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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME CORP.,
Petitioner,

v.

PFIZER INC.,
Patent Owner.

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Case IPR2017-02131
Patent 9,492,559 B2

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

FREDMAN, *Administrative Patent Judge*.

# DECISION
Institution of *Inter Partes* Review
*37 C.F.R. § 42.108*

# I. INTRODUCTION

## *A. Background*

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition (Paper 1, "Pet.") requesting an *inter partes* review of claims 1–10, 16–19, and 38–45 (the "challenged claims") of U.S. Patent No. 9,492,559 B2 (Ex. 1001, "the '559 patent"). *See* 35 U.S.C. §§ 311–319. Pfizer Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims of the '559 patent. Therefore, we institute an *inter partes* review for claims 1–10, 16–19, and 38–45 of the '559 patent.

## *B. Related Proceedings*

Petitioner indicates that three concurrent Petitions for *inter partes* review of the '559 patent were filed (IPR2017-02132, IPR2017-02136, IPR2017-02138), that IPR2017-00378, IPR2017-00380, and IPR2017-00390 were instituted with respect to US Patent 8,562,999, and that several PGR and IPR petitions were also filed with respect to US Patent 9,399,060 and 8,895,024. Pet. 5.

## *C. The '559 Patent (Ex. 1001)*

The '559 patent "relates to 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.

The '559 patent teaches the "etiological agent of pneumococcal diseases, *Streptococcus pneumoniae* (pneumococcus), is a Gram-positive encapsulated coccus,[1] surrounded by a polysaccharide capsule.[2] Differences in the composition of this capsule permit serological differentiation between about 91 capsular types." *Id.* at 1:49–53. "Pneumococcal conjugate vaccines (PCVs) are pneumococcal vaccines used to protect against disease caused by *S. pneumoniae* (pneumococcus)." *Id.* at 1:59–61. "There are currently three PCV vaccines[3] available on the global market: PREVNAR® (called PREVENAR® in some countries) (heptavalent vaccine), SYNFLORIX® (decavalent vaccine) and PREVNAR 13® (tridecavalent vaccine)." *Id*. at 1:61–64.

The '559 patent teaches "there is a need to address remaining unmet medical need for coverage of pneumococcal disease due to serotypes not

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

[2] "Pneumococcus is encapsulated with a chemically linked polysaccharide which confers serotype specificity. There are 90 known serotypes of pneumococci, and the capsule is the principle virulence determinant for pneumococci, as the capsule not only protects the inner surface of the bacteria from complement, but is itself poorly immunogenic." Ex. 1007, 2:10–14.

[3] The valency of a vaccine refers to the number of different serotypes of bacteria to which the vaccine induces immune response (e.g. a heptavalent vaccine protects against seven different bacterial strains).

found in PREVNAR 13® and potential for serotype replacement over time." *Id*. at 2:3–6.

*D. Illustrative Claims*

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

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

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

*E. The Asserted Grounds of Unpatentability*

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 6–7.

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

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

Petitioner relies on the Declaration of Dennis L. Kasper, M.D. Ex. 1004.

## *II.* ANALYSIS

### *A. Claim Interpretation*

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under the broadest reasonable interpretation approach, claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir.

[5] Caulfield et al., WO 2011/100151 A1, published Aug. 18, 2011 ("Merck 2011," Ex. 1006).
[6] Biemans et al., WO 2009/000825 A2, published Dec. 31, 2008 ("GSK 2008," Ex. 1007).
[7] "Pneumococcal Vaccine Polyvalent" revision to Japan's "Minimum Requirements for Biological Products" published on the website of Japan's National Institute of Infectious Diseases (as of March 2, 2013) ("PVP 2013," Ex. 1009).
[8] Hsieh, *Characterization of Saccharide-CRM$_{197}$ Conjugate Vaccines*, 103 DEV. BIOL. 93–104 (2000) ("Hsieh 2000," Ex. 1013).

2011); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

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

1. "*immunogenic*"

Petitioner "submits that the broadest reasonable interpretation of the term 'immunogenic' is 'elicits functional antibody against at least pneumococcus serotype 22F.'" Pet. 29 (citing Ex. 1004 ¶ 64). Patent Owner "does not dispute . . . the aspect of Merck's proposal requiring that the 'immunogenic' composition 'elicits functional antibody.'" Prelim. Resp. 10. Patent Owner "disagrees, however, with the inclusion of 'at least pneumococcus serotype 22F' in Merck's proposal." *Id.* According to Patent Owner, "[t]he proper construction of 'immunogenic' is 'elicits functional antibody against each serotype in the claimed composition.'" *Id.*

We agree with the parties that the preamble language gives life and meaning to the claims by limiting the composition to require an antibody response. *See* Ex. 1001, 141:27–33, claim 1. *See Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002) ("Diagnosis is thus the essence of this invention; its appearance in the [claim] gives 'life and meaning' to the manipulative steps."). Furthermore, consistent with the interpretations advanced by the parties, we determine that the broadest reasonable interpretation of "immunogenic" requires a composition that "elicits functional antibody."

The parties incorporate into their proposed constructions of "immunogenic" arguments concerning the identity of the serotypes for which functional antibody must be elicited. In particular, Petitioner contends that the recited "immunogenic composition" must "elicit[]

functional antibody against at least pneumococcus serotype 22F" (Pet. 32), whereas Patent Owner asserts that "term should be construed to require demonstration of immunogenicity against each serotype in the claimed composition" (Prelim. Resp. 11). We determine, based on the current record, that the claims, considered overall, require the "immunogenic" composition to elicit antibodies against serotype 22F glycoconjugate in claim 1. *See* Ex. 1001, 141:47–49, claim 5. Independent claim 1 does not specifically require any additional glycoconjugates besides 22F and, therefore, reasonably need not include other immunogenic serotypes.

