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Paper 10
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

PFIZER INC.,
Patent Owner.

Case IPR2018-00187
Patent 9,492,559 B2

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

FREDMAN, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

A. Background

Sanofi Pasteur Inc. and SK Chemicals Co., Ltd. ("Petitioner") filed a Petition (Paper 3, "Pet.") requesting an *inter partes* review of claims 1–45 (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 8 ("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 1–45 of the '559 patent.

B. Related Proceedings

Petitioner indicates that a concurrent Petition for *inter partes* review of the '559 patent was filed (IPR2018-00188) and that several IPRs were filed by a different petitioner (IPR2017-02131, IPR2017-02132, IPR2017-02136, IPR2017-02138). Pet. 3.

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 available on the global market: PREVNAR® (called PREVENAR® in some countries) (heptavalent[3] 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.

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

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

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

D. Illustrative Claims

Claim 1, the sole independent claim of the '559 patent is illustrative of the challenged claims and recites:

> 1. An immunogenic composition comprising a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2.

Ex. 1001, 141:28–34. Each of the remaining challenged claims, claims 2–45, depends either directly or indirectly from claim 1.

E. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 5–6.

Reference	Basis	Claims Challenged
GSK-711,[4] Merck-086[5]	§ 103	1, 3–19, 23–37, 41, 42, 45
GSK-711, Merck-086, Lees-2008,[6] PVP 2013,[7] Pfizer-605[8]	§ 103	2, 40, 43
GSK-711, Merck-086, GSK-531[9]	§ 103	20–22
GSK-711, Merck-086, Pfizer-605	§ 103	38, 39
GSK-711, Merck-086, Hsieh 2000[10]	§ 103	44

Petitioner relies on the Declaration of Andrew Lees, Ph.D. Ex. 1005.

[4] Biemans et al., WO 2007/071711 A2, published June 28, 2007 ("GSK-711," Ex. 1007).
[5] Caulfield et al., US 2011/0195086 A1, published Aug. 11, 2011 ("Merck-086," Ex. 1008).
[6] Lees et al., "*Chapter 11. Conjugation Chemistry*," In: Pneumococcal Vaccines: *The Impact of Conjugate Vaccine* (Ed. George R. Siber et al.); pp. 163–174 (2008) ("Lees-2008," Ex. 1011).
[7] "*Pneumococcal Vaccine Polyvalent*" revision to Japan's "*Minimum Requirements for Biological Products*" published on the website of Japan's National Institute of Infectious Diseases (as of March 2, 2013) ("PVP 2013," Ex. 1012).
[8] Prasad, A.K., US 7,955,605 B2, issued June 7, 2011 ("Pfizer-605," Ex. 1013).
[9] Biemans et al., WO 2011/110531 A2, published Sept. 15, 2011 ("GSK-531," Ex. 1014).
[10] Hsieh, *Characterization of Saccharide-CRM_{197} Conjugate Vaccines*, In: *Physico-Chemical Procedures for the Characterization of Vaccines* (Eds. Brown F., Corbel M., and Griffths E.); Vol. 103, pp. 93–104; Basel; Karger, 2000 ("Hsieh 2000," Ex. 1015).

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 this standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Only terms in controversy must be construed and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

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

1. *"immunogenic"*

Petitioner asserts the "term 'immunogenic' in the preamble only states an intended use or an inherent property. It does not further limit the scope of the claims." Pet. 27. Petitioner asserts that "[s]hould the Board determine that the preamble is limiting . . . Petitioner proposes that the term ['immunogenic'] be construed as 'capable of producing an immune response as determined by an immunogenic assay known in the art by a POSA including an OPA assay.'" Pet. 27–28.

Patent Owner asserts the "term 'immunogenic' is clearly a claim limitation because this term 'breathes life and meaning into the claim.'" Prelim. Resp. 12. Patent Owner asserts that the Examiner withdrew anticipation rejections based on the "immunogenic" limitation." Prelim. Resp. 12–13 (citing Ex. 1004, 23–24). 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 Patent Owner 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 agree with Patent Owner that the broadest reasonable interpretation of "immunogenic" requires a composition that "elicits functional antibody against each serotype in the claimed composition." Prelim. Resp. 12–13. 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. Independent claim 1 does not specifically require any additional glycoconjugates besides 22F.

B. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art;[11] and (4) where in evidence, objective indicia of nonobviousness. *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

[11] Petitioner states that the level of skill in the art at the time of the invention "would have had a Ph.D. or equivalent degree in chemistry, immunology, or other biological sciences or an MD and at least 2 years of experience in glycoconjugate vaccine research and development, or would have an M.S. degree and at least 4 years of relevant experience." Pet. 26, citing Ex. 1005 ¶ 77. Patent Owner "does not dispute Sanofi's proposed level of skill for the person having ordinary skill in the art." Prelim. Resp. 11. 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).

> 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).

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 GSK-711 and Merck-086, which are at the center of Grounds 1–5 of the Petition, are cumulative of WO 2009/000826 ('the WO '826 application'- EX2002) and US 2013/0273098 ('Blue'- EX2001) and, respectively, which were before the Patent Office during prosecution." Prelim. Resp. 16. Patent Owner contends that "GSK-711 is 'substantially the same' as the WO '826 application" and that "[m]uch of the text in GSK-711 relied upon by Sanofi is found verbatim in the WO '826 application." Prelim. Resp. 17. Patent Owner contends Petitioner relies "upon language in GSK-711 that is nearly identical to language [in] the WO '826 application." Prelim. Resp. 18.

Similarly, Patent Owner contends "Merck-086 is substantially the same as Blue." Prelim. Resp. 19. Patent Owner contends "[a]lthough the Examiner did not explicitly rely on Blue 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. 20.

Patent Owner contends Petitioner "and its expert, Dr. Lees, also refer to several European applications cited in Merck-086 that are cited in an identical context in Blue." Prelim. Resp. 20 (*citing* Pet. 41–43; Ex. 1005 ¶ 151). Patent Owner concludes: "The disclosures relied upon by Sanofi in Merck-086 and GSK-711 are largely identical and therefore substantially similar to the disclosures of the WO '826 application and Blue, respectively. Sanofi is merely presenting substantially the same prior art that was already presented to and considered by the Office." Prelim. Resp. 21.

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 Merck-086 and the WO '826 application are similar to the currently relied upon Merck 2013 and GSK-711, they are not cumulative of the references relied upon by the Examiner. In addition, although Merck 2013 and GSK-711 are among numerous cited references listed on the front of the '559 patent (Ex. 1001, references cited section) those references were not cited by the Examiner or specifically relied upon by the Examiner during prosecution. *See* Prelim. Resp. 20. Petitioner also relies on a declaration from Dr. Lees, 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 Lees 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. 1005 ¶¶ 57–60, 136–156.

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 GSK-711 and Merck-086

Petitioner contends that claims 1, 3–19, 23–37, 41, 42, and 45 are unpatentable under 35 U.S.C. § 103 as obvious over GSK-711, Merck-086, and the general knowledge of an ordinary artisan. Pet. 30–66. Patent Owner opposes this ground. Prelim. Resp. 22–47.

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

GSK-711 teaches a *Streptococcus pneumoniae* vaccine comprising "capsular saccharide antigens (preferably conjugated), wherein the saccharides are derived from at least ten serotypes of *S. pneumoniae*" that may include an "*S. pneumoniae* saccharide conjugate of 22F." Ex. 1007, 6:4, 24–26. GSK-711 teaches "*Streptococcus pneumoniae* capsular saccharides . . . may be conjugated to a carrier protein independently selected from the group consisting of . . . CRM197. . . ." Ex. 1007, 8:18–20. GSK-711 teaches "saccharide conjugates present in the immunogenic compositions of the invention may be prepared by any known coupling technique" and specifically, conjugates "can also be prepared by direct reductive amination methods. . . ." Ex. 1007, 15:9–10; 16:1. GSK-711 teaches "22F-PhtD administered within the 13-valent conjugate vaccine formulation [was] shown immunogenic in old C57BI mice." Ex. 1007, 67:36–37.

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

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

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

2. *Merck-086*

Merck-086 teaches "a multivalent immunogenic composition having 15 distinct polysaccharide-protein conjugates. Each conjugate consists of a

capsular polysaccharide prepared from a different serotype of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F or 33F) conjugated to a carrier protein, preferably CRM_{197}." Ex. 1008 ¶ 2. Merck-086 teaches "conjugates containing serotypes 22F and 33F provide[] robust antibody responses demonstrat[ing] the feasibility of expanding coverage of pneumococcal serotypes. . . ." Ex. 1008 ¶ 15. Merck-086 teaches the pneumococcal conjugate vaccine (PCV) with "induced high OPA[12] GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine." Ex. 1008 ¶ 114.

