatentable over the combination of Merck 2011, Pfizer 2012, and MMWR 2012.

We dismiss Patent Owner's Motion to exclude Exhibit 1088 ¶ 24, Exhibit 1094, and Exhibit 1095 as moot.

VI. ORDER

For the reasons given, it is

ORDERED, based on a preponderance of the evidence, that claims 11–15 and 20–37 are unpatentable;

FURTHER ORDERED, Patent Owner's Motion to Exclude Exhibit 1088 ¶ 24, Exhibit 1094, and Exhibit 1095 is dismissed as moot;

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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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

PFIZER INC.,
Patent Owner.

Case IPR2018-00187
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 1–45 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

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

I. INTRODUCTION

A. Background

Sanofi Pasteur Inc. and SK Chemicals Co., Ltd. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–45 of U.S. Patent No. 9,492,559 B2 (Ex. 1001, "the '559 patent"). Paper 3 ("Pet."). Pfizer Inc. ("Patent Owner") filed a Patent Owner's Preliminary Response. Paper 8 ("Prelim. Resp.").

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

Petitioner and Patent Owner both filed Motions to Exclude Evidence. Papers 44 and 45. Patent Owner and Petitioner both filed respective Oppositions to Motion to Exclude Evidence. Papers 48 and 49. Petitioner and Patent Owner both filed Replies in Support of the Motion to Exclude. Paper 53 and 54.

On February 12, 2019, 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 1–45 of the '559 patent are unpatentable. *See* 35 U.S.C. §316(e). Additionally, the Motions to Exclude Evidence by Petitioner and Patent Owner have been decided below in Sections IV and V and the Motion to Amend has been decided below in Section III.

B. Related Proceedings

A concurrent Petition for *inter partes* review of the '559 patent, IPR 2018-00188, was denied institution on June 5, 2018. Four *inter partes* reviews of the '559 patent were filed by a different petitioner, IPR2017-02131, IPR2017-02132, IPR2017-02136, and IPR2017-02138. Pet. 2. Decisions determining that the challenged claims of the '559 patent are unpatentable have issued in each of those proceedings. IPR2017-02131, Paper 59; IPR2017-02132, Paper 59; IPR2017-02136, Paper 43; IPR2017-02138, Paper 45.

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 1–45 depend either directly or indirectly from independent claim 1 of the '559 patent. Claim 1 is illustrative of the challenged claims and recites:

> 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.

Ex. 1001, 141:28–34.

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. 4, 15, 17):

Reference	Basis	Claims Challenged
GSK-711,[4] Merck-086[5]	§ 103	1, 3–19, 23–37, 41, 42, 45
GSK-711, Merck-086, Lees-2008,[6] PVP 2013,[7] Pfizer-	§ 103	2, 40, 43

[4] Biemans et al., WO 2007/071711 A2, published June 28, 2007 ("GSK-711," Ex. 1007).
[5] Caulfield et al., US 2011/0195086 A1, published Aug. 11, 2011 ("Merck-086," Ex. 1008).
[6] Lees et al., "*Chapter 11. Conjugation Chemistry*," In: Pneumococcal Vaccines: *The Impact of Conjugate Vaccine* (Ed. George R. Siber et al.); pp. 163–174 (2008) ("Lees-2008," Ex. 1011).
[7] "*Pneumococcal Vaccine Polyvalent*" revision to Japan's "*Minimum Requirements for Biological Products*" published on the website of Japan's National Institute of Infectious Diseases (as of March 2, 2013) ("PVP 2013," Ex. 1012).

Reference	Basis	Claims Challenged
605[8]		
GSK-711, Merck-086, GSK-531[9]	§ 103	20–22
GSK-711, Merck-086, Pfizer-605	§ 103	38, 39
GSK-711, Merck-086, Hsieh 2000[10]	§ 103	44

Petitioner relies on the Declaration of Andrew Lees, Ph.D. Ex. 1005. Petitioner also relies on the Declaration of Dr. Loek Van Alphen, Ph.D. Ex. 1101. Patent Owner relies on the Declaration of Dr. Peng Wang, Ph.D. Ex. 2058. Patent Owner also relies on the Declaration of Dr. Peter Paradiso, Ph.D. Ex. 2051.

ANALYSIS

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear.[11] 37 C.F.R. § 42.100(b). Under the broadest

[8] Prasad, A.K., US 7,955,605 B2, issued June 7, 2011 ("Pfizer-605," Ex. 1013).
[9] Biemans et al., WO 2011/110531 A2, published Sept. 15, 2011 ("GSK-531," Ex. 1014).
[10] Hsieh, *Characterization of Saccharide-CRM$_{197}$ Conjugate Vaccines*, In: *Physico-Chemical Procedures for the Characterization of Vaccines* (Eds. Brown F., Corbel M., and Griffths E.); Vol. 103, pp. 93–104; Basel; Karger, 2000 ("Hsieh 2000," Ex. 1015).

[11] 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).

reasonable interpretation approach, claim 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 against each serotype in the claimed composition." 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 disagrees with Petitioner's assertion that "the term 'immunogenic' means 'capable of producing an immune response as determined by an immunogenic assay known in the art by a POSA including an OPA assay.'" PO Resp. 16 (citing Pet. 27–28). Instead, Patent Owner points to the Specification, prosecution history, and statements by Dr. Lees to support its position that the "proper construction of 'immunogenic' is 'elicits functional antibody against each

serotype in the claimed composition.'" PO Resp. 16 (citing Ex. 2054, 62:2–12, Ex. 1004, 23–24, and Ex. 1001, 116:50–52).

Petitioner does not address Patent Owner's claim interpretation in its Reply.

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. 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. 1004, 33–34. The Examiner allowed the claims after amendment to include the ranges for molecular weight and ratio of polysaccharide to carrier protein. *See* Ex. 1004, 11. The Examiner did not address the claim construction issue.

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, to meet the limitations of claim 1 of the '559 patent, which recites a single immunogen, serotype 22F, only functional antibodies to serotype 22F would be required. However, for claim 3 of the '559 patent that requires serotypes 22F, 15B, and 33F, functional antibodies against all three serotypes would be 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;[12] and (4) where in evidence, objective indicia of nonobviousness.[13] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of

[12] Petitioner states that a person with the level of skill in the art at the time of the invention "would have had a Ph.D. or equivalent degree in chemistry, immunology, or other biological sciences or an MD and at least 2 years of experience in glycoconjugate vaccine research and development, or would have an M.S. degree and at least 4 years of relevant experience." Pet. 26, citing Ex. 1005 ¶ 77. Patent Owner "does not dispute Sanofi's proposed level of skill for the person having ordinary skill in the art." PO Resp 8. 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).

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

ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

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

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 GSK-711 and Merck-086

Petitioner contends that claims 1, 3–19, 23–37, 41, 42, and 45 are unpatentable under 35 U.S.C. § 103 as obvious over GSK-711, Merck-086,

and the general knowledge of an ordinary artisan. Pet. 30–66. 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. 1–5, 18–55. 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, 3–19, 23–37, 41, 42, and 45 would have been obvious over GSK-711, Merck-086, 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. *GSK-711 (Ex. 1007)*

GSK-711 teaches a *Streptococcus pneumoniae* vaccine comprising "capsular saccharide antigens (preferably conjugated), wherein the saccharides are derived from at least ten serotypes of *S. pneumoniae*" that may include an "*S. pneumoniae* saccharide conjugate of 22F." Ex. 1007, 6:4, 24–26.[14] GSK-711 teaches "*Streptococcus pneumoniae* capsular saccharides . . . may be conjugated to a carrier protein independently selected from the group consisting of . . . CRM197. . . ." Ex. 1007, 8:18–20. GSK-711 teaches "saccharide conjugates present in the immunogenic compositions of the invention may be prepared by any known coupling technique" and specifically, conjugates "can also be prepared by direct reductive amination methods. . . ." Ex. 1007, 15:9–10; 16:1. GSK-711 teaches "22F-PhtD administered within the 13-valent conjugate vaccine

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

formulation [was] shown immunogenic in old C57BI mice." Ex. 1007, 67:36–37.

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

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

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

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

Merck-086 teaches "a multivalent immunogenic composition having 15 distinct polysaccharide-protein conjugates. Each conjugate consists of a capsular polysaccharide prepared from a different serotype of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F or 33F) conjugated to a carrier protein, preferably CRM_{197}." Ex. 1008 ¶ 2. Merck-086 teaches "conjugates containing serotypes 22F and 33F provide[] robust antibody responses demonstrat[ing] the feasibility of expanding coverage of pneumococcal serotypes. . . ." Ex. 1008 ¶ 15. Merck-086 teaches the pneumococcal conjugate vaccine (PCV) with "induced high OPA[15] GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine." Ex. 1008 ¶ 114.

Merck-086 teaches "purified polysaccharides are chemically activated to make the saccharides capable of reacting with the carrier protein. . . . Coupling to the protein carrier (*e.g.*, CRM_{197}) can be by reductive amination via direct amination to the lysyl groups of the protein." Ex. 1008 ¶¶ 23, 25. Merck-086 teaches the "concentrated saccharide was mixed with CRM_{197} carrier protein in a 0.2 – 2 to 1 charge ratio. The blended saccharide-CRM_{197} mixture was filtered through a 0.2 µm filter." Ex. 1008 ¶ 94. Table 1 of Merck-086 shows a vaccine formulation comprising 32 µg of total polysaccharide and 32 µg of CRM_{197} carrier protein with the total polysaccharide being composed of 2 µg of 14 serotypes including 22F and 4 µg of serotype 6B. Ex. 1008 ¶ 104.

[15] Opsonophagocytosis.

3. *Analysis*

Petitioner asserts that GSK-711 and Merck-086 suggest immunogenic compositions of S. pneumoniae serotype 22F conjugated to carrier that have molecular weights and polysaccharide/carrier protein ratios within the ranges recited by claim 1 of the '559 patent. *See* Pet. 1–2, 17–21, 34–36.

Petitioner asserts "GSK-711 demonstrate[s] that a 13-valent vaccine formulation containing the 22F-PhtD glycoconjugate induced anti-22F immune response in old mice, young mice, and guinea pigs, respectively. . . ." Pet. 31 (citing Ex. 1005 ¶¶ 125–128; Ex. 1007, 68–73). Petitioner also asserts "Merck-086 discloses a PCV15 composition containing a 22F-CRM_{197} glycoconjugate that induced 22F specific immune response in animal models. . . ." Pet. 32–33 (citing Ex. 1005 ¶¶ 129–131; Ex. 1008, Tables 2–6).

Petitioner asserts "GSK-711 teaches that isolated polysaccharides from *S. pneumoniae* including 22F may be conjugated to a carrier protein independently selected from CRM_{197}." Pet. 34 (citing Ex. 1005 ¶ 134; Ex. 1007, 9:18–22, 11:4–27). Petitioner asserts the "22F-PhtD conjugate disclosed in Table 2 has the ratio of carrier protein to polysaccharide of 2.17. Lees [Ex. 1005] ¶137; Ex. 1007, Table 2. When converted to a polysaccharide to carrier protein ratio, this equals 0.46, which falls within the range claimed in claim 1." Pet. 34. Petitioner asserts:

> a POSA in view of the teachings in GSK-711 would (i) reasonably have expected that the 22F glycoconjugates disclosed in Table 2 would have molecular weights that also fall within the claimed range; or (ii) would have been motivated to make 22F glycoconjugates that fall within the claimed range with a reasonable expectation of success.

Pet. 36 (citing Ex. 1005 ¶ 140).

To support its obviousness position, Petitioner relies upon the Declaration of Dr. Lees, who states "there is nothing inventive to claims 1–45 of the '559 patent. As stated above, 22F polysaccharide-carrier protein conjugates had already been made before the earliest filing date of the '559 patent as part of multivalent PCV products developed by Merck and GSK and were shown to be immunogenic." Ex. 1005 ¶ 117.