*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;[9] and (4) where in evidence, objective

[9] Petitioner states that the level of skill in the art at the time of the invention "would have been an individual or team with Ph.D. degrees in the biological and chemical sciences and at least 3 years of work experience, or an M.D. degree and at least 6 years of work experience, developing conjugate vaccines, including specifically growing sufficient quantities of bacteria, extracting, purifying and analyzing bacterial polysaccharides, conjugating polysaccharides to a carrier protein (and analyzing the conjugates), and performing immunologic testing." Pet. 27–28, citing Ex. 1004 ¶ 59. Patent Owner "does not dispute Merck's proposed level of skill for the person

indicia of nonobviousness. *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).

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having ordinary skill in the art." Prelim. Resp. 10. 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).

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

*C. Section 325(d) – Discretion to Decline to Institute*

Patent Owner urges us to decline to institute the asserted grounds under 35 U.S.C. § 325(d) "because Merck 2011 and GSK 2008, which are at the center of Grounds 1-3 of the Petition, are cumulative of US 2013/0273098 ("Blue 2013"- EX2001) and WO 2009/000826 ("the WO '826 application"- EX2002), respectively, which were before the Patent Office during prosecution." Prelim. Resp. 11. Patent Owner contends that "Merck 2011 is substantially the same as Blue 2013" and that Petitioner "relies upon language in Merck 2011 concerning multivalent vaccines comprising a 22F glycoconjugate (Pet. at 45, 47-51; EX1006 at 11:31-33) that is identical to language in Blue 2013." Prelim. Resp. 13. Patent Owner contends: "Although the Examiner did not explicitly rely on Blue 2013 in rejecting the claims, the Examiner's signature on the PTO/SB/429 form indicates that the Examiner did in fact consider the submission." Prelim. Resp. 14.

Similarly, Patent Owner contends "GSK 2008 is 'substantially the same' as the WO '826 application. The WO '826 application was considered by the Examiner during prosecution of the '488 application (which later issued as the '559 patent), and is listed on the face of the '559 patent." Prelim. Resp. 14–15.

Patent Owner contends:

> The mailing of the Notice of Allowability confirms that the Examiner did not consider the '559 patent claims to be obvious over Blue 2013 or the WO '826 application. . . . Since the Examiner already considered and decided not to pursue the

> obviousness arguments based on prior art references substantially similar to those raised by the Petition, Pfizer requests the Board reject the Petition on this basis alone.

Prelim. Resp. 17.

Under § 325(d), we have discretion to "reject the petition or request because[] the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). While Blue 2013 and the WO '826 application are similar to the currently relied upon Merck 2013 and GSK 2008, they are among numerous cited references listed on the front of the '559 patent (Ex. 1001, references cited section) and were not cited by the Examiner or specifically relied upon by the Examiner during prosecution. *See* Prelim. Resp. 14. Petitioner also relies on a declaration from Dr. Kasper, which Patent Owner does not allege is duplicative of evidence previously presented to the Office. *See Tandus Flooring, Inc. v. Interface, Inc.*, Case IPR2013-00333, 2013 WL 8595289, at *2 (PTAB Dec. 9, 2013) (Paper 16) (declining to deny petition under § 325(d) where petitioner presented new declaration evidence). The Kasper Declaration presents the molecular weight and ratio evidence in a new light by explaining the underlying understanding of a person of ordinary skill in the art regarding molecular weight ranges and ratios for polysaccharide conjugates. Ex. 1004 ¶¶ 106–111, 114–119.

Considering all of the relevant facts and circumstances, Patent Owner's argument is insufficient to persuade us to exercise our discretion to deny the Petition under 35 U.S.C. § 325(d).

*D. Obviousness over Merck 2011 and GSK 2008*

Petitioner contends that claims 1, 3–10, 16–19, 39, 41, 42, and 45 are unpatentable under 35 U.S.C. § 103(a) as obvious over Merck 2011, GSK 2008, and the general knowledge of an ordinary artisan. Pet. 33. Patent Owner opposes this ground. Prelim. Resp. 18–47.

1. *Merck 2011 (Ex. 1006)*

Merck 2011 teaches "a multivalent immunogenic composition having 15 distinct polysaccharide-protein conjugates. Each conjugate consists of a capsular polysaccharide prepared from a different serotype of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F or 33F) conjugated to a carrier protein, preferably $CRM_{197}$." Ex. 1006, 1:7–11. Merck 2011 teaches "conjugates containing serotypes 22F and 33F provide[] robust antibody responses demonstrat[ing] the feasibility of expanding coverage of pneumococcal serotypes. . . ." Ex. 1006, 4:2–3. Merck 2011 teaches the pneumococcal conjugate vaccine (PCV) with "induced high OPA[10] 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."

[10] Opsonophagocytosis.

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

2. *GSK 2008*

GSK 2008 teaches a *Streptococcus pneumoniae* vaccine comprising "capsular saccharide antigens (preferably conjugated), wherein the saccharides are derived from at least ten serotypes of *S. pneumoniae*" that may include an "*S. pneumoniae* saccharide conjugate of 22F." Ex. 1007, 8:5–19. GSK 2008 teaches "*Streptococcus pneumoniae* capsular saccharides . . . may be conjugated to a carrier protein independently selected from the group consisting of . . . CRM197. . . ." Ex. 1007, 10:12–14. GSK 2008 teaches "saccharide conjugates present in the immunogenic compositions of the invention may be prepared by any known coupling technique" and specifically, conjugates "can also be prepared by direct reductive amination methods. . . ." Ex. 1007, 17:1–28. GSK 2008 teaches "22F-PhtD administered within the 13-valent conjugate vaccine formulation [was] shown immunogenic and induced opsono-phagocytic titers in young OF1 mice." Ex. 1007, 77:21–22.