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

3. *Analysis*

Petitioner asserts that GSK-711 and Merck-086 suggest immunogenic compositions of *S. pneumoniae* serotype 22F conjugated to carrier that have

[12] Opsonophagocytosis.

molecular weights and polysaccharide/carrier protein ratios within the ranges recited by claim 1 of the '559 patent. *See* Pet. 1–2, 17–21, 34–36.

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

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

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

Pet. 36 (citing Ex. 1005 ¶ 140).

To support their obviousness position, Petitioner's rely upon the Declaration of Dr. Lees, who states "there is nothing inventive to claims 1–45 of the '559 patent. As stated above, 22F polysaccharide-carrier protein

conjugates had already been made before the earliest filing date of the '559 patent as part of multivalent PCV products developed by Merck and GSK and were shown to be immunogenic." Ex. 1005 ¶ 117.

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

Dr. Lees, addressing the limitation in claim 1 for a glycoconjugate molecular weight between 1000 kDa and 12,500 kDa, acknowledges "molecular weights are not explicitly provided for the two 22F glycoconjugates (PS22F-PhtD and PS22F-AHPhtD) shown in Table 2" but states "Table 2 discloses the conjugate sizes for ten (10) different pneumococcal glycoconjugates with different serotype and carrier protein combinations, all of which fall within and span most of the range of 'between 1000 kDa and 12,500 kDa' recited in claim 1." Ex. 1005 ¶¶ 138–139 (citing Ex. 1007, 54). Dr. Lees states "one would have reasonably expected that the sizes of the two 22F conjugates disclosed in Table 2, *if measured*, would also fall within the range between 1,000 KDa and 12,500 KDa." Ex. 1005 ¶ 141. Dr. Lees states regarding the lower end of the range that because

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

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

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

Dr. Lees, addressing the issue of a reasonable expectation of success in forming a 22F conjugate within the claimed molecular weight range, states "CDAP or reductive amination chemistry naturally results in glycoconjugates with highly crosslinked lattice structures with multiple saccharide molecules linked to multiple carrier protein molecules in each

lattice." Ex. 1005 ¶ 151. Dr. Lees states the "fact that GSK-711 discloses 10 different pneumococcal glycoconjugates with molecular weights all falling within the claimed range of 1,000 kDa and 12,500 kDa confirms a reasonable expectation of success." Ex. 1005 ¶ 152 (citing Ex. 1007, 54).

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. 25. Patent Owner contends the different glycoconjugates in Table 2 of GSK-711 would not have been expected to have similar molecular weights because the

> conjugation protocols are not the "same" for each of the glycoconjugates tested in Table 2 of GSK-711. . . . Table 1 notes that the conjugation reactions for each glycoconjugate differed in terms of input concentrations for polysaccharides, input concentrations for carrier proteins, initial protein to polysaccharide ratios, CDAP concentrations, and pH values for the conjugation reactions.

Prelim. Resp. 25. Patent Owner asserts that this dissimilarity based on differences in conjugation is shown because "four of the six parameters for which data was provided for the serotype 19A and 22F glycoconjugates in Table 2 of GSK-711, the data was almost entirely non-overlapping with the data provided for the other serotype glycoconjugates." Prelim. Resp. 27. 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. 27–28.

On the current record, we find this argument unpersuasive. While Table 2 in GSK-711 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, 53. The differences identified by Patent Owner regarding input concentrations, ratios, and pH were art recognized optimizable variables for conjugation. *See* Ex. 1011, 168 ("Since each capsular serotype has a different structure, reaction conditions, including concentrations, molar ratios of periodate, oxidation times, and pH, must be optimized for each.") Thus, we agree with Petitioner that GSK-711 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. 40–43; Ex. 1007, 53:9–54:2.

"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-711 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-711 supports a reasonable likelihood at this stage of the proceeding 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 that Petitioner's analysis and calculations for the molecular weight of the 22F glycoconjugate were flawed, specifically that: "Both the 22F polysaccharide and the PhtD carrier protein have complex three dimensional structures, and Sanofi has not shown that the hydroxyl

groups and lysine residues thereof referenced by Sanofi would in fact be available for conjugation reactions." Prelim. Resp. 28. Patent Owner also asserts "Sanofi has not explained why the specific reaction parameters described in Example 2 and Table 1 of GSK-711 would be likely to result in a serotype 22F glycoconjugate having the claimed molecular weight parameters." *Id.* 28–29. Patent Owner asserts "Table 2 does not state that the 22F polysaccharide size in the actual PS22F-PhtD glycoconjugate was 160 kDa." *Id*. 29.