Dr. Lees, addressing the limitation in claim 1 for a ratio of polysaccharide to carrier protein that is between 0.4 and 2, states "GSK-711 teaches, among preferred ratios, a carrier protein to polysaccharide ratio of 'between 1:2 and 2.5:1' (w/w). . . . When converted to a polysaccharide to carrier protein ratio, this equals to the ratio of 'between 0.4 and 2' required by claim 1." Ex. 1005 ¶ 136 (citing Ex. 1007, 20:1–6). Dr. Lees notes "the example PS22F-PhtD glycoconjugate described in Table 2 has a specific carrier:polysaccharide ratio of 2.17 . . . which equals to a polysaccharide:protein ratio of 0.46, falling within the range of 0.4–2.0." Ex. 1005 ¶ 137 (citing Ex. 1007, 54).

Dr. Lees, addressing the limitation in claim 1 for a glycoconjugate molecular weight between 1000 kDa and 12,500 kDa, acknowledges "molecular weights are not explicitly provided for the two 22F glycoconjugates (PS22F-PhtD and PS22F-AHPhtD) shown in Table 2" but states "Table 2 discloses the conjugate sizes for ten (10) different pneumococcal glycoconjugates with different serotype and carrier protein combinations, all of which fall within and span most of the range of 'between 1000 kDa and 12,500 kDa' recited in claim 1." Ex. 1005 ¶¶ 138–139 (citing Ex. 1007, 54). Dr. Lees states "one would have reasonably expected that the sizes of the two 22F conjugates disclosed in Table 2, if

measured, would also fall within the range between 1,000 KDa and 12,500 KDa." Ex. 1005 ¶ 141. Dr. Lees states regarding the lower end of the range that because

> GSK-711 Table 2 discloses that the carrier protein to polysaccharide ratio is 2.17, the total weight of the carrier protein PhtD in this "smallest" lattice would be 694.4 kDa (about 7 molecules of PhtD11). As a result, the molecular weight of this "smallest" 22F-PhtD conjugate lattice would be at least 1014.4 kDa (320 kDa +694.4 kDa).

Ex. 1005 ¶ 143. Dr. Lees states with regard to the higher end of the range that "a POSA would have understood that the GSK inventors would have been targeting at 22F glycoconjugates with a molecular weight well below 12,500 kDa by using a Sephacryl S400HR column (exclusion limit below 8,000 kDa) to purify the conjugates. . . ." Ex. 1005 ¶ 144.

Dr. Lees, next addressing the obviousness of the glycoconjugate molecular weight range, states "[t]his range (1000–12,500 kDa) is desirable also for the following reasons: On one hand, if conjugates are too small (with molecular weights below 1000 kDa), they are difficult to separate from unconjugated free polysaccharides. As discussed above, unconjugated polysaccharides are less immunogenic in infants, elderly and immunocompromised patients." Ex. 1005 ¶ 148 (citing Ex. 1019, 103). Dr. Lees further notes: "On the other hand, large glycoconjugates (with molecular weights above 12,500 kDa) are difficult to purify and difficult to analyze . . . Overconjugation may also result in the reduction or elimination of T-cell epitopes required for eliciting an immune response." Ex. 1005 ¶ 149 (Citing Ex. 1011, 11–12).

Dr. Lees, addressing the issue of a reasonable expectation of success in forming a 22F conjugate within the claimed molecular weight range,

states "CDAP or reductive amination chemistry naturally results in glycoconjugates with highly crosslinked lattice structures with multiple saccharide molecules linked to multiple carrier protein molecules in each lattice." Ex. 1005 ¶ 151. Dr. Lees states the "fact that GSK-711 discloses 10 different pneumococcal glycoconjugates with molecular weights all falling within the claimed range of 1,000 kDa and 12,500 kDa confirms a reasonable expectation of success." Ex. 1005 ¶ 152 (citing Ex. 1007, 54).

Having reviewed the cited evidence, and the record as a whole, we find that Petitioner has accurately described the above stated teachings of GSK-711 and Merck-086, which we adopt as our own. *See* Pet. 30–50. 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 dependent claims require that the recited serotype 22F glycoconjugate 'has a molecular weight of between 1,000 kDa and 12,500 kDa. . . .' GSK-711, Merck-086 and the general knowledge do not alone or in combination teach or suggest this limitation." PO Resp. 19 (internal citation omitted).

i. Optimization of molecular weight

Patent Owner asserts "GSK-711 does not provide the molecular weight for either of its serotype 22F glycoconjugates. Merck-086 does not

provide the molecular weight for any of its glycoconjugates." PO Reply 19 (citing Ex. 2058 ¶¶ 50, 51) (internal citations omitted).

Patent Owner asserts a "POSA would have understood that the determination of an appropriate molecular weight for a specific serotype glycoconjugate was not a matter of routine optimization of existing conjugation procedures." PO Reply 21 (citing Ex. 2058 ¶ 52). Patent Owner asserts that a "number of variables affect the post-conjugate molecular weight and/or immunogenicity of a specific serotype glycoconjugate." PO Reply 21 (citing Ex. 2058 ¶ 52).

Patent Owner asserts:

> As illustrated in Table 1 of GSK-711, the conjugation chemistries used to make the different serotype glycoconjugates differed in terms of polysaccharide concentration, solvent for polysaccharide dilution, carrier protein concentration, type of carrier protein (four different carrier proteins were utilized), initial carrier protein to polysaccharide ratio, CDAP concentration, and reaction pH condition.

PO Resp. 22 (citing Ex. 2058 ¶ 53, Ex. 1007, Table 1). Patent Owner points to Dr. Lees' statement that "the choice of carrier protein is quite complex." PO Reply 23 (citing Ex. 2054, 71:8–72:16).

Patent Owner asserts "[t]able 2 of GSK-711 provides data for six different parameters tested for thirteen distinct serotype conjugates" and that "this table does not provide any molecular weight data for the two referenced serotype 22F glycoconjugates, 'PS22F-AH-PhtD' and 'PS22F-PhtD.'" PO Reply 23–24 (citing Ex. 1007, Table 2). Patent Owner asserts that "[b]ecause the serotype 19A and 22F glycoconjugates differed from the other listed glycoconjugates with regard to four of the six parameters provided in Table 2 of GSK-711, a POSA would have concluded that the

serotype 19A and 22F glycoconjugates were distinct from the other glycoconjugates." PO Reply 24–25 (citing Ex. 2058 ¶ 55).

Patent Owner asserts "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 Reply 25 (citing Ex. 1011, 8). Patent Owner concludes that the "teachings of Lees-2008 show that more than routine experimentation would be needed to determine the appropriate molecular weight (or polysaccharide to protein ratio) of any given serotype glycoconjugate. . . ." PO Reply 26.

Patent Owner acknowledges Petitioner's argument that "using the size exclusion chromatography columns described in GSK-711 (*i.e.*, Sephacryl S400HR and TSK5000-PWXL), a POSA would have been targeting serotype 22F glycoconjugates well below the 12,500 kDa limit recited in the '559 patent claims." PO Reply 26 (citing Pet. 40, Ex. 1005 ¶ 144). Patent Owner asserts that "[h]owever, the size limits for each of the columns cited by Sanofi are for globular proteins, not for glycoconjugates." PO Reply 26 (citing Ex. 2058 ¶ 57, Ex. 1060, 2, Ex.1061, 15). Patent Owner asserts a "POSA would have further understood that unless the correct mobile phase of SEC was selected for purifying a glycoconjugate, it was possible that the glycoconjugate analyte could elute earlier or later than expected." PO Reply 27 (citing Ex. 2058 ¶ 57).

Patent Owner asserts that "GSK-711 itself demonstrates that it is not possible to predict the upper limit of the glycoconjugates by simply looking at the SEC columns used in its experiments" because "GSK-711 teaches that one of its glycoconjugates (PS9VPD) purified using the Sephacryl S400HR column had a molecular weight of 9,052-9,572 kDa, *i.e., larger* than the

supposed exclusion limit for the Sephacryl S400HR column." PO Reply 27 (citing Ex. 2058 ¶ 58).

We agree with Petitioner that these arguments are not persuasive because they are not supported by a preponderance of the evidence of record (*see* Pet. Reply 3–5, 13–16).

Merck-086 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. 1008 ¶ 17. Merck-086 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. 1008 ¶ 17 (emphasis added). Merck-086 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. 1008 ¶ 86.

Thus, Merck-086 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. 1008 ¶¶ 17, 86. Thus, rather than fabricating desired sizes, Merck 2011 specifically provides methods to constrain polysaccharide sizes within a particular size range. Ex. 1006 ¶ 86.

GSK-711 teaches "[p]olysaccharides are isolated from bacteria and may be sized to some degree by known methods. . . . in order to reduce viscosity in polysaccharide samples and/or to improve filterability for conjugated products." Ex. 1007, 12:5–8. GSK-711 teaches "the *S. pneumoniae* saccharides are sized by mechanical cleavage, for instance by microfluidisation or sonication." Ex. 1007, 14:20–21.

GSK-711 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, 15:9–16:3. GSK-711 is replete with suggestions to conjugate pneumococcal polysaccharides of various serotypes to CRM_{197}. *See, e.g.*, Ex. 1007, 6.

GSK-711 teaches an "immunogenic composition of the invention may thus comprise one or more saccharide conjugates wherein the average size (e.g. weight-average molecular weight; Mw) of each saccharide before conjugation is above . . . 1000kDa." Ex. 1007, 13:5–8. GSK-711 exemplifies 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, 53 (Table 2).

GSK-711 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, 13:1–3. GSK-711 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, 12:31–34. GSK-711 teaches "that saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease." Ex. 1007, 13:1–3. GSK-711 recognizes optimization for larger size saccharide-protein conjugates, limited only by a requirement to be "filterable through a 0.2 micron filter." Ex. 1007, 13:12.

Thus, GSK-711 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. Lees states that the 22F size in GSK-711 would have been expected to fall within the claimed molecular weight range. Dr. Lees states that "a 22F-PhtD conjugate synthesized using the CDAP chemistry would naturally result in highly crosslinked lattices, each of which contains multiple saccharide molecules and multiple carrier protein molecules." Ex. 1005 ¶ 142. Dr. Lees continues:

> a "smallest" lattice structure includes 2 molecules of a 22F polysaccharide. . . . Because GSK-711 Table 2 discloses that the carrier protein to polysaccharide ratio is 2.17, the total

> weight of the carrier protein PhtD in this "smallest" lattice would be 694.4 kDa . . . . As a result, the molecular weight of this "smallest" 22F-PhtD conjugate lattice would be at least 1014.4 kDa (320 kDa +694.4 kDa).

Ex. 1005 ¶ 143. Dr. Lees further states "the glycoconjugates described in Table 2, including 22F glycoconjugates, were purified using Sephacryl S400HR gel filtration, which has a size exclusion limitation under 8,000 kDa." Ex. 1005 ¶ 144. Dr. Lees concludes, based on the teachings of GSK-711 and Merck-086, that:

> It would therefore only require routine optimization of the conjugation conditions, such as varying the relative amounts of starting polysaccharides and carrier proteins in the reaction mixture and monitoring the conjugation chemistry, to achieve 22F glycoconjugates with molecular sizes above 1000 kDa. A POSA can also quench the conjugation reaction at a desired time before the molecular sizes reach 12,500 kDa to facilitate purification, characterization and to avoid precipitation or forming a gel.

Ex. 1005 ¶ 151.

Dr. Lees' position is supported by Dr. Kasper's[16] statement that "[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. 2037 ¶ 101.

[16] Ex. 2037 is a Declaration by Dr. Kasper submitted by the Petitioner in IPR2017-02131 in support of a petitioner asserting the unpatentability of claims of the '559 patent. Ex. 2037 ¶ 2.

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

> POSA would have understood that, simply because several specific serotype glycoconjugates had a molecular weight falling within a particular range does not necessarily mean that any other serotype glycoconjugate (*e.g.*, serotype 22F glycoconjugate) would also have a molecular weight falling within that same range. Numerous variables can impact the molecular weight, polysaccharide to protein ratio, and/or immunogenicity of a specific serotype glycoconjugate.

Ex. 2058 ¶ 52. Dr. Wang points to Lees-2008 as teaching that "numerous factors should be regarded before determining the appropriate molecular weight of any glycoconjugate." Ex. 2058 ¶ 56.