GSK 2008 teaches: "Preferably the ratio of carrier protein to *S. pneumoniae* saccharide is between 1:5 and 5:1; e.g. between 1:0.5–4:1, 1:1–3.5:1, 1.2:1–3:1, 1.5:1–2.5:1; e.g. between 1:2 and 2.5:1; 1:1 and 2:1 (w/w)." Ex. 1007 20:24–26. Table 2 of GSK 2008 teaches fourteen different conjugates—the smallest conjugate size was PS4-PD of 1303 kDa and the largest conjugate size was PS9V-PD of 9572 kDa. Ex. 1007, 54–55, Table

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

GSK 2008 claims a conjugate where "the average size (e.g. $M_w$) of the 22F saccharide is between 50 and 800 kDa. . . ." Ex. 1007, 93, claim 56. GSK 2008 further teaches in claim 61 an "immunogenic composition of any preceding claim wherein the average size (e.g. $M_w$) of the saccharides is above 50 kDa, e.g, 50–1600. . . ." Ex. 1007, 94.

GSK 2008 teaches "immunogenic conjugates prone to hydrolysis may be stabilised by the use of larger saccharides for conjugation. The use of larger polysaccharides can result in more cross-linking with the conjugate carrier and may lessen the liberation of free saccharide from the conjugate." Ex. 1007, 14:18–21. GSK 2008 teaches "that saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease." Ex. 1007, 14:23–25. GSK 2008 recommends optimization for larger size saccharide-protein conjugates, limited only by a requirement to be "filterable through a 0.2 micron filter. . . ." Ex. 1007, 14:34.

3. *Analysis*

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

that approximate molecular weight range." Pet. 36 (citing Ex. 1004 ¶ 106). Petitioner also asserts "Merck 2011 and GSK 2008 both disclose the claimed range of conjugate polysaccharide to protein ratios (0.4 to 2), and reflect a POSITA's general understanding that conjugate polysaccharide to protein ratios in the claimed range are typical for immunogenic conjugates." Pet. 42 (citing Ex. 1004 ¶ 114).

Petitioner's Declarant, Dr. Kasper, states that a "POSITA would have considered the disclosure of pre-conjugation polysaccharide to $CRM_{197}$ ratios in the range of 0.2 to 2 indicative of a final conjugate ratio in that range." Ex. 1004 ¶ 115 (citing Ex. 1006 17:24–25). Dr. Kasper notes "the pre-conjugation ratios of Merck 2011 resulted in an average polysaccharide to protein ratio in the conjugates of approximately 1 (~32 μg of polysaccharide and ~32 μg of protein), squarely in the claimed range." Ex. 1004 ¶ 115 (citing Ex. 1006, 19:3–8). Dr. Kasper also notes "a POSITA's general understanding that conjugate polysaccharide to protein ratios in the claimed range (0.4 to 2) are typical for immunogenic conjugates" and cites a monograph disclosing ratios of saccharide to protein in a pneumococcal $CRM_{197}$ conjugate vaccine with seven serotypes, concluding that each "disclosed ratio overlaps to a large extent with the claimed ratio of 0.4 to 2, consistent with the general understanding in the art as of January 21, 2014 that such ratios are typical for immunogenic conjugates." Ex. 1004 ¶¶ 118–119 (citing Ex. 1085, 20–24).

Dr. Kasper states "GSK 2008 discloses that '[p]referably the ratio of carrier protein to *S. pneumoniae* saccharide is . . . between 1:2 and 2.5:1 . . . (w/w),' which translates to a polysaccharide to protein ratio of 1:2.5 to 2:1, *i.e.*, the claimed polysaccharide to protein ratio of 0.4 to 2." Ex. 1004 ¶ 116

(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. 1004 ¶ 116 (citing Ex. 1007 54:27 to 55:1). Dr. Kasper also relies upon a monograph that "specifies the acceptable range of 'Saccharide content/protein ratio' (which a POSITA would have understood to be a w/w ratio)" and that "[e]ach disclosed ratio overlaps to a large extent with the claimed ratio of 0.4 to 2. . . ." Ex. 1004 ¶¶ 118–119 (citing Ex. 1085, 20–24).

Dr. Kasper states "the conjugate molecular weights that were determined (for every conjugate of the underlying 10-valent composition) ranged from 1,303-9,572 kDa, squarely within the claimed molecular weight range." Ex. 1004 ¶ 106. Dr. Kasper states "GSK 2008 discloses that the serotype 22F polysaccharide in its immunogenic conjugates can be, *e.g.*, 'between 50 and 800 kDa.'" Ex. 1004 ¶ 107 (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. 1004 ¶ 108 (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. 1004 ¶ 108 (citing Ex. 1006 16:30–31 and Ex. 1007 14:13–15).

Dr. Kasper states a "POSITA's motivation and reasonable expectation of success would have been further supported by the fact that Patent Owner

disclosed in a scientific meeting in 2012 that the 'Typical Mass (kDa)' for a glycoconjugate is '500-5000,' largely overlapping with the range recited in GSK 2008 (and claim 1)." Ex. 1004 ¶ 109 (citing Ex. 1008, 6). Dr. Kasper states "Patent Owner even disclosed in a scientific meeting in 2007 that its own pneumococcal conjugates can be as large as ~7,000 to ~12,000 kDa, again overlapping with the range of GSK 2008 (and completely within the claimed range)." Ex. 1004 ¶ 109 (citing Ex. 1027, 21). Dr. Kasper states:

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

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

We find that the current evidence of record in Merck 2011 and GSK 2008, as supported by Dr. Kasper, provides a reasonable likelihood that the references render the subject matter of claims 1, 3–10, 16–19, 39, 41, 42, and 45 obvious because the evidence currently of record supports Petitioner's position that an immunogenic composition comprising an *S. pneumoniae* serotype 22F glycoconjugate with a molecular weight within the range 1000 and 12,500 kDa and a polysaccharide to carrier protein ratio between 0.4 and 2 would have been obvious to the ordinary artisan at the time of invention.