On the current record, we find this argument unpersuasive because Dr. Lees has explained why the 22F size in GSK-711 would have been expected to fall within the claimed molecular weight range. Dr. Lees has opined that "a 22F-PhtD conjugate synthesized using the CDAP chemistry would naturally result in highly crosslinked lattices, each of which contains multiple saccharide molecules and multiple carrier protein molecules." Ex. 1005 ¶ 142. Dr. Lees continues

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

Ex. 1005 ¶ 143. Dr. Lees further states "the glycoconjugates described in Table 2, including 22F glycoconjugates, were purified using Sephacryl S400HR gel filtration, which has a size exclusion limitation under 8,000 kDa." Ex. 1005 ¶ 144. Thus, Dr. Lees has persuasively explained why the 22F glycoconjugate disclosed in GSK-711 would have been expected to

exceed the lower limit of the 1000 kDa range but remain below the upper limit of 12,500 kDa recited in claim 1.

Patent Owner asserts "Table 2 does not state that the 22F polysaccharide size in the actual PS22F-PhtD glycoconjugate was 160 kDa. Rather, Table 2 indicates that this was the size of the 22F polysaccharide used prior to the activation and conjugation reactions." Prelim. Resp. 29–30. Patent Owner asserts "it is likely that some level of fragmentation of the serotype 22F polysaccharides occurred during the activation and conjugation reactions described in GSK-711, and that the final polysaccharides in the serotype glycoconjugate reactions were smaller than the molecular weight sizes listed in Table 2." *Id*. 30–31.

On the current record, we find this argument unpersuasive because this represents a mere assertion with limited and general supporting evidence of record (*see* Ex. 1011, 166–167, col. 1), particularly as balanced against the expert declaration of Dr. Lees stating "a POSA would reasonably expect that the average molecular weight of all lattices in the 22F-PhtD conjugate should be well above 1000 kDa." Ex. 1005 ¶ 143. [A]rguments of counsel cannot take the place of evidence lacking in the record." *Estee Lauder Inc. v. L'Oréal, S.A*., 129 F.3d 588, 596 (Fed. Cir. 1997) (*citing Knorr v. Pearson*, 671 F.2d 1368, 1375 (CCPA 1982)).

Patent Owner performs a calculation for the serotype 1 polysaccharide and calculates "the "smallest" possible glycoconjugate determined using Sanofi's calculation *exceede*d the actual PS1-PD glycoconjugate sizes as provided in Table 2." Prelim. Resp. 32. Based on their calculation, Patent Owner concludes Petitioner's "'calculation' should be dismissed." *Id*.

On the current record, we find this argument unpersuasive. We note that even the calculations performed by Patent Owner results in values fairly close to the final actual molecular weights. *See* Prelim. Resp. 32. Moreover, the actual data in Table 2 shows that for a conjugate of PS4-PD, with a lower starting polysaccharide size and an identical protein carrier to polysaccharide ratio as the PS1 calculated by Patent Owner, the actual conjugate size exceeds a relative calculated size with a measured size of 1303–1606 kDa. *See* Ex. 1007, 53.

> Patent Owner asserts Petitioner cites
>
> documents (GSK-711, Merck-086, EP 0497524, EP0497525) that disclose extremely broad ranges of molecular weights for polysaccharides (from 80-1000 kDa). *Id*.; EX1005 at ¶¶ 148, 151. . . . Nowhere in any of the documents cited by [Petitioner] is there any guidance as to what molecular weight size should be selected for a serotype 22F polysaccharide.

Prelim. Resp. 33.

On the current record, we find this argument unpersuasive because the overlapping range itself suggests that molecular weight values within the overlapped range are obvious. *Peterson*, 315 F.3d at 1329. The obviousness of the claimed range is evident when the ranges overlap, as here, with the higher end point of the GSK-711 range overlapping the lower endpoint of the claimed range. *See In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (overlap only at the end points). Moreover, GSK-711 teaches in claim 61 an "immunogenic composition of any preceding claim wherein the average size (e.g. M_w) of the saccharides is above 50 kDa, e.g., 50–1600." Ex. 1007, 82. Thus, GSK-711 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 molecular weight added by the

CRM_{197} protein carrier. Ex. 1007, 82; Ex. 1005 ¶ 52. "Such overlap itself provides sufficient motivation to optimize the ranges." *In re Applied Materials, Inc*., 692 F.3d 1289, 1295 (Fed. Cir. 2012).