However, under deposition, Dr. Wang acknowledged that "[c]hemists have all kind of tricks to control, at least I've tried to do as much as they can, to come up with the desired product. That's why the conjugation chemistry and the vaccine industry is a special field." Ex. 1106, 156:11–16. Dr. Wang stated that "in order to better control your conjugation, you want the reaction a little slow and with certain time so you can really control that." Ex. 1106, 157:2–5.

Also, in response to a question as to whether Dr. Wang identified "any claims in the '559 patent that in [Dr. Wang's] opinion are directed to the particular conjugation chemistry or conditions of the conjugation chemistry that you would use in order to make the 22F glycoconjugate," Dr. Wang stated "No." Ex. 1106, 160:16–24. In this discussion, Dr. Wang did not identify any specific teaching in the '559 patent that demonstrated that the

optimization of the size of the serotype 22F conjugate would have had any specific issues or concerns. *See* Ex. 1106, 162:21 to 164:8.

Dr. Kasper made statements that address Dr. Wang's concerns regarding glycoconjugation factors (*see* Ex. 2058 ¶¶ 52, 56), noting that "a POSITA would have required only routine experimentation to obtain a conjugate molecular weight within the desirable range." Ex. 2035 ¶ 110.

Petitioner's declarant, Dr. Lees, stated during deposition that glycoconjugate size "is part of their routine optimization that I described before. The ability to control the extent of the reaction is one of the elements can be in that reaction time." Ex. 2054, 82:14–18. Dr. Lees further stated regarding conjugation for each seryotype that

> it is a routine matter. To determine the reaction time, you just simply take an aliquot, describe how to quench and stop the reaction, and that gives them plenty of time to then run those samples because there would be no further reaction changes. So it is a very routine type of thing to monitor it, and then you decide, okay, for the serotype, that is a good length of time.

Ex. 2054, 83:4–13. Dr. Lees explains that at the time of invention, ordinary artisans used a "statistical approach called design of experiment, and we can work out many of these conditions in this way, and you will come up -- this polysaccharide, this works" and that the "fact that these are all variable is a pretty routine type of experimentation." Ex. 2054, 88:10–22.

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. Wang acknowledged that with regard to conjugation conditions, that "you can really control [them]." Ex. 1106, 157:2–5. This is also supported by Dr. Lees' statements and testimony that optimization of conjugate sizes was routine. Ex. 1005 ¶ 151,

Ex. 2054, 88:11–22. This evidence supports a determination that routine optimization of conjugate size would have been obvious within the size range of Table 2 of GSK-711 (Ex. 1007, 54) and the express 50–1600 kilodalton range of GSK-711. Ex. 1007, 82. This routine optimization would have been particularly obvious when combined with the teachings of Merck-086 to optimize the size of the polysaccharides using known techniques, including the serotype 22F polysaccharide; with teachings of GSK-711 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 "routine conjugation techniques and conditions readily achieved those disclosed molecular weights." Ex. 2037 ¶ 101.

We recognize, but find unpersuasive, Patent Owner's assertion that "teachings of Lees-2008 show that more than routine experimentation would be needed to determine the appropriate molecular weight (or polysaccharide to protein ratio) of any given serotype glycoconjugate." PO. Response 26.

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. 1011, 5. Lees-2008 teaches that "[s]ize fractionation is usually necessary" (Ex. 1011, 7) 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. 1011, 8. 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. 1011, 9. 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. 1011, 8.

Thus, Lees-2008 demonstrates not only that serotype 22F pneumococcal vaccines are desirable, but provides detailed discussion regarding the known parameters necessary to optimize the size of these glycoconjugates.

We recognize, but find unpersuasive, Patent Owner's assertion that "a POSA would not have turned to the size exclusion limits of the SEC columns used in GSK-711 to make any conclusions about the final sizes of the serotype 22F glycoconjugates described in Table 2." PO Response 28. As Dr. Lees notes, GSK-711's use of particular size exclusion columns designed for sizes overlapping the 1,000 to 12,500 kDa range of claim 1 "would certainly suggest to someone that, yeah, you could purify these conjugates on there." Ex. 2054, 120:20–22.

We recognize that Dr. Wang stated a "POSA would have understood at the priority date of the '559 patent that size exclusion chromatography ('SEC') for glycoconjugates was not the same as that for proteins, and that SEC of glycoconjugates 'presents special difficulties' and was associated with 'pitfalls.'" Ex. 2058 ¶ 57. However, as Dr. Lees stated:

> a POSA would have reasonably expected that the size of GSK-711's 22F glycoconjugate, *if measured*, would also fall within the claimed range given that the same conjugation chemistry

> and SEC columns were used to generate, purify and analyze the 22F glycoconjugate as those other glycoconjugates. At the very least, a POSA would have been motivated to make 22F glycoconjugates that fall within the claimed molecular weight range and would have had a reasonable expectation that a 22F glycoconjugate with such a molecular weight could be successfully made using routine methods available well before 2014.

Ex. 1005 ¶ 118. Therefore, while the actual sizes of the particular 22F glycoconjugates disclosed in GSK-711 may or may not themselves fall within the claimed range, we agree with Petitioner that GSK-711's use of these size exclusion columns suggests the desirability and optimizability of glycoconjugates falling within the ranges analyzed by these columns. Pet. 44, Ex. 1005 ¶ 118.

We find that a preponderance of the evidence of record demonstrates that conjugate size is a results effective variable associated with improved stability of conjugates and good immune response, limited only by filter size, thereby rendering "optimization within the grasp of one of ordinary skill in the art." *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-711, would have been consistent with the ranges optimized and used to generate multivalent vaccines. Pet. 40–44; 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). *See also E.I. DuPont de Nemours & Company v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (reaffirming this obviousness doctrine).

ii. CDAP conjugation and serotype 22F glycoconjugate molecular weight

Patent Owner asserts that Petitioner contends "the CDAP chemistry used to generate the glycoconjugates described in Table 2 of GSK-711 would be 'likely to produce a 22F-PhtD conjugate with an average molecular weight above 1000 kDa.'" PO Response 28 (citing Pet. 37).

Patent Owner asserts Petitioner "oversimplified the conjugation process" because Petitioner "has not shown how many of (or even a rough approximation of) the hydroxyl groups or lysine residues referenced by [Petitioner] would actually be available for conjugation reactions." PO Response 29 (citing Ex. 2058 ¶¶ 59–60). Patent Owner acknowledges that "a POSA would have understood that the actual number of activated hydroxyl groups would need to be carefully controlled during a conjugation reaction" but asserts Dr. Lees "has failed to explain how a POSA should control the serotype 22F activation step such that only the appropriate number of activated hydroxyl groups would be made available to react with those two lysine groups." PO Response 29–30 (citing Ex. 2058 ¶ 60, Ex. 2054, 132:1–8).

Patent Owner concludes that Petitioner "does not explain why the specific reaction parameters described in Example 2 and Table 1 of GSK-

711 would be likely to result in a serotype 22F glycoconjugate having the claimed molecular weight parameters." PO Response 31.

We agree with Petitioner that these arguments are not persuasive because they conflate anticipation with obviousness and are not supported by a preponderance of the evidence of record (*see* Pet. Reply 10–13).

As already noted, GSK-711 produced fourteen conjugates as disclosed in Table 2, ten of which had conjugate sizes within the range required by claim 1 of the '559 patent, and four whose conjugate size was not measured including a 22F-PhtD conjugate. Ex. 1007, 53. Dr. Lees persuasively explained that even assuming minimal conjugation for the 22F-PhtD glycoconjugate, the "molecular weight of this 'smallest' 22F-PhtD conjugate lattice would be at least 1014.4 kDa" and that "a POSA would reasonably expect that the average molecular weight of all lattices in the 22F-PhtD conjugate should be well above 1000 kDa." Ex. 1005 ¶ 143.

In rebuttal, Dr. Wang states "it is possible that the referenced serotype 22F glycoconjugates could each have only one polysaccharide" and therefore "the resulting serotype 22F glycoconjugates would be half the size" of the lower limit recited by claim 1 of the '559 patent. Ex. 2058 ¶ 62.

However, when deposed, Dr. Wang stated regarding the CDAP conjugation process that "it's hard to control, it's a – it's react very fast." Ex. 1106, 108:24–25. When Dr. Wang was then asked whether this fast conjugation process made it "unlikely that you would see very, very small glycoconjugates," Dr. Wang answered "You may still achieve some linkage. It's all depend [sic] on the -- you know, the procedure, the operation." Ex. 1106, 109:6–14. Thus, Dr. Wang acknowledges that the ordinary artisan would expect CDAP activation to result in larger, rather than smaller,

glycoconjugates consistent with Dr. Lees' position, and that the size of these glycoconjugates may be controlled if the artisan is very careful to do the operation. Ex. 1106, 109:18–19.

This understanding is reinforced by Dr. Lees, who stated under deposition that CDAP "is a controllable reaction." Ex. 2081, 61:24. Dr. Lees further states that "[i]n my experience working with CDAP conjugation in particular, pretty much routine conditions. I've worked with a very large number of polysaccharides using CDAP chemistry, and we make conjugates that are immunogenic by the standards." Ex. 2081, 83:2–7.

We recognize, but find unpersuasive, Patent Owner's assertion that Petitioner "does not explain why the specific reaction parameters described in Example 2 and Table 1 of GSK-711 would be likely to result in a serotype 22F glycoconjugate having the claimed molecular weight parameters" (PO Resp. 31), because the issue is the obviousness of routine optimization of conjugate sizes, not inherent anticipation by GSK-711. Instead, we agree with Petitioner that "a POSA would still have reasonably expected lattice sizes well above 1,000 kDa because the conjugation conditions can be readily optimized to increase cross-linking." Pet. Reply 18.

iii. GSK-711 table 2 molecular weight calculations

Patent Owner asserts that Petitioner

> relies upon an oversimplified calculation that does not work in practice. EX2058, ¶62. As Dr. Wang points out, it is unclear why Sanofi concludes that the smallest serotype 22F glycoconjugate would be a lattice including at least two polysaccharides. *Id*. After considering the activation and conjugation methods described in GSK-711, a POSA would have understood that the referenced serotype 22F glycoconjugates could each have had only one polysaccharide. *Id*. In such a situation, the resulting serotype 22F

> glycoconjugates would be half the size concluded by Sanofi, *i.e.*, 507.2 kDa.

PO Reply 32. Patent Owner further asserts that in Table 2 of GSK-711 "the listed size for the 22F polysaccharide is *prior* to the activation and conjugation reactions" and the "activation and conjugation reactions could process a polysaccharide so that it is smaller when incorporated into the final glycoconjugate." PO Reply 33 (citing Ex. 2058 ¶ 63).

Patent Owner asserts that an example in Table 2 of GSK-711 supports this reasoning because "the 'smallest' possible glycoconjugate determined using Sanofi's calculation *exceeded* the actual PS1-PD glycoconjugate sizes as provided in Table 2." PO Reply 35 (citing Ex. 2058 ¶ 64). Patent Owner asserts that "even if these values are close, this does not change the fact that Sanofi's calculation and conclusions are unreliable." PO Reply 36 (citing Ex. 2058 ¶ 65). Patent Owner concludes that "there is no reason why the actual serotype 22F glycoconjugate of GSK-711 could not be similarly below Sanofi's calculated value and below the lower limit specified in the challenged claims." PO Reply 35.

We agree with Petitioner that these arguments are not persuasive because they are not supported by a preponderance of the evidence (*see* Pet. Reply 16–20).

Dr. Lees states "[e]xcept for PS1-PD, all other conjugates in Table 2 with measured MWs are above the 'smallest' hypothetical lattice size, and therefore conform to my calculations. The size of the PS1-PD conjugates is among the smallest of all the conjugates in Table 2 and appears to be the only outlier in this respect." Ex. 1108 ¶ 30. Table 2 of GSK-711 shows that several serotypes with polysaccharide sizes smaller than the 159–167 kDa

size of serotype 22F, including serotypes 4 (93–100 kDa), 18C (89–97 kDA), and 19F (133–143 kDa), all after conjugation result in final glycoconjugates within the 1,000 to 12,500 kDa range recited in claim 1 of the '559 patent. Ex. 1007, 53. Under deposition Dr. Lees states "[a]ll of the numbers, whether it's 1,499 or 1,745, they are all within the claims that -- of the seven -- of the '599 patent. For the reason, this is kind of the general range you're targeting, is greater than 1,000" kDa. Ex. 2081, 147:5–10.