In particular, we recognize that both Merck 2011 and GSK 2008 suggest multivalent immunogenic compositions comprising *S. pneumoniae* serotype 22F conjugated to a carrier protein. Moreover, as Petitioner points out, Table 2 of 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; Ex. 1006, 1:7–11; Ex. 1007, 8:5–19.

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

Patent Owner asserts "[t]here is no motivation, however, to obtain a serotype 22F glycoconjugate having a molecular weight disclosed for the non-serotype 22F glycoconjugates in Table 2." Prelim. Resp. 20. Patent Owner asserts for "four of the six parameters for which data was provided for the serotype 19A and 22F glycoconjugates in Table 2 of GSK 2008, the data was almost entirely non-overlapping with the data provided for the other serotype glycoconjugates." Prelim. Resp. 21. Patent Owner concludes "a POSA would not have expected the serotype 19A and 22F glycoconjugates to have the same molecular weight parameters as the other glycoconjugates tested in Table 2." Prelim. Resp. 21. Patent Owner also asserts "neither the Petition nor Merck's expert, Dr. Kasper, provides any rationale as to why a POSA would have expected a serotype 22F glycoconjugate to have the same molecular weight as that of the other serotype glycoconjugates." Prelim. Resp. 22.

On the current record, we find this argument unpersuasive. While Table 2 in GSK 2008 shows that conjugate size for neither of the serotype 22F conjugates was determined, Table 2 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. Thus, we agree with Petitioner that GSK 2008 reasonably suggests that conjugate sizes between 1303 and 9572

kDa represent a desirable range because these conjugates may be used to generate multivalent vaccines. Pet. 39; Ex. 1007, 55:2–10.

"In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). Here, the range of conjugates disclosed within GSK 2008 all fall within the range recited in claim 1. While the standard for an issued patent in *inter partes* review is not "prima facie obviousness" because the burden is placed on Petitioner to demonstrate actual obviousness, we conclude the evidence of GSK 2008 supports a reasonable likelihood that the ordinary artisan would have had a reason to produce a serotype 22F glycoconjugate within the range of 1303 to 9572 kDa.

Patent Owner asserts Petitioner "does not provide any reason *why* reductive amination or CDAP conjugation chemistries would have resulted in serotype 22F glycoconjugates falling within the claimed molecular weight range." Prelim. Resp. 23. Patent Owner also asserts

> Merck has failed to explain why a POSA would not have elected to use a smaller serotype 22F polysaccharide (*e.g.*, 50-100 kDa) and an average-sized protein carrier (e.g., $CRM_{197}$ at ~58 kDa) in reductive amination or CDAP conjugation chemistries to generate a serotype 22F glycoconjugate well below the claimed molecular weight range in the '559 patent. Even if multiple 22F polysaccharides were cross-linked to multiple protein carriers, Merck has provided no evidence that the combination of these multiple polysaccharides or protein carriers would necessarily add up to a molecular weight within the claimed range.

Prelim. Resp. 24.

We find this argument unpersuasive because GSK 2008 specifically teaches a composition in claim 56 where "the average size (e.g. $M_w$) of the 22F saccharide is between 50 and 800 kDa. . . ." Ex. 1007, 93. 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. Thus, GSK 2008 suggests that saccharides, including the 22F saccharide, may be as large as 1600 kDa, a value that falls squarely within the range required by claim 1, even excluding the addition 58 kDa added by the $CRM_{197}$ protein carrier. Ex. 1007, 94; Ex. 1008, 20. "Such overlap itself provides sufficient motivation to optimize the ranges." *In re Applied Materials, Inc*., 692 F.3d 1289, 1295 (Fed. Cir. 2012).

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 (*cf*. Pet. 38, 44). 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, *cf*. Pet. 38.

Therefore, GSK 2008 teaches 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." *Applied Materials*, 692 F.3d at 1295. "[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). Patent Owner has, so far, provided no evidence demonstrating any secondary consideration regarding the conjugate sizes.

Patent Owner asserts "[w]hile Ground 1 appears to rely on just Merck 2011, GSK 2008 and general knowledge, the arguments in Ground 1 actually refer to numerous additional exhibits. Indeed . . . Merck actually refers to more than *twenty* additional documents. . . ." Prelim. Resp. 25. Patent Owner asserts "[t]his is improper. Pursuant to 37 C.F.R. § 42.104(b)(5), Merck is required to identify 'the relevance of the evidence' to its obviousness challenge, as well as the 'specific portions of the evidence that support the challenge.' Merck has not complied with the rule." Prelim. Resp. 25.

While Petitioner's obviousness position does not require the additional cited references, nor do we rely upon these additional references, Petitioner does not cite the additional references to establish limitations in the claims but rather to illustrate the understanding of the person of ordinary skill in the art.