Patent Owner asserts Petitioner "has not identified any disclosure in GSK-711 or Merck-086 that would have directed a POSA, at the priority date of the '559 patent, to utilize any particular sized serotype 22F polysaccharide, or to choose a larger polysaccharide over a smaller polysaccharide." Prelim. Resp. 34.

On the current record, we find this argument unpersuasive because GSK-711 provides specific reasons to optimize the saccharide conjugates for larger sizes by teaching "immunogenic conjugates prone to hydrolysis may be stabilised by the use of larger saccharides for conjugation. The use of larger polysaccharides can result in more cross-linking with the conjugate carrier and may lessen the liberation of free saccharide from the conjugate." Ex. 1007, 12:31–34. GSK-711 teaches "that saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease." Ex. 1007, 13:1–3. GSK-711 recognizes optimization for larger size saccharide-protein conjugates, limited only by a requirement to be "filterable through a 0.2 micron filter." Ex. 1007, 13:12, *cf*. Pet. 39.

Therefore, GSK-711 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 provided no evidence of any secondary consideration and asserts they were "not required to submit any data or evidence of non-obviousness during prosecution of the '559 patent because the Examiner *never rejected* the claims for being obvious." Prelim. Resp. 35.[13]

We acknowledge that Patent Owner was not previously under any obligation to submit evidence of secondary considerations, and does not identify any such secondary consideration evidence currently present in the '559 Specification. However, now that the obviousness issue has been raised, Patent Owner may move to introduce such evidence under 37 C.F.R. § 42.123(a).

Patent Owner asserts: "Neither Merck-086 nor the referenced documents cited in Merck-086 (neither of which was submitted as a formal exhibit) teaches or suggests a molecular weight of a serotype 22F polysaccharide." Prelim. Resp. 38.

On the current record, we find this argument unpersuasive because Merck-086, which teaches multivalent immunogenic vaccine compositions including 22F, was relied upon to show that the ratio of carrier protein to polysaccharide. Pet. 20–21, citing Ex. 1008 ¶ 104.

[13] We note that the absence of an obviousness rejection by the Examiner supports institution under § 325(d), because none of the same prior art, statutory section of 35 U.S.C. § 103, or arguments was previously presented to the Office. *See* 35 U.S.C. § 325(d).

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

Patent Owner asserts a "POSA would not have found it obvious to generate the claimed compositions having the recited polysaccharide to carrier protein ratio based on the disclosures of GSK-711 and Merck-086 because GSK-711 teaches away from the claimed ratio." Prelim. Resp. 38. Patent Owner asserts "Table 1 of GSK-711 provides a pre-conjugation polysaccharide to protein ratio for a serotype 22F/protein carrier mixture that is outside the '559 patent claimed range." *Id*. 40, citing Ex. 1007 50–51. Patent Owner asserts "GSK-711 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. 42.

On the current record, we find this argument unpersuasive. Patent Owner acknowledges that GSK-711 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* Prelim. Resp. 41. 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-711 shows the immunogenicity for the two serotype 22F conjugates as either 37% or 28–31%, demonstrating similar results for both conjugates. Ex. 1007, 53. Indeed, GSK-711 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, 53:12–14. Thus, GSK-711 is reasonably understood as recognizing that either 22F conjugate may be used in the multivalent vaccine. Patent Owner points to no teaching in GSK-711 that criticizes, discredits, or discourages the use of a ratio within the range required by claim 1.

> Patent Owner asserts Petitioner
>
> points to several ranges selected from one of several long lists in GSK-711 that refer to a polysaccharide to protein range between 0.4 to 2; 0.4 and 0.67; and 0.5 and 1. Pet. at 34-35; EX1007 at 20:1-6. [Petitioner] alleges that this range is the same as the ratio range claimed in the '559 patent. Pet. at 35. However, the referenced list includes various different ratio ranges that are generic to all S. *pneumoniae* polysaccharides, and nothing in this list specifies any particular range for a serotype 22F glycoconjugate.

Prelim. Resp. 42–43. Patent Owner asserts "other sections of GSK-711 refer to a variety of other polysaccharide to protein ratio ranges that fall well *outside* of the claimed range." Prelim. Resp. 43.

On the current record, we find this argument unpersuasive because GSK-711 discloses a range of ratios of polysaccharide to carrier protein that includes and fully overlaps the range claimed. Ex. 1007, 19:1–6. *Peterson*, 315 F.3d at 1329. To the extent that GSK-711 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.")