Dr. Kasper confirms that a "POSITA would have understood that, given the molecular weights of the polysaccharides and carrier proteins (all of which had a combined weight several-fold smaller than the corresponding conjugate molecular weights), the conjugates had been crosslinked into high molecular weight lattice structures containing multiple polysaccharide and carrier proteins." Ex. 2037 ¶ 84.

As we have already noted, GSK-711 is not relied upon for anticipation, but rather for obviousness. Consequently, even if the smallest possible size conjugate was slightly below the claimed range as argued by Patent Owner, it is not necessary for obviousness for the ordinary artisan to predict conjugation conditions that will result in the desired range prior to performance of actual experimentation to routinely optimize glycoconjugate size. Instead, there must be a reason to optimize to the desired range, and in addition to Table 2 of GSK-711 teaching a number of examples within the range recited by claim 1 of the '559 patent, GSK-711 suggests that larger conjugates are better because "saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease" with an upper size limit constrained by a

requirement for the glycoconjugate to be "filterable through a 0.2 micron filter." Ex. 1007, 13:1–3, 12.

Therefore, we agree with Petitioner that "a POSA would still have reasonably expected lattice sizes well above 1,000 kDa because the conjugation conditions can be readily optimized to increase cross-linking." Pet. Reply 18 (citing Ex. 1108 ¶ 29). We conclude that the molecular weight calculations provide some additional evidence supporting the obviousness of generating a serotype 22F glycoconjugate within the 1,000 to 12,500 kDa range recited by claim 1 of the '559 patent.

iv. Serotype 22F glycoconjugate size relative to polysaccharide

Patent Owner asserts "there is no support in GSK-711 or anywhere else in the art for the general rule that a glycoconjugate should be at least 3-5 fold larger than its respective polysaccharide." PO Resp. 37 (citing Ex. 2058 ¶ 67). Patent Owner asserts "Dr. Lees did not provide any specific basis for the arbitrary selection of this '3-5 fold' range." PO Resp. 37 (citing Ex. 2054, 150:3–12).

Patent Owner asserts that "if the serotype 22F glycoconjugate were 3-5 fold larger than its preconjugation polysaccharide . . . then the resulting serotype 22F glycoconjugate would only be 477-835 kDa, well below the 1,000-12,500 kDa range recited in the '559 patent." PO Resp. 37–38 (citing Ex. 2058 ¶ 69).

Patent Owner asserts that:

> In *Applied Materials*, the claims recited dimensions that overlapped with those disclosed in a prior art. [*In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012]. There is no overlap between the molecular weights in GSK-711 and the challenged claims. The challenged claims recite the molecular

> weight of the 22F glycoconjugate and not the unconjugated polysaccharide. GSK-711 does not disclose molecular weights of either serotype 22F glycoconjugate. At best, GSK-711 discloses generic molecular weight ranges of one component, *i.e.*, the pre-conjugation size of the 22F polysaccharide. The pre-conjugation size of 22F does not indicate the polysaccharide size in the final product or the molecular weight of the glycoconjugate. EX2058, ¶71.

PO Resp. 38–39. Patent Owner asserts "[t]here is no reason why a POSA would have selected a polysaccharide having a molecular weight on the upper end (800 kDa) of the range recited in GSK-711, as opposed to the lower end (50 kDa) to prepare glycoconjugates." PO Resp. 40 (citing Ex. 2058 ¶ 71). Patent Owner asserts that based on the size of the serotype 22F polysaccharide in Table 2 and "on the small sizes of the specific carrier proteins referenced by [Petitioner], it is not reasonable to assume that the molecular weight of a serotype 22F glycoconjugate would have a molecular weight over 1,000 kDa." PO Resp. 41 (citing Ex. 2058 ¶ 74).

We agree with Petitioner that these arguments are not persuasive because they are not supported by a preponderance of the evidence of record. *See* Pet. Reply 13–16, 22–24.

To the extent that Dr. Lees discusses a purported rule that "to effectively separate conjugates from unconjugated polysaccharides using an SEC column . . . the size of the conjugates preferably needs to be at least 3–5 fold larger than the unconjugated polysaccharides" (Ex. 1005 ¶ 148), we agree that the rule reflects a parameter that would be considered by the ordinary artisan in optimizing glycoconjugate sizes. *See, e.g.*, Pet. Reply 23.

We appreciate Patent Owner's argument that the sole basis of the 3–5 fold rule is found in Dr. Lees' Declaration, but under deposition Dr. Lees

explained that the underlying reasoning for this rule is that to separate materials in sizing columns "you need to have a physical size difference between the two in order to be able to separate them." Ex. 2054, 150:10–12. Dr. Lees is simply pointing out that the greater the size difference between two molecular components, the more effectively they can be distinguished and separated using a sizing column, as acknowledged by Dr. Wang that "[i]n order to separate well, the difference, the larger the better, of course." Ex. 1006, 124:5–6. Additionally, the Cross Flow Filtration Method Handbook explains that "[a]n ultrafiltration filter with a nominal molecular weight cut-off (NMWC) that is 3× to 5× less than the molecular weight of the target molecule is generally recommended." Ex. 1110, 19. Thus, the ordinary artisan would have had reason to maximize these size differences to improve the efficacy of separation.

As to Patent Owner's arguments regarding optimization, we have already extensively addressed the evidence supporting optimization of glycoconjugate sizes above, but we will reiterate some of the key evidence below. GSK-711 teaches a range for the saccharide glycoconjugates that overlaps the 1,000 to 12,500 kDa range recited in claim 1 of the '559 patent, specifically teaching "saccharide conjugates of the invention should have an average size of saccharide pre-conjugation of 50-1600" kDa. Ex. 1007, 13:8–10. Table 2 of GSK-711 teaches ten different serotypes of *S. pneumoniae* with final glycoconjugate sizes ranging from 1,499 to 9,572 kDa. Ex. 1007, 53.

More directly, GSK-711 provides reasons to optimize the size of the glycoconjugates and in particular, larger saccharides because "saccharide conjugate vaccines retaining a larger size of saccharide can provide a good

immune response against pneumococcal disease." Ex. 1007, 13:1–3. GSK-711 teaches "[p]olysaccharides can be sized in order to reduce viscosity in polysaccharide samples and/or to improve filterability for conjugated products." Ex. 1007, 12:7–8.

GSK-711 teaches sizes may be measured by MALLS (see Ex. 1007, 15:10–15) and teaches "conjugates were purified by gel filtration using a Sephacryl S400HR gel filtration column equilibrated with 0.15M NaCl (S500HR for 18C) to remove small molecules (including DMAP) and unconjugated PS and protein." Ex. 1007, 50:16–18.

Under deposition, Dr. Lees stated that glycoconjugates "take on a characteristic that are intermediate between the two components. So it's not running like a polysaccharide. It's not running like a globular protein. It will run at something in between" polysaccharides and globular proteins. Ex. 2081, 46:18–22. Patent Owner, in the Lees' deposition, asks whether for a Sephacryl S400HR gel filtration column, "the size limit for dextrans is 2000 kilodaltons . . . And the size limit for globular proteins for the S400 HR column is 8,000 kilodaltons." Ex. 2081, 45:7–13 (citing Ex. 1060, table 1). Dr. Lees answered "That's correct." Ex. 2081, 45:14. Thus, there is no dispute that the Sephacryl S400 column used by GSK-711 for purification of glycoconjugates have useful purification range of "2 x 10^4–8 x 10^6" kDa for globular proteins and "1 x 10^4–2 x 10^6" for the carbohydrate, dextran. Ex. 1060, Table 1. As Dr. Lees noted under deposition "somebody reviewing the literature at that time in 2014 would be well aware that you could use an S-400 column." Ex. 2054, 123:2–4.

These teachings regarding the purification range of a Sephacryl S400 column, in combination with Dr. Lees' statement that polysaccharide

conjugates will fall somewhere between the globular protein and dextran ranges, evidences that the ordinary artisan would have understood the minimum size of glycoconjugates being purified by GSK-711 would have been no lower than 1 x 10^4 kDa, or 1,000 kDa, equivalent to the lower end of the range recited in claim 1 of the '559 patent. Thus, the ordinary artisan would have known to optimize the lower size range of the glycoconjugates to a size around 1,000 kDa.

v. Merck-086 and molecular weight

Patent Owner asserts that "[n]either Merck-086 nor the two specific documents cited in Merck-086 teaches or suggests a molecular weight of a serotype 22F polysaccharide." PO Resp. 42 (citing Ex. 2058 ¶ 75).

We agree with Patent Owner that Merck-086 has very limited disclosure regarding the size of glycoconjugates, only teaching that polysaccharides such as 22F can be conjugated to carrier proteins such as CRM_{197}. Ex. 1008, ¶¶ 17–18. However, the obviousness analysis is based on the combination of the disclosures of Merck-086 with GSK-711, not Merck-086 alone. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981) ("The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.")

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

Patent Owner asserts "[c]laim 1 and its dependent claims require that the 'ratio (w/w) of the polysaccharide to the carrier protein is between 0.4

and 2' for the recited 22F glycoconjugate. EX1001 at claims 1, 3-19, 23-37, 41-42, 45. GSK-711 teaches away from the claimed ratio. EX2058, ¶76." PO Resp. 43.

i. GSK-711 does not teach away from the claimed polysaccharide to protein ratio

Patent Owner asserts that while one of the two different serotypes exemplified by GSK-711, PS22F-PhtD, "translates to a polysaccharide to protein w/w ratio of 1/2.17, or 0.46" that is within the polysaccharide to protein ratio range of the '559 claims (PO Resp. 43), the other serotype, PS22F-AHPhtD, "translates to a pre-conjugation polysaccharide to protein ratio of 1:3, or 0.33, which is outside the ratio range of the '559 patent claims." PO Resp. 44 (citing Ex. 2058 ¶ 78). Patent Owner asserts that, based on pre-conjugation ratios for both exemplified serotypes, a "POSA would have understood that it was an objective of the inventors of GSK-711 to generate a serotype 22F glycoconjugate having a polysaccharide to protein ratio below the ratio range recited in the '559 patent claims." PO Resp. 44.

Patent Owner asserts that because of the significant "immunogenic superiority of the PS22F-AH-PhtD over the PS22F-PhtD glycoconjugate," "a POSA trying to make an immunogenic serotype 22F glycoconjugate would have turned to PS22F-AHPhtD rather than PS22F-PhtD." PO Resp. 45 (citing Ex. 2058 ¶ 79). Patent Owner asserts that because the "serotype 22F glycoconjugate was one of only two glycoconjugates described in GSK-711 that was made using a linker . . . a POSA likely would have believed that the ADH linker chemistry was adopted for the serotype 22F

glycoconjugate because the data show insufficient immunogenicity for the direct conjugate." PO Resp. 48 (citing Ex. 2058 ¶ 82).

Patent Owner also asserts that "consistency between the starting and final ratios indicates a very efficient conjugation for the PS22F-AH-PhtD" while the "drop in protein to polysaccharide ratios from starting to final material for the PS22F-PhtD glycoconjugate clearly suggests a less efficient conjugation." PO Resp. 49 (citing Ex. 2058 ¶ 83). Patent Owner asserts that a "POSA would desire a conjugation chemistry that was more efficient because it would provide more predictability and ease in purification." PO Resp. 49. Patent Owner concludes "[d]ue to the highly significant inferiority of the PS22F-PhtD glycoconjugate, a POSA would have been discouraged from generating this glycoconjugate." PO Resp. 47.

We agree with Petitioner that these arguments are not persuasive because they are not supported by a preponderance of the evidence of record. *See* Pet. Reply 6–10.

