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Paper 43
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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 IPR2017-02136
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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