Regarding dependent claims 3–19, 23–37, 42, 42, and 45, Patent Owner only asserts regarding claims 3 and 4 that "neither GSK-711 nor Merck-086 exemplifies any immunogenic compositions that include serotype 10A, 11A or 15B glycoconjugates." Prelim. Resp. 47.

On the current record, we find this argument unpersuasive because Petitioner points out that GSK-711 specifically recites that in "one embodiment the multivalent pneumococcal vaccine of the invention will be selected from the following serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F." Ex. 1007, 7:1–3, *cf*. Pet. 50, 51. Therefore, contrary to Patent Owner's assertion, GSK-711 specifically suggests the use of 10A, 11A, and 15B in pneumococcal vaccine compositions. *Cf*. Pet. 50, 51; Ex. 1005 ¶¶ 160–161.

We find that the current evidence of record in GSK-711 and Merck-086, as supported by Dr. Lees, provides a reasonable likelihood that the references render the subject matter of claims 1, 3–19, 23–37, 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 GSK-711 and Merck-086 suggest multivalent immunogenic compositions comprising *S. pneumoniae* serotype 22F conjugated to a carrier protein. Ex. 1007, 67:36–37; Ex. 1008 ¶ 114. Moreover, as Petitioner points out, Table 2 of GSK-711 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, 53.

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, 3–19, 23–37, 41, 42, and 45 as obvious over GSK-711 and Merck-086.

E. Obviousness over GSK-711, Merck-086, Lees-2008, PVP-2013, and Pfizer-605

Petitioner contends that claims 2, 40, and 43 are unpatentable under 35 U.S.C. § 103 as obvious over GSK-711, Merck-086, Lees-2008, PVP-2013, and Pfizer-605. Pet. 66–70.

Petitioner asserts "Lees-2008 establishes that O-acetyl groups on polysaccharides were considered desired epitopes." Pet. 67. Petitioner asserts PVP-2013 "indicates that for 22F polysaccharides, the permitted O-acetylation level by NIID is '0.5–1.5' mM acetate per mM polysaccharide unit, which again is well above the threshold in claim 2. Lees ¶227; Ex. 1012, 3, 4." Pet. 68. Petitioner asserts Pfizer-605 taught "to prepare glycoconjugates and preserve O-acetyl groups on the native polysaccharide. Lees ¶232." Pet. 69.

Petitioner asserts it would have been obvious to "use reductive amination in DMSO as disclosed Pfizer-605 and would have had a

reasonable expectation that such a modified conjugation process would successfully preserve the O-acetylation level on the native 22F polysaccharide." Pet. 69–70.

Patent Owner asserts the "minimum acetate content requirements of claims 2, 40 and 43 would not have been obvious in view of GSK-711, Merck-086, Lees-2008, PVP 2013, or Pfizer-605, whether viewed alone or in combination." Prelim. Resp. 48. Patent Owner asserts: "In the context of several specific pneumococcal glycoconjugates, Lees-2008 teaches that *O*-acetylation is not necessary. . . . As such, a POSA would have been more likely to consider *O*-acetyl groups to be non-essential for inducing immunogenicity" Prelim. Resp. 49–50.

Patent Owner asserts

> The 23-valent free unconjugated polysaccharide vaccine, referred to in PVP-2013, is a different type of pneumococcal vaccine as compared to that claimed in the '559 patent. EX1012 at 1, 4. There is no carrier protein in the PVP-2013 free polysaccharide compositions, as the polysaccharides in a free polysaccharide-based vaccine composition are not conjugated to any carrier protein. EX 1011 at 4-5; EX 1017 at 1.

Prelim. Resp. 51. Patent Owner asserts "Even assuming that PVP-2013 did suggest the importance of *O*-acetylation for all pneumococcal glycoconjugates, PVP-2013 does not provide any guidance about how to preserve *O*-acetylation during a conjugation reaction." Prelim. Resp. 52. Patent Owner asserts: "Nowhere does Pfizer-605 state that DMSO would have any effect on preserving *O*-acetylation, or that it would have any utility for serotype 22F glycoconjugates." Prelim. Resp. 54. Patent Owner asserts:

> In fact, Pfizer-605 suggests that DMSO would not be useful for glycoconjugates such as serotype 22F glycoconjugates. Pfizer-

> 605 states that DMSO conjugation may be useful for serotypes polysaccharides that contain phosphodiester linkages between their repeat units . . . At the priority date of the '559 patent, a POSA understood that a serotype 22F polysaccharide did not include any phosphodiester linkages.