GSK-711 discloses a range of ratios of polysaccharide to carrier protein that includes and fully overlaps the range claimed. Ex. 1007, 19:1–6. *Peterson*, 315 F.3d at 1329. GSK-711 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, 19:1–6. Dr. Lees further explains 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. 1005 ¶ 58 (citing Ex. 1019, 119 ("For pneumococcal conjugate vaccines the ratio is typically in the range 0.3–3.0 but varies with the serotype.")). Patent Owner also acknowledges that GSK-711 teaches an example of 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. 43. 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. 1005 ¶ 57.

The exemplary serotype 22F-PhtD conjugate with a 0.46 ratio, along with the overlapping ranges disclosed and claimed by GSK-711, the overlapping Merck-086 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 have selected ratios for the serotype 22F conjugate within the range required by claim 1 of the '559 patent. Ex. 1007, 19:1–6; Ex. 1008, 11 ¶ 94; Ex. 1005 ¶ 58; Ex. 1019, 119.

We recognize that Figure 6 of GSK-711 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* PO Resp. 46 (citing Ex. 1007, 93). We also recognize that Dr. Wang states that "a POSA would have focused on the glycoconjugate having the significantly superior immunogenicity, *i.e.*, PS22FPhtD." Ex. 2058 ¶ 81.

However, GSK-711 expressly 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, 54:12–14. Thus, the plain text of GSK-711 teaches that either conjugate may be used. Therefore, even if the GSK-711 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.").

Also, GSK-711 shows the immunogenicity for the two serotype 22F conjugates as either 37% or 28–31%, demonstrating similar results for both conjugates. Ex. 1007, 53, Table 2. Patent Owner points to no teaching in GSK-711 that criticizes, discredits, or discourages the use of a ratio within the range required by claim 1. Indeed, in response to the question of whether GSK-711 stated "if you want to make an immunogenic 22F glycoconjugate, do not use the glycoconjugate that does not have a linker," Patent Owner's expert Dr. Wang answered "the patent did not say specifically that." Ex. 1006, 127:10–17.

Moreover, the other reference relied upon in the obviousness analysis, Merck-086, also suggests conjugation of polysaccharide to protein in

overlapping amounts to those recited in the claims of the '559 patent. 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. 1008, ¶ 104. 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. 2037 ¶ 115.

ii. GSK-711 suggests overlapping polysaccharide to protein ratios

Patent Owner asserts GSK-711 discloses "ratio range[s] between 0.4 to 2; 0.4 and 0.67; and 0.5 and 1" but Petitioner "has failed to explain why a POSA would have adopted the specific polysaccharide range of 0.4 to 2 from this generic list." PO Resp. 50. Patent Owner points out that GSK-711 includes "polysaccharide to protein ratio ranges that fall entirely *outside* of the claimed range." PO Resp. 50 (citing Ex. 2058 ¶ 84).

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. 52 (citing Ex. 1054, 13 "[t]he optimal [polysaccharide-protein] ratio has to be determined by experiment in pre-clinical studies or clinical trials.")

We do not find these arguments persuasive. 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, GSK-711 and Merck-086, specifically direct the ordinary artisan to incorporate serotype 22F conjugates into pneumococcal vaccines. *See* Ex. 1008, ¶15 ("[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, 4:12–15 ("The present invention provides an immunogenic composition . . . [that] comprises a 22F saccharide conjugate.").

Moreover, as discussed above, the GSK-711 and Merck-086 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, 19:1–6; Ex. 1008, 11–12; Ex. 1005 ¶ 58. In addition, the ordinary artisan was aware of desirable ranges of polysaccharide to carrier protein. Ex. 1019, 119. As Dr. Kasper noted "the acceptable range of 'Saccharide content/protein ratio' . . . for each of the seven disclosed conjugates," though not including 22F, "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 ¶¶ 112–113.

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-711 demonstrates an immunogenic serotype 22F glycoconjugate with an overlapping polysaccharide to carrier protein ratio and Merck-086 demonstrates an immunogenic serotype 22F glycoconjugate in a 1:1 polysaccharide to carrier protein ratio. Ex. 1007, 19:1–6; Ex. 1008, 11–12, Table 1. Patent Owner provides no evidence showing that any serotype 22F glycoconjugate fails to result in an immunogenic response.

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 GSK-711, Merck-086, and the knowledge of the ordinary artisan, including the WHO guidelines.

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. 53–54 (citing Ex. 2058 ¶ 88). Patent Owner asserts that "[n]either GSK-711 nor Merck-086 exemplifies the generation of a serotype 15B glycoconjugate (as required by claim 3) or a serotype 12F, 10A, 11A or 8 glycoconjugate (as required by claim 4)." PO Resp. 55 (citing Ex. 2058 ¶ 89). 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. 55 (citing Ex. 2058 ¶ 89).

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 GSK-711, Merck-086, and the knowledge of the person of ordinary skill in the art.

GSK-711 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, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F." Ex. 1007, 7:1–3. Thus, GSK-711 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-711 containing multiple serotypes also requires induction of an immune response, otherwise there would be no need to include a serotype unable to induce such a response. And indeed, GSK-711 uses the same term, immunogenic, to describe the pneumococcal vaccine composition. *See* Ex. 1007, 4:12.

We recognize that Dr. Wang correctly notes that "[n]either GSK-711 nor Merck-086 exemplifies the generation of a serotype 15B glycoconjugate (as required by claim 3) or a serotype 12F, 10A, 11A or 8 glycoconjugate (as required by claim 4)." Ex. 2058 ¶ 89. 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 based on the prior art disclosures "a POSITA would have been motivated with a reasonable expectation of success to additionally include a serotype 15B conjugate." Ex. 2037 ¶¶ 44, 88, 120. Dr. Kasper also noted that the "claimed serotypes were well-known to be prevalent and had already been included in the Pneumovax® 23 polysaccharide vaccine." Ex. 2037 ¶ 122.

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. 1005 ¶¶ 158–59.

We, therefore, conclude that incorporation of known immunogenic serotypes such as 10A, 11A, 15B, and 33F into the vaccine suggested by GSK-711, Merck-086, 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 GSK-711, Merck-086, Lees-2008, PVP-2013, and Pfizer-605

Petitioner asserts that "Lees-2008 establishes that O-acetyl groups on polysaccharides were considered desired epitopes" because "O-acetyl groups could be important for protective immunogenicity." Pet. 67 (citing Ex. 1011, 5, 7). Petitioner asserts that "it was known that the O-acetylation level on native 22F polysaccharide is 0.8 mM acetate per mM of polysaccharide repeating unit." Pet. 67 (citing Ex. 1026, 9).

Petitioner asserts PVP-2013 states "that for 22F polysaccharides, the permitted O-acetylation level by NIID is '0.5–1.5' mM acetate per mM polysaccharide unit." Pet. 68 (citing Ex. 1012, 3, 4). Petitioner asserts that "Lees-2008 and/or PVP-2013 clearly establish a motivation to meet the threshold recited in claim 2." Pet. 68. Petitioner asserts "Pfizer had already used such an approach (*i.e.*, reductive amination in DMSO) in its earlier Pfizer-605 patent to prepare glycoconjugates and preserve O-acetyl groups on the native polysaccharide." Pet. 69 (citing Ex. 1013, Ex 1005 ¶ 232).

Patent Owner asserts "GSK-711 and Merck-086, and the 'general knowledge' do not teach or suggest the minimum acetate levels required by claims 2, 40 and 43" and "Lees-2008, PVP 2013, and Pfizer-605 do not remedy the deficiencies." PO Resp. 56. Patent Owner asserts "Lees-2008 is silent with regard to serotype 22F glycoconjugate" and "emphasizes the uncertainty in the field regarding the role of *O*-acetylation in glycoconjugates." PO Resp. 57 (citing Ex. 1011, 5, Ex. 2058 ¶ 92).

Patent Owner asserts "23-valent free unconjugated polysaccharide vaccine referred to in PVP2013 is not the same as the glycoconjugate compositions that are claimed" because "[t]here is no carrier protein in the PVP-2013 free polysaccharide compositions." PO Resp. 58. 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. 58. Patent Owner asserts "Pfizer-605 does not refer to any serotype 22F glycoconjugates, and, therefore, does not teach an appropriate molecular weight or polysaccharide to protein ratio for a serotype 22F glycoconjugate." PO Resp. 59.

1. *Lees-2008 (Exhibit 1011)*

Lees-2008 is titled "Conjugation Chemistry" and is included in a volume on Pneumococcal Vaccines. Ex. 1011, 2, 4. Lees-2008 identifies a number of pneumococcal serotypes including 22F. Ex. 1011, 5. Lees-2008 states that for some polysaccharides "O acetylation is necessary in order for the conjugates to induce protective antibodies" but that "O-acetyl groups in serotype 9V and 18C PSs [polysaccharides] may not be required for the PS to induce functional antibodies." Ex. 1011, 5).

2. *PVP-2013 (Exhibit 1012)*

PVP-2013 is titled "Pneumococcal Vaccine Polyvalent" and was published on the website of Japan's National Institute of Infectious Diseases (*see* Pet. 68). 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. 1012, 1. PVP-2013 teaches various tests used to analyze polysaccharides used in the vaccines including, among others, an *O*-acetate content test. Ex. 1012, 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. 1012, 4.

3. *Pfizer-605 (Exhibit 1013)*

Pfizer-605 is a patent drawn to a "multivalent immunogenic composition comprising 13 distinct polysaccharide-protein conjugates" of *Streptococcus pneumoniae*. Ex. 1013, 2:8–9. Pfizer-605 teaches the "conjugation step is performed in DMSO via a reductive amination mechanism in the presence of sodium cyanoborohydride." Ex. 1013, 12:32–34. Pfizer-605 teaches the "ratio of O-acetyl concentration to total saccharide concentration gave μmoles of O-acetyl per mg of saccharide." Ex. 1013, 16:34–36.

4. Analysis

We find Patent Owner's 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. 2037 ¶ 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. 1012, 3, 4. Dr. Lees further performs a calculation on the PVP-2013 analysis, finding that "the permitted minimum ratio of O-acetylation level . . . is at least 0.625." Ex. 1005 ¶ 229.

We recognize Dr. Wang's statement that "the PVP-2013 compositions include free polysaccharides that are not conjugated to any carrier protein" (Ex. 2058, 94) but find this argument unpersuasive because Dr. Wang

provides no reasoning as to why the O-acetyl levels necessary for free polysaccharides to function as immunogens would differ when the polysaccharides were conjugated.

Indeed, Dr. Kasper explained that the prior art evidences "that O-acetyl groups can contribute to the immunogenicity of pneumococcal polysaccharides." Ex. 2037 ¶ 143. This teaching evidencing that O-acetyl groups are associated with immunogenicity, in combination with the teaching of PVP-2013 to incorporate acetate into serotype 22F in particular at levels within the scope of the claims of the '559 patent, 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.

We therefore conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by GSK-711, Merck-086, 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 and Lees-2008 using known methods such as those of Pfizer-605.

E. Obviousness of GSK-711, Merck-086, and GSK-531

Petitioner asserts that "Claims 20–22 are directed to combination vaccines" and require "the claimed immunogenic composition further includes an antigen from other pathogens." Pet. 70. Petitioner asserts "GSK-531 specifically teaches that its disclosed pneumococcal glycoconjugates (including a 22F glycoconjugate) can be mixed with other antigens, including those specifically recited in claim 21." Pet. 71 (citing Ex. 1014, 20:25–31). Petitioner asserts "[c]ombination vaccines are desirable because they provide broad coverage and reduce the number of vaccine injections that need to be administered to infants, among other benefits. . . . Therefore, a POSA would have been motivated to include an antigen from other pathogens in the claimed composition." Pet. 71 (citing Lees ¶ 235) (internal citations omitted).

Patent Owner asserts Petitioner "has not demonstrated that claim 1 is obvious over GSK-711, Merck-086, GSK-531 and the "general knowledge." Therefore, [Petitioner] has likewise not met its burden in showing that claims 20-22 are obvious." PO Resp. 58–59. Patent Owner asserts "GSK-531 does not teach or suggest any methods of preparing a pneumococcal serotype 22F glycoconjugate, much less a serotype 22F glycoconjugate having the molecular weight and polysaccharide to protein ratio limitations recited in the '559 patent claims." PO Resp. 60 (citing Ex. 2058 ¶ 98).