Therefore, while Patent Owner contends that "[n]owhere in Pfizer 2012[11] is there any mention of pneumococcal glycoconjugates, much less a serotype 22F glycoconjugate" and that Pfizer 2012 "is not limited to

[11] Brown et al., *Characterization of Complex Prophylactic Vaccines with Protein and Glycoconjugate Components*, 9th CASSS Symposium (Sept. 12, 2012). The parties refer to Exhibit 1008 as "Pfizer 2012."

pneumococcal glycoconjugates and is only a statement about the general range of all glycoconjugates without respect to source," we understand the citation to Pfizer 2012 as evidencing that 500 to 5000 kDa was a known size range for glycoconjugates consistent with the disclosure of a range up to 1600 kDA disclosed by GSK 2008. *See* Prelim. Resp. 27–28, Ex. 1008 6, Ex. 1007, 94 (*cf*. Pet. 19, 39).

Patent Owner similarly asserts that Jones 2005,[12] Wyeth 2007,[13] and Lees 2008[14] provide "no reason why molecular weight information for a glycoconjugate from one species would have informed a POSA how to make a glycoconjugate having a polysaccharide from a completely different species" and that "desirable characteristics of one serotype glycoconjugate may not be true for another serotype glycoconjugate." Prelim. Resp. 29–30, Pet. 39.

We find this argument unpersuasive because we understand Petitioner's citations to 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 as evidentiary in nature. *See* Pet. 37, 39–

[12] Jones, C., *Vaccines based on the cell surface carbohydrates of pathogenic bacteria*, 77 Anais da Academia Brasileira de Ciências 293324 (2005). The parties refer to Exhibit 1026 as "Jones 2005."
[13] Turula et al., *The Application of SEC-MALS in Vaccine Development*, International Light Scattering Colloquium 2007 1–48 (2007). The parties refer to Exhibit 1027 as "Wyeth 2007."
[14] Lees et al., *Conjugation Chemistry*, in Pneumococcal Vaccines: the Impact of Conjugate Vaccine 163–174 (2008). The parties refer to Exhibit 1035 as "Lees 2008."

40; Ex. 1026, 7; Ex. 1027, 21; Ex. 1035, 7. That is, these additional references are provided to establish that the person of ordinary skill in the art, at the time of invention, 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 the "ratio of the '559 patent claims and the ratio of Merck 2011 are presented in terms of two different units of measurement." Prelim Resp. 33. Patent Owner asserts the "terms 'w/w' and 'charge' are not the same, and Merck has therefore failed to demonstrate that Merck 2011 teaches or suggests the polysaccharide to protein ratio (w/w) limitation required of the '559 patent claims." Prelim. Resp. 33. Patent Owner also asserts

> neither Table 1 nor any other text in Merck 2011 states that all of the polysaccharides in the referenced formulation are actually conjugated to carrier protein. Table 1 merely indicates that the conjugate, polysaccharide and carrier protein components were mixed with each other to arrive at the total recited amounts. EX1006 at 19, Table 1. A POSA would have understood from prior art documents such as GSK 2008 that polysaccharides are not always conjugated to carrier proteins in a glycoconjugate formulation, and that some portion of the polysaccharides present in such a formulation is made up of "free" or unconjugated polysaccharides.

Prelim. Resp. 34–35.

While 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 teach the 0.4 to 2 w/w ratio required by claim 1, Merck's teaching does

suggest that the ratio of polysaccharide to carrier protein represents an optimizable variable.

We are not persuaded by Patent Owner's argument regarding Merck 2011 Table 1, because in that table Merck 2011 discloses an example that would reasonably have been expected to result in a 1:1 w/w ratio of the 22F polysaccharide to the $CRM_{197}$ carrier protein. Ex. 1006, 19:5–9; Ex. 1087 ¶ 120. This expectation is supported by Dr. Kasper's statement that the ratios "resulted in an average polysaccharide to protein ratio in the conjugates of approximately 1." Ex. 1004 ¶ 115.

As this stage of the proceeding, Patent Owner provides no direct evidence that the pre-conjugation data disclosed in Table 1 of Merck 2011 would not have resulted in an approximately 1:1 w/w ratio for serotype 22F. However, Patent Owner points to GSK 2008 and asserts

> GSK 2008 demonstrates the opposite, *i.e.*, the polysaccharide to protein ratios may differ substantially between pre-conjugation and final conjugation compositions. 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.

Prelim. Resp. 33–34 (citing Ex. 1007 52–55).

Even crediting this indirect evidence related to other serotypes, 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 to 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. S*ee, 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.")

Patent Owner asserts "Merck points to a single range selected from one of several long lists in GSK 2008 that refers to a polysaccharide to protein range between 1:2 and 2.5:1. . . ." Prelim. Resp. 37. Patent Owner asserts "the referenced list includes several different ratio ranges generic to all *S. pneumoniae* polysaccharides, and nothing in this list specifies any particular range for a serotype 22F glycoconjugate." Prelim. Resp. 37. Patent Owner asserts "other sections of GSK 2008 refer to a variety of other polysaccharide to protein ratio ranges that fall well *outside* of the claimed range. For instance, GSK 2008 refers to protein to polysaccharide (without disclosing the specific serotype) ratio ranges of 6:1 to 3:1 (*i.e.*, a polysaccharide to protein ratio of 1:6 and 1:3, which translates to 0.17 to 0.33)." Prelim. Resp. 37.

We are not persuaded by this argument because 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. To the extent that GSK 2008 teaches ratios outside the ratio required by claim 1, the ordinary artisan would have found all of these ratios obvious, rather than discarding those that render claim 1 obvious. *Cf. Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [prior art] discloses a multitude of effective combinations does not render any particular [composition] less obvious.")