Prelim. Resp. 54–55.

On the current record, 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. While we recognize that Lees-2008 states "*O*-acetyl groups in serotype 9V and 18C PSs may not be required for the PS to induce functional antibodies", Lees-2008 also states "*O*-acetyl . . . moieties, are integral components of several of the pneumococcal capsular PSs and are considered to be important immunodominant epitopes." Ex. 1011 164. Dr. Lees states "In the native 22F polysaccharide, O-acetyl groups are present in ~ 80% (*i.e.,* 0.80) of the repeating units of the polysaccharide. Ex. 1026 at 9." Ex. 1005 ¶ 225. Consistent with Dr. Lees' statement, PVP 2013 states the "*O*-acetate content (*O*-acetyl/polysaccharide unit molar ratio) shall be within the range of the following specification" where the range for serotype 22F is given as "0.5–1.5." Ex. 1012, 3–4. Consequently, PVP 2013 provides an express suggestion to utilize a molar ratio of acetate to polysaccharide for serotype 22F in an actual pneumococcal polyvalent vaccine that falls within the requirements of claims 2, 40, and 43.

Dr. Lees supports a finding of a reasonable expectation of success in obtaining an acetate range as desired by PVP 2013 for 22F. Dr. Lees states that obtaining an *O*-acetate content within the range desired by PVP 2013 "can be achieved by using those conjugation conditions that do not alter or

remove the O-acetyl groups present on the native 22F polysaccharide." Ex. 1005 ¶ 231. Dr. Lees states, without evidentiary contradiction, that:

> It was a well-known scientific principle that a protic solvent such as water is required to donate protons in order to alter or remove O-acetyl moieties on polysaccharides. An "aprotic solvent" such as DMSO cannot donate protons. Therefore, using DMSO in reductive amination prevents the potential loss of O-acetyl groups.

Ex. 1005 ¶ 232. Dr. Lees states "Pfizer-605 specifically teaches methods of preparing glycoconjugates using reductive amination in DMSO." *Id*. Pfizer-605 teaches a "conjugation step is performed in DMSO via a reductive amination mechanism in the presence of sodium cyanoborohydride." Ex. 1013, 12:32–34. Thus, the evidence of record supports Petitioner's position that an ordinary artisan "would have had a reasonable expectation that such a modified conjugation process would successfully preserve the O-acetylation level on the native 22F polysaccharide." Pet. 70.

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 as obvious over GSK-711, Merck-086, Lees-2008, PVP-2013, and Pfizer-605.

F. Obviousness over GSK-711, Merck-086, GSK-531

Petitioner contends that claims 20–22 are unpatentable under 35 U.S.C. § 103 as obvious over GSK-711, Merck-086, and GSK-531. Pet. 70–72.

> Petitioner asserts:
>
> Combination vaccines are desirable because they provide broad coverage and reduce the number of vaccine injections that need to be administered to infants, among other benefits. Lees [Ex. 1005] ¶235; Ex. 1081, 2. Therefore, a POSA would have been motivated to include an antigen from other pathogens in the claimed composition, as recited in claims 20–22.

Pet. 71. Petitioner asserts

> GSK-531 specifically teaches that its disclosed pneumococcal glycoconjugates (including a 22F glycoconjugate) can be mixed with other antigens, including those specifically recited in claim 21, such as diphtheria toxoid (DT), tetanus toxoid (TT), and pertussis components such as detoxified Pertussis toxoid (PT) and filamentous haemagglutinin (FHA) with optional pertactin (PRN) and/or agglutinin 1 +2, and Hepatitis B surface antigen (HepB). Lees [Ex. 1005] ¶237; Ex. 1014, 20:25-31. It also teaches that its pneumococcal glycoconjugates (including a 22F glycoconjugate) can be mixed with other antigens, including those recited in claim 22, such as conjugates of a capsular saccharide from *N. meningitidis* A, C, W or Y. Lees [Ex. 1005] ¶238; Ex. 1014, 21:1-3.

Pet. 71–72.

Patent Owner asserts "neither Sanofi nor its expert, Dr. Lees, has demonstrated that claim 1 is obvious over GSK-711, Merck-086 or GSK-531 and the 'general knowledge.' Therefore, Sanofi has likewise not met its burden to show that claims 20-22 are obvious." Prelim. Resp. 56.