1. *GSK-531 (Exhibit 1014)*

GSK-531 discusses forming a vaccine through conjugation of bacterial capsular saccharides, including *Streptococcus pneumoniae* serotype 22F, by reductive amination to proteins including CRM_{197}. Ex. 1014, 2:35–3:17, 7:34, 9:21. GSK-531 teaches including additional antigens in the

vaccine including "Diphtheria toxoid (DT), tetanus toxoid (TT), and pertussis components" as well as a "capsular saccharide from *N. meningitides*." Ex. 1014, 20:25–21:3.

2. *Analysis*

We have already concluded that a preponderance of the evidence of record supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that an ordinary artisan would have found it obvious to combine the pneumococcal vaccine including the 22F serotype with other known vaccines because Dr. Lees explains that "combination vaccines were known to be desirable because they provide broad coverage and reduce the number of vaccine injections that need to be administered to infants, among other benefits." Ex. 1005 ¶ 235. While Patent Owner is correct that GSK-531 is not relied upon by Petitioner for either the molecular weight or ratio requirements, GSK-711 and Merck-086 render these limitations of claim 1 obvious for the reasons discussed above.

We, therefore, conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by GSK-711, Merck-086, and the knowledge of the ordinary artisan by combining it with the combination vaccine of GSK-531.

F. Obviousness of GSK-711, Merck-086, and Pfizer-605

Petitioner asserts "Pfizer-605 describes the use of size exclusion chromatography with a CL-4B column to profile the relative molecular size distribution of the pneumococcal conjugates." Pet. 73 (citing Ex. 1005 ¶ 243; Ex. 1013, 36–37). Petitioner asserts that Pfizer-605 teaches "that a preferred value for conjugate molecular sizes is about 70% 0.3 K_d in a CL-4B column, which is well above the recited limitation of 'at least 30%' in

claim 38." Pet. 73 (citing Ex. 1005 ¶ 243; Ex. 1013, 36–37). Petitioner asserts "a POSA would have had the motivation to optimize the glycoconjugation process of GSK-711 according to what's taught in Pfizer-605 to achieve the threshold recited in Claim 38." Pet. 74.

Patent Owner asserts Petitioner "has not demonstrated that claim 1 is obvious over GSK-711, Merck-086, Pfizer-605 and the 'general knowledge.' Therefore, Sanofi has likewise not met its burden in showing that claims 38 and 39 are obvious." PO Resp. 61. Patent Owner asserts "Pfizer-605 does not refer to any serotype 22F glycoconjugates, and, therefore, does not provide guidance as to what would be an appropriate molecular weight range and polysaccharide to protein ratio range for a serotype 22F glycoconjugate." PO Resp. 61 (citing Ex. 2058 ¶ 100).

1. *Pfizer-605 (Exhibit 1013)*

Pfizer-605 discusses "a multivalent immunogenic composition, wherein the capsular polysaccharides are from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9v, 14, 18C, 19A, 19F and 23E of *Streptococcus pneumoniae*, the carrier protein is CRM_{197}, and the adjuvant is an aluminum-based adjuvant." Ex. 1013, 2:24–28. Pfizer-605 teaches "[c]haracterization of the conjugate . . . include[ed] use of size exclusion chromatography media (CL-4B) to profile the relative molecular size distribution of the conjugate." Ex. 1013, 36:50–53. Pfizer-605 teaches "a preferred value for conjugate molecular size is about 70% 0.3 Kd, with a preferred free saccharide level below about 20–25%." Ex. 1013, 24.

2. *Analysis*

We have already concluded that a preponderance of the evidence of record supports the obviousness of claim 1 for the reasons discussed. We

further agree with Petitioner that claims 38 and 39 would have been obvious because Pfizer-605 discloses that size exclusion chromatography (SEC) with CL-4B sepharose is used to assess molecular size and Pfizer-605 teaches preferred values for conjugate size and free saccharide levels that overlap those of claims 38 and 39. "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, 1330 (Fed. Cir. 2003).

Dr. Lees stated that, based on Pfizer-605,

> a POSA would have had motivation to prepare a 22Fglycoconjugate that meets the minimum percentage value "at least 30%" as measured by a K_d value below or equal to 0.3 in a CL-4B column as recited in claim 39 and would also have had a reasonable expectation of success that such a minimum threshold may be achieved by routine optimization of the conjugation process available in 2014.

Ex. 1005 ¶ 244.

We, therefore, conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by GSK-711, Merck-086, and the knowledge of the ordinary artisan with the sizing and purification techniques of Pfizer-605 to obtain quality conjugates.

G. Obviousness over GSK-711, Merck-086, and Hsieh-2000

Petitioner asserts that "the degree of conjugation recited in claim 44 had already been achieved in many glycoconjugates before the earliest possible priority date." Pet. 76 (citing Lees ¶ 250). Petitioner asserts that Hsieh-2000

> characterized saccharide-CRM_{197} conjugates included in *Hib*, pneumococcal and meningococcal vaccines successfully

> developed by Wyeth and observed that the formulation of the covalent bonds between lysines and polysaccharides had been "consistent in the range of 6–9," (Ex. 1015, 8), which falls entirely within the range of 2–15 as claimed in claim 44.

Pet. 76. Petitioner asserts that "it would have been obvious for a POSA to optimize the conjugation process of GSK-711 in view of Hsieh-2000 to prepare a 22F glycoconjugate with the degree of conjugation between 2–15 as recited in claim 44." Pet. 76.

Patent Owner asserts Petitioner "has not demonstrated that claim 1 is obvious over GSK-711, Merck-086, GSK-531 and the 'general knowledge.' Therefore, Sanofi has likewise not met its burden in showing that claim 44 is obvious." PO Resp. 62. Patent Owner asserts "Hsieh 2000 does not refer to serotype 22F glycoconjugates. Ex. 2058, ¶102. 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 1015)*

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. 1015, 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. 1015, 2. Hsieh 2000 teaches that important parameters for conjugate vaccines include molecular size and polysaccharide to protein ratio among others. *See* Ex. 1015, 6. Hsieh

explains that "[i]t is essential to demonstrate the covalent linkage of the saccharide to the carrier protein." Ex. 1015, 8.

2. *Analysis*

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that claim 44 would have been obvious because Hsieh-2000 discloses that size 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. Ex. 2035 ¶¶ 94–96. 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. 2035 ¶ 153. Dr. Lees similarly states that "Hsieh-2000 teaches that a typical degree of conjugation of a successful polysaccharide-CRM_{197} conjugate is 6–9, entirely within the claimed range of 'between 2 and 15' in claim 44." Ex. 1005 ¶ 252. 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. 1015, 8. Thus, the only evidence of record, Hsieh 2000, teaches a degree of conjugation between 6 and 9. Ex. 1015, 8.

We recognize that Dr. Wang raises general concerns about variation in glycoconjugates, without providing specific evidence of unpredictability for 22F. Ex. 2058 ¶ 102. However, Dr. Wang's concerns, balanced against

the statements of Dr. Kasper and Dr. Lees and the specific teachings of Hsieh-2000 do not persuade us that the specific conjugation degree of claim 44 would have been unobvious because 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 GSK-711, Merck-086, 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 <u>22F</u> 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 <u>CRM_{197}</u> 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. Definiteness, Written Description, and Enablement

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 are definite and have adequate written description support.

1. *Claims 46–52 are not indefinite*

i. Claim 46 and 48–52

Petitioner asserts that "the '559 patent fails to provide a definition or other disclosure with respect to how or under what conditions the '2-Log IgG Increase' required by the claims should be measured." Pet. Opp. 3. Petitioner asserts that "[d]ifferent doses can elicit different IgG responses"; "that IgG concentrations can be measured using different assays"; and that

"[i]ndividual animals can have very different baselines for a given serotype." Pet. Opp. 4–5. Petitioner asserts that "a POSA would not be able to determine whether a given immunogenic composition would meet the 2-Log IgG Increase limitation encompassed by the claims." Pet. Opp. 6–7.

Patent Owner asserts Petitioner "offers no evidence to suggest that a variation in any of the parameters of dose, type of assay, or measurement of baseline could affect the comparative analysis across all serotypes of the multivalent vaccine as required by the proposed substitute claims." PO Reply 2.

We agree with Patent Owner that the phrase "2-log IgG increase above baseline" in claim 46 is definite because the dose, assay, and baselines "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 911 (2014).

As to dose, EMA teaches that there is a maximal dose because EMA observes a "dose-dependent increase in IgG level that significantly levelled off with increasing dose increment was demonstrated for most serotypes." Ex. 1102, 14. Merck-086 also states "there did not appear to be a significant benefit in increasing the amount of polysaccharide-conjugate in the vaccine." Ex. 1008 ¶ 118. Dr. Paradiso supports this understanding of doses in pneumococcal vaccines, stating a "POSA would have understood well-known techniques for determining and optimizing dosage, and would also have been aware of studies showing that IgG levels taper off with increased dosage in pneumococcal conjugate vaccines." Ex. 2074 ¶ 6.

We recognize Petitioner's argument that the "fact that Merck and EMA investigated the dose effect shows a general concern that dose could

impact IgG response" (Sur-Reply 4) but find it unpersuasive because the results of the investigation of Merck-086 and EMA demonstrate that as doses increase, the IgG levels stop rising and therefore resolve the concern about dose and IgG response. Moreover, we are also persuaded by Dr. Paradiso that optimizing dosages was well known at the time of invention, and the ordinary artisan would have been known how to optimize doses to obtain a 2-log IgG increase above baseline as required by claim 46.

As to assays and baselines, the World Health Organization (WHO) guidelines state that "[i]mmune responses to pneumococcal conjugate vaccines can be assessed by . . . Determination of serotype-specific IgG antibody geometric mean concentrations (GMCs) based on measurement of binding to polysaccharides (e.g. using an ELISA method). Appendix 1 provides a detailed consideration of the development and standardization of ELISA methods. . . ." Ex. 1019, 126–127. Goldblatt[17] explains that different assays may be standardized to the WHO guidelines using known bridging techniques, specifically stating:

> Subsequent international efforts were therefore focused on establishing guidelines for the performance of a pneumococcal enzyme-linked immunosorbent assay (ELISA) that could match the data obtained by the Wyeth ELISA. The importance of matching the data obtained with the Wyeth assay was underlined with the publication of correlates of protection derived from three efficacy studies, each of which had antibodies measured by the Wyeth assay. These correlates were incorporated into guidelines for licensing new vaccines that rely on assessment of the proportions of samples achieving antibody

[17] Goldblatt et al., *Comparison of a New Multiplex Binding Assay versus the Enzyme- Linked Immunosorbent Assay for Measurement of Serotype-Specific Pneumococcal Capsular Polysaccharide IgG*, 18 Clinical and Vaccine Immunology 1744–51 (2011) (Ex. 2069).

> concentrations above the protective threshold of 0.35 µg/ml by the World Health Organization (WHO) reference ELISA. The guidelines also state that it may be acceptable for manufacturers to employ an alternative threshold value when using a specific in-house assay, provided it can be demonstrated by a well-conducted bridging study to correspond to an IgG concentration of 0.35 µg/ml in the WHO reference ELISA. Therefore, it is critical to use assays that are bridged and are comparable to the original Wyeth assays.

Ex. 2069, 1 (internal citations omitted). Based on these disclosures, Dr. Paradiso concludes a "POSA would have been very familiar with how to measure IgG increases (including fold increases) in NZWR and would have had no uncertainty regarding assay conditions in the context of the proposed substitute claims." Ex. 2074 ¶ 7.