Patent Owner asserts "Example 2 of GSK 2008 provides a specific protocol for generating a serotype 22F glycoconjugate . . . The GSK 2008 conjugation procedure therefore results in a polysaccharide to protein ratio

value *below* the '559 patent claimed range of 0.4 to 2.0." Prelim Resp. 38–39. Patent Owner acknowledges that "PS22F-PhtD in Table 2 of GSK 2008 has a protein to polysaccharide ratio of 2.17, which allegedly translates to a polysaccharide to protein ratio of 1:2.17, or 0.46" but asserts "data for a second glycoconjugate referred to as 'PS22F-AHPhtD'" shows the "polysaccharide to protein ratio for the PS22F-AHPhtD clearly falls *outside* of the '559 patent claimed range." Prelim. Resp. 40 (citing Ex. 1007 54–55).

Patent Owner asserts "GSK 2008 states that the glycoconjugate having the ratio outside the claimed range, *i.e.*, PS22F-AH-PhtD, 'was shown [to be] much more immunogenic' than PS22F-PhtD (the glycoconjugate allegedly having a ratio within the claimed range) in terms of both IgG levels and opsonophagocytic titres." Prelim. Resp. 40–41.

We find this argument unpersuasive. Patent Owner 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. To the extent that this conjugate with a 0.46 ratio had lower immunogenicity than a different conjugate of 22F with a lower polysaccharide to protein ratio, 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). *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. Indeed, GSK 2008 teaches 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. Thus, GSK 2008 is reasonably understood as recognizing that either 22F conjugate may be used in the multivalent vaccine. 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 asserts that Petitioner relies on a webpage from the Japanese National Institute of Infectious Diseases ("JNIID")[15] "to allege that a POSA would have considered the polysaccharide to carrier protein ratio of 0.4 to 2.0 to be 'typical for immunogenic compositions.'" Prelim. Resp. 42 (citing Pet. 44–45, Ex. 1085, 23). Patent Owner asserts Petitioner "fails to provide any explanation as to why a POSA would have understood the ratio to be a w/w ratio" and that "JNIID is completely silent regarding serotype 22F glycoconjugates. A POSA would have understood from documents such as GSK 2008 that serotype 22F required special consideration with regard to polysaccharide to protein ratios." Prelim. Resp. 42 (citing Pet. 44–45).

[15] Japanese National Institute of Infectious Diseases, http://web.archive.org/web/20130105152418/http://www.nih.go.jp/niid/ja/mrbp.html (2012). The parties refer to Exhibit 1085 as "JNIID."

We understand JNIID is used by Petitioner to establish that the person of ordinary skill in the art, at the time of invention, recognized selection of saccharide content to protein ratios represents a known, optimizable variable. Dr. Kasper specifically states JNIID "specifies the acceptable range of 'Saccharide content/protein ratio' (which a POSITA would have understood to be a w/w ratio). . . ." Ex. 1004 ¶ 118; Pet. 44–45. As we balance this statement by an expert based on evidence in the record with Patent Owner's assertions without evidence, we find that the current record better supports Petitioner's position that JNIID supports the understanding of the ordinary artisan that saccharide to protein ratios generally range from as low as 0.3 to as high as 2.6 to 1. *See* Ex. 1085, 23; Ex. 1004 ¶ 118.

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

Patent Owner asserts "neither Merck 2011 nor GSK 2008 discloses immunogenic compositions that include a conjugate of pneumococcal serotype 15B, as required by claims 3 and 4." Prelim. Resp. 46. Patent Owner asserts "there are four serotypes in serogroup 15, *i.e.*, serotypes 15A, 15B, 15C and 15F (EX2003 at Table 1), and neither Merck nor its expert has shown why a POSA would be motivated to select serotype 15B based on the disclosure of Merck 2011 and GSK 2008." Prelim. Resp. 46. Patent Owner also asserts "neither Merck 2011 nor GSK 2008 exemplifies any immunogenic compositions that include serotype 10A and 11A glycoconjugates, as required by claim 4 under the proper construction." Prelim. Resp. 47.

We find this argument unpersuasive because Dr. Kasper evidences that a "POSITA would have understood that 'serotype 15' in GSK 2008 includes all serotypes within serogroup 15, including serotype 15B as

claimed." Ex. 1004 ¶ 121; *cf*. Pet. 46. Dr. Kasper further states "the claimed serotypes were well-known to be prevalent and had already been included in the Pneumovax® 23 polysaccharide vaccine." Ex. 1004 ¶ 121 (citing Ex. 1031, 2 and Ex. 1054, 4). Dr. Kasper also states "GSK 2008 discloses compositions with conjugates of serotypes 22F, 15B, 33F, 12F, 10A, 11A and 8. . . ." Ex. 1004 ¶ 122 (citing Ex. 1007 27:20–24; *cf*. Pet. 46–47). GSK 2008 therefore specifically suggests incorporation of serotypes 10A and 11A into vaccine compositions along with serotype 22F. Ex. 1007, 27:20–24. Thus, the evidence currently of record better supports Petitioner's position that there is a reasonable likelihood that serotypes 15B, 10A, and 11A would have been envisaged by and obvious to the person of ordinary skill. *See In re Petering*, 301 F.2d 676, 681 (CCPA 1962).

At this stage of the proceeding, having considered the evidence and arguments of record, we determine that Petitioner has sufficiently shown a reasonable likelihood that it would prevail in demonstrating claims 1, 3–10, 16–19, 39, 41, 42, and 45 as obvious over Merck 2011 and GSK 2008.

*E. Obviousness over Merck 2011, GSK 2008, and PVP 2013*

Petitioner contends that claims 2, 40, and 43 are unpatentable under 35 U.S.C. § 103(a) as obvious over Merck 2011, GSK 2008, and PVP 2013. Pet. 56–62. *See* Prelim Resp. 47–55.