We recognize Petitioner's argument that "IgG concentrations can be measured using different assays" and that "[d]ifferent IgG assays can output different values in different units that could affect the ratio calculation against the baseline." Pet. Opp. 4. We also recognize Petitioner's argument that "without defining what specific assay and assay conditions should be used to measure the serum IgG concentrations, a POSA would not be able to determine if a given immunogenic composition is able to achieve the 2-Log IgG Increase limitation intended by the claims." PO Opp. 5 (citing Ex. 1101 ¶ 33). We find these arguments unpersuasive, however, because the evidence of record, including the WHO guidelines, supports Patent Owner's position that "calculation of the claimed IgG response is explained by the claim and well understood in the art." PO Reply 4. To the extent that the claim broadly encompasses any assay result with a two-log increase from baseline as required by the claim, even "undue breadth is not indefiniteness." *In re Johnson*, 558 F.2d 1008, 1016 n. 17 (CCPA 1977).

ii. Claim 47

Petitioner asserts "claim 47 is indefinite because claim 46 recites 14 different glycoconjugates and it is unclear which glycoconjugate is referred to in claim 47." Pet. Opp. 21

Patent Owner asserts "[t]hat "the glycoconjugate" recited by claim 47 refers to the 22F conjugate of claim 46 is apparent from the context of claim 47 itself. Moreover, "claim 47 narrows the acetate limitation from original claim 2" and is supported by disclosures relating to a 22F conjugate." PO Reply 6.

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.

We, therefore, conclude that a preponderance of the evidence supports the definiteness of proposed amended claims 46–52.

2. *Claim 46–52 have written description support*

i. Claims 46 and 48–52

Petitioner asserts that

> the 2-Log IgG Increase may be impacted by various factors such as the dose amounts administered, the IgG assays used to measure the IgG levels, and the baselines of the NZWRs. Therefore, the '559 patent does not provide sufficient examples to show that any "2-Log IgG Increase" from any "baseline" measured using any assay under any conditions or any dose amounts is an indicator of immunogenicity or efficacy.

Pet. Opp. 7. Petitioner asserts "the '559 patent does not describe any structural difference that correlates with the ability to achieve the 2-Log IgG Increase" and therefore "the substitute claims fail to satisfy the written description requirement because the '559 patent fails to disclose a correlation between structure and function." Pet. Opp. 9–10.

Patent Owner responds that Petitoner "itself admits that this correlation was well known to a POSA, stating: 'IgG levels are one of the indicators of immunogenicity' and a POSA was motivated to achieve the 2-log IgG Increase." PO Reply 1.

We agree with Patent Owner. The '559 patent provides express descriptive support for the phrase "more than a 2-log increase above baseline in serum IgG levels in New Zealand White Rabbits" in claim 46, teaching "[s]erum IgG levels increased more than 2-logs above baseline" in an experiment performed in in New Zealand White Rabbits. Ex. 1001, 123:35–36.

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (*quoting LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005).

As discussed above regarding definiteness, and as will be discussed below regarding obviousness, the Specification demonstrates possession of the 2-log increase limitation. The person of skill in the art would have been familiar with dosing, serum IgG assays, and baselines from the prior art and would have found obtaining a 2-log increase in IgG levels a matter of simple routine optimization based on the detailed knowledge in the art. Ex. 2069, 1; Ex. 2027 ¶ 231, Table 3.

ii. Claim 47

Petitioner asserts that "nothing supports 'at least 0.8 mM acetate per mM polysaccharide' recited in claim 47." Pet. Opp. 21.

Patent Owner asserts "'claim 47 narrows the acetate limitation from original claim 2' and is supported by disclosures relating to a 22F conjugate." PO Reply 6.

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.

We, therefore, conclude that a preponderance of the evidence demonstrated descriptive support in the '559 patent for proposed amended claims 46–52.

3. *Claim 46–52 are enabled*

Petitioner asserts "[i]f Pfizer asserts that a POSA would not have had a reasonable expectation that additional serotypes could be successfully

added to Prevnar13® due to immune interference, then claim 46 is not enabled for the full scope of the claim." Pet. Opp. 21.

Patent Owner asserts the "'559 patent provides detailed guidance on how the conjugates were created, formulation of the immunogenic composition, and the tests for the measurement of the 2-log IgG Increase. Sanofi identifies no lack of guidance in the '559 patent nor experimentation that is undue." PO Reply 5.

We agree with Patent Owner that there is no evidence of record to support a finding that claims 46–52 are not enabled for their full scope. By contrast, prior art including Hausdorff, Merck-086, and GSK-711, demonstrate the immunogenicity of pneumococcal vaccines, along with the disclosure of the '559 patent itself. Ex. 2027 ¶ 231, Table 3; Ex. 1008 ¶ 114; Ex. 1007, 67:36–37; Ex. 1001, 123:35–36. Petitioner provides no evidence of unpredictability or lack of teaching by the '559 patent. Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

We, therefore, conclude that a preponderance of the evidence supports enablement of the '559 patent for proposed amended claims 46–52.

D. Unpatentability

Petitioner asserts that proposed substitute claims 46–52 are unpatentable as obvious over the combination of Hausdorff, Merck-086, GSK-711, and the knowledge of the ordinary artisan. Pet. Opp. 10–21; *see also* Pet. Sur-Reply 6–12. To support its Opposition, Petitioner proffers the declaration of Dr. Van Alphen and the deposition of Dr. Paradiso. Ex. 1101; Ex. 1105.

Patent Owner disagrees. PO Reply 6–12. To support its Reply, Patent Owner proffers the declarations of Dr. Paradiso (Ex. 2051; Ex. 2074).

We determine that claims 46 and 48–52 would have been obvious over the combination of Hausdorff, Merck-086, GSK-711, and the knowledge of the skilled artisan. We determine that claim 47 would have been obvious with the further addition of PVP-2013 and Lees-2008.

1. Claims 46 and 48–52 are obvious over Hausdorff, Merck-086, GSK-711, 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 6B) formulated with or without $AlPO_4$ (100 μg/dose). Sera were collected at various time points. Serotype specific IgG was

measured by ELISA and functional activity was assessed by OPA.

Ex. 2027 ¶ 230.

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

TABLE 3

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

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

[a]GMTs of pooled sera consisted of equal volumes of serum from each individual rabbit within a group

[b]Statistically different (p = 0.022) from treatment group without $ALPO_4$

Table 3, reproduced above, shows 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-086 (Ex. 1008)

As discussed above in Section II.C.1, Merck-086 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. 1008 ¶ 2. Table 1 of Merck-086 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. 1008 ¶ 104.

Merck-086 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. 1008 ¶ 115.

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.

Merck-086 teaches the "fold-rise in antibody levels to the non-Prevnar® serotypes from Day 0 to Day 28 (Post-dose 2, PD-2) are summarized in Table 4." Ex. 1008 ¶ 117.

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

c. GSK-711 (Ex. 1007)

As discussed above in Section II.C.2, GSK-711 teaches "the multivalent pneumococcal vaccine of the invention will be selected from the following serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F." Ex. 1007, 7:1–3. GSK 2008 teaches conjugation of polysaccharides to the carrier protein CRM_{197} (*see* Ex. 1007, 10:4–6) and teaches "[p]referably the ratio of carrier protein

to *S. pneumoniae* saccharide is between 1:5 and 5:1." Ex. 1007, 19:1. GSK-711 further teaches in claim 61 an "immunogenic composition of any preceding claim wherein the average size (e.g. M_w) of the saccharides is above 50 kDa, e.g[.], 50-1600. . . ." Ex. 1007, 82.

d. Analysis

i. Claim 46

Petitioner asserts "proposed substitute claim 46 is obvious over the prior art." Pet. Opp. 10. Petitioner asserts "Merck-086 discloses an immunogenic PCV15 composition including pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, all individually conjugated to CRM197." Pet. Opp. 10 (citing Ex. 1008 ¶¶ 2, 86, 102, 103). Petitioner asserts that "PCV15 also contained an aluminum phosphate adjuvant (APA), which is an aluminum salt adjuvant." Pet. Opp. 10 (citing Ex. 1008 ¶¶ 41, 42). Petitioner points out that consistent with our decision on the original claims above, Patent Owner "cannot rely on the molecular weight and ratio ranges for patentability of claim 46 because these features have already been determined to be obvious." Pet. Opp. 11. Petitioner concludes that "[t]herefore, Merck-086 discloses all relevant structural features recited in substitute claim 46." Pet. Opp. 10–11.

Petitioner asserts, regarding the functional requirement of a 2-log IgG increase, that "Merck-086 demonstrates that its PCV15 composition is highly immunogenic in infant rhesus monkeys and NZWRs." Pet. Opp. 11 (citing Ex. 1008 ¶ 122). Petitioner asserts that "Merck-086 discloses that some, but not all, serotypes in PCV15 achieved the recited 2-Log IgG Increase in NZWRs." Pet. 11 (citing Ex. 1008, Table 4).

Petitioner asserts that "Hausdorff showed that 13vPnPC (Prevnar13®) achieved a 2-Log IgG Increase or higher across all serotypes (at least in one study)." Pet. Opp. 13 (citing Ex. 2027, Table 3). Petitioner asserts that "[b]ecause Prevnar13® has become one of the most successful multivalent PCVs since its approval in 2009, a POSA seeking to add serotype 22F to Prevnar13® in January 2014 would have been motivated to achieve the same." Pet. Opp. 13 (citing Ex. 1101 ¶¶ 59–64).

Petitioner asserts that Hausdorf's "data demonstrated that for a reasonably immunogenic multivalent PCV composition, a 2-Log IgG Increase across all serotypes can be achieved by optimizing the baseline, and/or the dose or adjuvant amounts." Pet. Opp. 14 (citing Ex. 1101 ¶ 61). Petitioner asserts that "[i]n Hausdorff, routine optimization of the baseline, the dose and the adjuvant amount resulted in approximately a **3-fold** difference in IgG fold increase from baseline for serotype 1 in 13vPnPC, i.e., from **76.5-fold** in Study #HT01-0036 (Table 5) to **222-fold** in Study #HT01-0021 (Table 3)." Pet. Opp. 14 (citing Ex. 1101 ¶ 63).

Petitioner asserts that "Merck-086 recognized the variability issue associated with NZWRs and other animals, especially when a small number of animals is used in studies." Pet. Opp. 17 (citing Ex. 1101 ¶ 70). Petitioner asserts that because Merck-086 found "'2.5 fold was regarded as a meaningful response threshold'" then "serotype-specific IgG responses were not meaningfully different if the difference was within 2.5-fold." Pet. Opp. 17 (citing Ex. 1101 ¶70).

Petitioner also asserts that Dr. Paradiso held the position in a published paper that "CRM_{197}-based conjugates made it possible to induce good immunity to new '***without negatively affecting the components***

already in the vaccine.'" Pet. Opp. 18 (citing Ex. 1107, 3 (emphasis added in Pet. Opp.)). Petitioner asserts that Dr. Paradiso testified "that immune interference only means that there is a reduced immune response and that the existence of immune interference *per se* would not preclude one from developing an efficacious vaccine.'" Pet. Opp. 19 (citing Ex.1105, 81:13–84:8–17).

Patent Owner asserts Petitioner "has not directed the PTAB to prior art of record that teaches the claimed limitations of "molecular weight" and "ratio (w/w) of the [22F] polysaccharide to the [CRM_{197}] carrier protein" required by every proposed substitute claim." PO Reply 6.

Patent Owner asserts "[e]ven if a POSA could have tripled the IgG-fold increases of the PCV-15 in Merck-086 through routine optimization, as Sanofi asserts (*see* Opp. at 14-15), a POSA would have no basis to believe that the tripled unknown values would meet the claimed 2-log IgG Increase across all serotypes" PO Reply 7 (citing Ex. 2074 ¶ 14). Patent Owner asserts "Table 4 of Merck-086 shows that serotypes 1 and 3 (required by all proposed substitute claims) and 33F (required by proposed substitute claim 48) of PCV-15 of Merck-086 never achieved a 2-log IgG Increase across four separate groups of NZWR." PO Reply 7 (citing Ex. 2074 ¶ 16). Patent Owner asserts "Figure 2 of Merck-086 shows that after two doses, the vaccine failed to elicit a 2-log IgG Increase in serum IgG levels in IRM for at least serotypes 1, 3, 5, 6A, 7F, 19A, and 22F." PO Reply 8 (citing Ex. 2051 ¶ 67). Patent Owner asserts "[l]acking any supporting disclosure in the art, Sanofi instead alleges that a POSA would have been motivated to 'optimize' the PCV-15 described by Merck-086 to achieve the 2-log

increase, but Dr. Van Alphen admits that this is based on hindsight." PO Reply 7–8 (citing Ex. 2073, 115:17–116:23).