Petitioner asserts "PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an 'O-acetyl/polysaccharide unit molar ratio' of '0.5 - 1.5'; that entire specified range meets the claimed ratio of 'at least 0.1.'" Pet. 57 (citing Ex. 1009, 4). Petitioner asserts "a POSITA would have understood that O-acetyl groups can contribute to the immunogenicity of pneumococcal

polysaccharides." Pet. 57 (citing Ex. 1004 ¶ 143 (that cites Ex. 1086)). Petitioner asserts "DMSO was commonly used in the art to preserve O-acetylated polysaccharides" and that "the prior art had already disclosed the use of a DMSO solvent in a reductive amination reaction for the preparation of serotype 22F conjugates." Pet. 59 (citing Ex. 1036, 2; Ex. 1037, 14–16; Ex. 1038, 15; Ex. 1039 ¶ 56). Petitioner asserts:

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

Pet. 60, citing Ex. 1004 ¶ 148.

Patent Owner asserts the "minimum acetate content requirements of claims 2, 40 and 43 would not have been obvious in view of Merck 2011, GSK 2008 or PVP 2013, whether viewed alone or in combination." Prelim. Resp. 48. Patent Owner asserts "[b]ecause PVP 2013 does not mention any carrier proteins or glycoconjugates, PVP 2013 would not have taught a POSA about how to arrive at the specific polysaccharide to protein ratio (w/w) recited in the '559 patent claims." Prelim. Resp. 49. Patent Owner asserts

> Rajam 2007[16] does not teach or suggest that the immunogenicity of all pneumococcal polysaccharides is linked to their *O*-acetylation state. Neither Merck nor its expert, Dr. Kasper, has explained why the *O*-acetylation of serotype 15B

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

> would be relevant to any other serotype, much less serotype 22F. Even assuming that Rajam 2007 did suggest the importance of *O*-acetylation for all pneumococcal glycoconjugates, Rajam 2007 does not provide any guidance about how to preserve *O*-acetylation during a conjugation reaction. Therefore, a POSA would have had no motivation to make, or a reasonable expectation of success in making, a glycoconjugate of serotype 22F with the claimed acetate levels of claims 2, 40 or 43.

Prelim. Resp. 49–50. Patent Owner asserts "Rowley 2013[17] has nothing to do with vaccines or even infectious diseases. Rowley 2013 concerns generating labeled antibodies to the polysaccharide xylan . . . Rowley 2013 is non-analogous art, and a POSA would not have turned to this document in order to prepare the compositions of the '559 patent." Prelim. Resp. 51–52. Patent Owner asserts "nowhere in the specifications of either Biemans 2012[18] or Biemans 2013[19] is there any teaching or suggestion that a serotype 22F glycoconjugate should be prepared in DMSO." Prelim. Resp. 54. Patent Owner asserts

> While Park 2015 refers to a DMSO serotype 22F conjugation reaction, Park 2015 does not articulate a reason why a POSA should prepare a serotype 22F glycoconjugate in DMSO, particularly a serotype 22F glycoconjugate having a molecular weight and polysaccharide to protein ratio range recited in the '559 patent claims.

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[17] Rowley et al., *Efficient extraction of xylan from delignified corn stover using dimethyl sulfoxide*, 3 BIOTECH 4338 (2013) ("Rowley 2013," Ex. 1036).
[18] Biemans et al., US 2012/0321660 A1, published Dec. 20, 2012 ("Biemans 2012," Ex. 1037).
[19] Biemans et al., US 2013/0344103 A1, published Dec. 26, 2013 ("Biemans 2013," Ex. 1038).

Prelim. Resp. 54.

We find Petitioner has the better position. Claim 2 requires "at least 0.1 mM acetate per mM polysaccharide" and claims 40 and 43 require a mM ratio that "is at least 0.6." Ex. 1001, 141:35–37, 144:15–18, 27–30. Dr. Kasper states "PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an 'O-acetyl/ polysaccharide unit molar ratio' of '0.5 - 1.5'; that entire specified range meets the claimed ratio of 'at least 0.1.'" Ex. 1004 ¶ 142 (citing Ex. 1009 4). Consistent with Dr. Kasper's statement, PVP 2013 states the "O-acetate content (O-acetyl/polysaccharide unit molar ratio) shall be within the range of the following specification" where the range for serotype 22F is given as "0.5–1.5." Ex. 1009, 3.

Consequently, PVP 2013 provides an express suggestion to utilize a molar ratio of acetate to polysaccharide for serotype 22F that falls within the requirements of claims 2, 40, and 43. We have considered Patent Owner's assertions, but find them unpersuasive. In particular, we have already found the ratio of polysaccharide to protein obvious for claim 1 as discussed above and claims 2, 40, and 43 are drawn to further ratios of acetate to polysaccharide suggested by PVP 2013, not ratios of polysaccharide to protein.

While Petitioner does not rely upon Rajam 2007 for the primary obviousness case, Dr. Kasper explains that Rajam 2007 evidences "that O-acetyl groups can contribute to the immunogenicity of pneumococcal polysaccharides." Ex. 1004 ¶ 143 (citing Ex. 1086). Rajam 2007 states "the primary functional epitope of 15B-Ps is linked to the O acetylation of the monosaccharide residues. Removal of this O-acetyl group results in loss of

the functional antibody activity." Ex. 1086, 4. This teaching, in combination with the teaching of PVP 2013 to incorporate acetate into serotype 22F in particular, demonstrates that the evidence of record better supports Petitioner's position that use of acetate in the molar ratios suggested by PVP 2013 would have been expected to improve vaccine activity. We need not address the remaining references because Merck 2011, GSK 2008, and PVP 2013, as supported by Dr. Kasper, provides sufficient evidence of record to provide a reasonable likelihood that claims 2, 40, and 43 would have been obvious.