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

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

Ex. 2074 ¶ 27). Patent Owner asserts "a POSA would have concluded that PCV-15 of Merck-086 likely suffered from immune interference." PO Reply 11 (citing Ex. 2074 ¶ 28).

Patent Owner also asserts "[l]ong felt need for the immunogenic compositions of the proposed substitute claims and the failure of others to formulate a composition eliciting the efficacy associated with the 2-log IgG Increase further demonstrate that the proposed substitute claims are not obvious.'" PO Reply 11–12. Patent Owner asserts "Pfizer's 16- and 20-valent pneumococcal conjugate vaccines, embodiments of the proposed substitute claims, meet the long felt need for coverage of serotypes 22F (claim 46), 33F, and 15B (claim 48) with a 2-log IgG Increase maintained for all serotypes in the vaccine." PO Reply 12 (citing Ex. 2074 ¶ 30). Patent Owner asserts "[t]o date, there are no licensed vaccines that cover the serotypes required by claim 46 and its dependent claims." PO Reply 12 (citing Ex. 2074 ¶ 31).

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-086 and GSK-711—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-086 states "the addition of new polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses [and]

demonstrates the feasibility of expanding coverage of pneumococcal serotypes not covered by existing pneumococcal vaccines." Ex. 1008 ¶ 15. GSK-711 states:

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

Ex. 1007, 5:18–22. Thus, both Merck-086 and GSK-711 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. Van Alphen states that

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

Ex. 1101 ¶ 59–60. Dr. Van Alphen states that the data in Hausdorf "demonstrated that for a reasonably immunogenic multivalent PCV composition, a 2-Log IgG Increase from baseline across all the serotypes can be achieved by routine optimization of test conditions, for example, the baseline (using different animals), the dose or adjuvant amounts, and others." Ex. 1101 ¶ 61.

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

We are also unpersuaded by Patent Owner's assertion that "a POSA would not have been able to optimize the baseline because it is not feasible to procure NZWR with a specific baseline or exclude certain NZWR from experiments." PO Reply 9. Dr. Van Alphen stated "[t]here was a clear

motivation to further increase the IgG levels above the baseline for all serotypes as serum IgG levels are one of the indicators of immunogenicity of vaccine." Ex. 1101 ¶ 51 (citing Ex. 1053, 100–101). Dr. Van Alphen further stated with regard to Hausdorf that "for a reasonably immunogenic multivalent PCV composition, a 2-Log IgG Increase from baseline across all the serotypes can be achieved by routine optimization of test conditions, for example, the baseline (using different animals)." Ex. 1101 ¶ 61.

Dr. Van Alphen's optimization reasoning is supported by Dr. Paradiso's response to the question "what are some of the factors that would impact the level of the baseline," where Dr. Paradiso stated "previous exposure to the bacteria or previous immunization, two that come to mind." Ex. 1105, 104:11–18. Thus, the baseline could be routinely reduced by selecting germ-free animals that were never immunized or increased by selecting exposed animals already subjected to immunization, rendering this a results optimizable variable known in the prior art. Ex. 1101 ¶ 61; Ex. 1105, 104:11–18.

We recognize Patent Owner correctly notes that Merck-086 only obtained a 2-log increase of serum IgG levels in serotype 22F conjugates in two of the four arms, and annotates Figures 3 and 4 in Merck 2011 to identify particular experimental results that did not satisfy the 2-log increase. PO Reply 7–8. 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-086 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. *See* Ex. 1008 ¶¶ 7, 117, Table 4.

We note that "this is not the case where the prior art teaches merely to pursue a 'general approach that seemed to be a promising field of experimentation' or 'gave only general guidance as to the particular form of the claimed invention or how to achieve it.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) (*quoting O'Farrell*, 853 F.2d at 903; *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1167 (Fed. Cir. 2006)). Here, both Merck-086 and GSK-711 specifically suggested incorporation of 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. 1008 ¶ 15; Ex. 1007, 5:18–22; Ex. 2027 ¶ 231, Table 3.

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

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

We also conclude that even if some degree of immune interference resulted from the addition of the serotype 22F conjugate, Dr. Van Alphen states "the overall benefit of the new multivalent conjugate vaccine composition based on both epidemiology consideration and regulatory

consideration could outweigh the reduced immune response to a particular serotype and the new multivalent conjugate vaccine could still be efficacious and approved." Ex. 1101 ¶ 80. This is consistent with Patent Owner's expert, Dr. Paradiso's opinion, who answered "Correct" in response to a question asking "one of the trade-offs that you would consider is whether a reduced immune response with respect to an individual serotype in the multivalent immunogenic composition made it worth – still worthwhile or not worthwhile to develop the vaccine, correct?" Ex. 1105, 82:20–83:2.

Thus, we find that a preponderance of the evidence supports a determination that there would have been a reasonable expectation of success in obtaining a fourteen serotype pneumococcal vaccine composition as required by claim 46 with 2-fold increases in IgG responses in New Zealand White Rabbits because Merck-086 itself exemplifies 2-fold increases in IgG responses in New Zealand White Rabbits for serotype 22F conjugates, and because Paradiso-2009 supports 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. 1008 ¶ 15; Ex. 1107, 3.

We are not persuaded by Patent Owner's assertion of long-felt need because, as Petitioner points out, Patent Owner "fails to produce any objective evidence that the need for the immunogenic compositions of the substitute claims, specifically eliciting the 2-log IgG Increase is an art-recognized problem." Pet. Sur-Reply 10. Indeed, Patent Owner provides no objective evidence establishing any of the three elements necessary for long felt need: (i) the need must have been a persistent one that was recognized by ordinarily skilled artisans (ii) the long-felt need must not have been

satisfied by another before Appellants' invention; and (iii) the invention must, in fact, satisfy the long-felt need. *In re Gershon*, 372 F.2d 535, 538 (CCPA 1967); *Newell Companies, Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988); *In re Cavanagh*, 436 F.2d 491, 496 (CCPA 1971).

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

Lastly, Patent Owner does not provide objective evidence that the claimed invention satisfies the need because Patent Owner acknowledges that "[t]o date, there are no licensed vaccines that cover the serotypes required by claim 46 and its dependent claims." PO Reply 12. To the extent that Patent Owner asserts that the only way to satisfy the long-felt need is by a licensed vaccine, rather than a disclosed composition such as PCV-15, Patent Owner has not established with objective evidence that the composition of claim 46 is a licensed vaccine. We do not, however, take such a narrow view of satisfying the long-felt need, but instead find that PCV-15 itself can reasonably be identified as satisfying the long-felt need consistent with Dr. Paradiso's statement that PCV-15 and Prevnar 13 would

show "[c]omparability using the WHO standard." Ex. 1116, 43:10. Thus, even if we credit the claimed composition as also satisfying the long-felt need, there is no evidence that it was not previously satisfied by PCV-15.

We conclude that claim 46 would have been obvious over Hausdorff, Merck-086, GSK-711, and the knowledge of the ordinary artisan.

IV. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude Exhibit 1101. Paper 45 ("Patent Owner Mot. to Exclude").

Patent Owner asserts that we should exclude Exhibit 1101 because Dr. Van Alphen "analyzed the proposed amended claims by considering only select limitations and disregarding entirely the limitations reciting molecular weight" and "ratio (w/w) of the [22F] polysaccharide to the [CRM_{197}] carrier protein" required by every proposed substitute claim." Paper 45, 2. Patent Owner asserts that Dr. Van Alphen "failed to apply reliable principles and methods to the facts of the case in contravention of Fed. R. Evid. 702." Paper 45, 3.

Petitioner asserts that "Dr. Van Alphen carefully considered and addressed each and every limitation recited in the proposed substitute claims, and reliably applied the obviousness legal standard to the facts of this case." Paper 49, 2. Petitioner asserted that Dr. Van Alphen "specifically explained that he based his opinion also on the *lack of any evidence* provided by Pfizer suggesting that combining a 22F-CRM_{197} conjugate with the recited 'MW' and 'PS-to-protein' ratio ranges with the 13 serotypes from Prevnar13® individually conjugated to CRM_{197} is inventive." Paper 49, 4.

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).

Pursuant to FRE 702, a witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of opinion. Patent Owner does not dispute that Dr. Van Alphen is an expert, only that he relied upon Petitioner's prior evidence that the molecular weight and serotype 22F polysaccharide to carrier protein ratio would have been obvious. This argument goes more towards the weight we should afford the Declaration of Dr. Van Alphen, rather than its admissibility. It is within our discretion to assign the appropriate weight to the testimony offered by Dr. Van Alphen. *See, e.g., Yorkey v. Diab*, 601 F.3d 1279, 1284 (Fed. Cir. 2010) (holding the Board has discretion to give more weight to one item of evidence over another "unless no reasonable trier of fact could have done so"); *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) ("[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations.").

We deny Patent Owner's request to exclude Exhibit 1101.

V. PETITIONER'S MOTION TO EXCLUDE

Petitioner moves to exclude the following Exhibits, or portions thereof: Exhibits 2016–2019, Exhibit 2051 in part, Exhibit 2058, and Exhibit 2074 in part. Paper 44 ("Petitioner Mot. to Exclude").

As to Exhibits 2016–2019 and Exhibit 2051, we do not rely on any of these Exhibits in making our ultimate determination on the patentability of

the challenged claims. Accordingly, we need not decide Petitioner's motion as to those exhibits and paragraphs, and we dismiss that portion of Petitioner's motion as moot.

Petitioner asserts, regarding Exhibit 2058, that "Dr. Wang failed to reliably apply the correct legal standard for obviousness to the facts of this case. Therefore, Dr. Wang's opinions are unreliable and should be excluded under FRE 702." Paper 44, 10. Petitioner asserts, regarding Exhibit 2074, that "Dr. Paradiso's opinions . . . are unreliable because Dr. Paradiso failed to provide sufficient underlying data such that a POSA would have a reasonable basis to believe that his conclusion is correct." Paper 44, 13. Petitioner similarly asserts that other portions of Dr. Paradiso's testimony lack sufficient underlying data. Paper 44, 14.

Patent Owner asserts, regarding Exhibit 2058, that Petitioner's "argument goes to the sufficiency of the evidence and is not a proper basis to exclude all of Dr. Wang's testimony." Paper 48, 10. Patent Owner asserts, regarding Exhibit 2074, that Petitioner's "challenge is directed to the sufficiency, rather than admissibility of the evidence and is improper." Paper 48, 6, 9.

As already noted, FRE 702 authorizes a witness who is qualified as an expert by knowledge, skill, experience, training, or education to testify in the form of opinion. Petitioner does not dispute that either Dr. Wang or Dr. Paradiso are experts, only that they either relied upon an incorrect legal standard in formulating their opinions or lacked sufficient underlying data. These arguments go more towards the weight we should afford the Declarations of Dr. Wang and Dr. Paradiso, rather than their admissibility. It is within our discretion to assign the appropriate weight to the testimony

offered by Dr. Wang and Dr. Paradiso. *Yorkey,* 601 F.3d at 1284; *In re Am. Acad. of Sci. Tech Ctr*., 367 F.3d at 1368.

We deny Petitioner's request to exclude Exhibit 2058 and Exhibit 2074.

V. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that (1) claims 1, 3–19, 23–37, 41, 42, and 45 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, (2) claims 2, 40, and 43 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, Lees-2008, PVP 2013, Pfizer-605; (3) that claims 20–22 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, GSK-531; (4) that claims 38 and 39 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, Pfizer-605; and (5) that claim 44 is unpatentable as obvious over the combination of GSK-711, Merck-086, 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.

We deny Patent Owner's Motion to exclude Exhibit 1101.

We dismiss Petitioner's Motion to exclude Exhibit 2016–2019 and Exhibit 2051 as moot.

We deny Petitioner's Motion to exclude Exhibits 2058 and 2074.

VI. ORDER

For the reasons given, it is

ORDERED, based on a preponderance of the evidence, that claims 1–45 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 Exhibit 1101 is denied;

FURTHER ORDERED, Petitioner's Motion to Exclude Exhibits 2016–2019 and 2051 is dismissed as moot;

FURTHER ORDERED, Patent Owner's Motion to Exclude Exhibits 2058 and 2074 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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