At this stage of the proceeding, having considered the evidence and arguments of record, we determine that Petitioner has sufficiently shown a reasonable likelihood that it would prevail in demonstrating claims 2, 40, and 43 are unpatentable under 35 U.S.C. § 103(a) as obvious over Merck 2011, GSK 2008, and PVP 2013.

*F. Obviousness over Merck 2011, GSK 2008, and Hsieh 2000*

Petitioner contends that claims 38 and 44 are unpatentable under 35 U.S.C. § 103(a) as obvious over Merck 2011, GSK 2008, and Hsieh 2000. Pet. 62–64. *See* Prelim Resp. 48–50.

Petitioner asserts regarding claim 38 that "[b]ased on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to obtain at least 30% of the conjugates of claim 1 with a $K_d$ below or equal to 0.3 in a CL-4B column." Pet. 62 (citing Ex. 1004 ¶ 152). Petitioner asserts "Hsieh 2000 discloses that pneumococcal conjugates should generally have a $K_d$ below or equal to 0.3 in a CL-4B column." Pet. 62 (citing Ex. 1013, 6).

Petitioner asserts regarding claim 44 that "[b]ased on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to construct the conjugate of claim 1 with a 'degree of conjugation' between 2 and 15." Pet. 63 (citing Ex. 1004 ¶ 153). Petitioner asserts "Hsieh 2000 discloses a degree of conjugation for pneumococcal $CRM_{197}$ conjugates in the range of 6-9, entirely within the claimed range." Pet. 63–64 (citing Ex. 1013, 8).

Patent Owner asserts "[s]ince GSK 2008 teaches that 22F glycoconjugates were unique, a POSA would not have expected that the general disclosure of Hsieh 2000 regarding $K_d$ values in a CL-4B column (claim 38) or the degree of conjugation (claim 44) would be applicable to serotype 22F glycoconjugates." Prelim. Resp. 56. Patent Owner asserts Petitioner

> has not provided any evidence that a POSA would have been able to successfully modify the general disclosure of Hsieh 2000 in order to make an immunogenic, serotype 22F glycoconjugate composition that meets the other limitations (*e.g.*, the molecular weight or polysaccharide to protein ratio ranges) recited in the '559 patent claims.

Prelim. Resp. 56. Patent Owner asserts "Hsieh 2000 cautions that before settling on an optimal vaccine composition, 'detailed analyses' of each parameter is required." Prelim. Resp. 57 (citing Ex. 1013, 11).

We find Petitioner has the better position. Claim 38 requires the glycoconjugates to "have a $K_d$ below or equal to 0.3 in a CL-4B column." Ex 1001, 144:7–9. Dr. Kasper states "Hsieh 2000 discloses that pneumococcal conjugates should generally have a $K_d$ below or equal to 0.3 in a CL-4B column." Ex. 1004 (citing Ex. 1013, 6). Hsieh 2000 analyzed saccharide-$CRM_{197}$ conjugates and stated:

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

Ex. 1013, 6. Thus, the only evidence of record, Hsieh 2000, directly suggests that for pneumococcal saccharide-$CRM_{197}$ conjugates a 0.3 value $K_d$ value obtained from a CL-4B column is desirable. Ex. 1013, 6. Patent Owner provides no evidence, as opposed to argument, that there would be any difficulty or unpredictability in performing Hsieh's assay on the conjugates suggested by Merck 2011 and GSK 2008. *See In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) ("Attorney's argument in a brief cannot take the place of evidence.").

Claim 44 requires the "degree of conjugation of said glycoconjugate is between 2 and 15." Ex. 1001, 144:32–34. Dr. Kasper states "[b]ased on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to construct the conjugate of claim 1 with a 'degree of conjugation' between 2 and 15." Ex. 1004 ¶ 153, citing Ex. 1013, 8. Hsieh 2000 teaches "[f]or saccharide-$CRM_{197}$ conjugates, there is a limited number of exposed lysines on surface $CRM_{197}$, which can participate in the conjugation reaction. The loss of lysine has been relatively consistent in the range of 6–9." Ex. 1013, 8. Thus, the only evidence of record, Hsieh 2000, teaches a degree of conjugation between 6 and 9. Ex. 1013 8. Patent Owner raises general concerns about variation in glycoconjugates, without providing specific evidence of unpredictability for 22F, but the requirement

is not an absolute expectation of success but rather a reasonable expectation of success based on the teachings of the prior art. "Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009). Based on the teachings of Merck 2011 and GSK 2008 regarding conjugation of the 22F glycoconjugate to $CRM_{197}$, and Hsieh's teachings regarding the specific ratio, we find the evidence currently of record supports a finding of a reasonable expectation of success. Ex. 1006 1:7–11, Ex. 1007 8:5–19, 10:12–14, Ex. 1013, 8.

At this stage of the proceeding, having considered the evidence and arguments of record, we determine that Petitioner has sufficiently shown a reasonable likelihood that it would prevail in demonstrating claims 38 and 44 as obvious over Merck 2011, GSK 2008, and Hsieh 2000.

## III. CONCLUSION

After reviewing the information presented in the Petition and the Preliminary Response, as well as the evidence of record thus far, we determine that Petitioner has established a reasonable likelihood that it will prevail in showing that claims 1–10, 16–19, and 38–45 of the '559 patent are unpatentable.

## IV. ORDER

Accordingly, it is

ORDERED that Pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following grounds;

| Reference | Basis | Claims Challenged |
|---|---|---|
| Merck 2011, GSK 2008 | § 103(a) | 1, 3–10, 16–19, 39, 41, 42, 45 |

| | | |
|---|---|---|
| Merck 2011, GSK 2008, PVP 2013 | § 103(a) | 2, 40, 43 |
| Merck 2011, GSK 2008, Hsieh 2000 | § 103(a) | 38, 44 |

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this Decision.

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