We find Petitioner has the better position. Claims 20 and 22 depend from claim 1 and claim 21 depends from claim 20. Patent Owner does not argue that claims 20–22 are independently patentable. As discussed above, on this record, Petitioner has established a reasonable likelihood that claim 1 would have been obvious over GSK-711 and Merck-086. GSK-531 teaches

combination vaccines, and Petitioner provides cogent reasons supporting the use of such combination vaccines. Pet. 70–72, Ex. 1014, 19–20.

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 20–22 as obvious over GSK-711, Merck-086, and GSK-531.

G. Obviousness over GSK-711, Merck-086, Pfizer-605

Petitioner contends that claims 38 and 39 are unpatentable under 35 U.S.C. § 103 as obvious over GSK-711, Merck-086, and Pfizer-605. Pet. 73–75.

Petitioner asserts

> Pfizer-605 describes the use of size exclusion chromatography with a CL-4B column to profile the relative molecular size distribution of the pneumococcal conjugates. Lees [Ex. 1005] ¶243; Ex. 1013, 36–37. Specifically, Example 17 characterizes 19A-CRM_{197} glycoconjugates using CL-4B column. *Id*. Additionally, in connection with a long-term stability study, it specifically teaches that a preferred value for conjugate molecular sizes is about 70% 0.3 K_d in a CL-4B column, which is well above the recited limitation of "at least 30%" in claim 38. Lees [Ex. 1005] ¶243; Ex. 1013, 36–37, Table 7.

Pet. 73. Petitioner asserts "POSA would have had the motivation to optimize the glycoconjugation process of GSK-711 according to what's taught in Pfizer-605 to achieve the threshold recited in Claim 38." Pet. 74. Petitioner similarly asserts for claim 39 that "Pfizer-605 specifically teaches that a preferred free saccharide level in pneumococcal glycoconjugates below 20–25%." Pet. 74–75.

Patent Owner asserts: "Neither Sanofi nor its expert, Dr. Lees, has demonstrated that claim 1 is obvious over GSK-711, Merck-086, Pfizer-605

and the 'general knowledge.' Therefore, Sanofi has likewise not met its burden to show that claims 38 or 39, which incorporate all of the limitations of claim 1, are obvious." Prelim. Resp. 58.

We find Petitioner has the better position. Claims 38 and 39 depend from claim 1. Patent Owner does not argue that claims 38 and 39 are independently patentable. As discussed above, on this record, Petitioner has established a reasonable likelihood that claim 1 would have been obvious over GSK-711 and Merck-086. Pfizer-605 teaches particular free polysaccharide levels in pneumococcal conjugates, and Petitioner provides cogent reasons supporting the use of such combination vaccines. Pet. 73–75, Ex. 1013, 36–37.

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 39 as obvious over GSK-711, Merck-086, and Pfizer-605.

H. Obviousness over GSK-711, Merck-086, Hsieh 2000

Petitioner contends that claim 44 is unpatentable under 35 U.S.C. § 103 as obvious over GSK-711, Merck-086, and Hsieh 2000. Pet. 75–76.

Petitioner assets

> While GSK-711 does not specifically characterize the degree of conjugation in its 22F-glycoconjugates, the degree of conjugation recited in claim 44 had already been achieved in many glycoconjugates before the earliest possible priority date. Lees [Ex. 1005] ¶250. For example, Hsieh-2000 characterized saccharide-CRM_{197} conjugates included in *Hib*, pneumococcal and meningococcal vaccines successfully developed by Wyeth and observed that the formulation of the covalent bonds between lysines and polysaccharides had been "consistent in the range of 6–9," (Ex. 1015, 8), which falls entirely within the

> range of 2–15 as claimed in claim 44. Lees [Ex. 1005] ¶¶251-252.

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

Patent Owner asserts: "Since GSK-711 teaches that 22F glycoconjugates were unique, a POSA would not have expected that the general disclosure of Hsieh-2000 regarding degree of conjugation would be applicable to serotype 22F glycoconjugates." Prelim. Resp. 60. Patent Owner asserts

> Hsieh-2000 concludes that "[n]o single parameter can be used to indicate the potency of a conjugate vaccine. Detailed analyses of these parameters are needed to ensure consistency of the manufacturing process." EX1015 at 11. Thus, Hsieh-2000 cautions that before settling on an optimal vaccine composition, "detailed analyses" of each parameter is required. *Id*. This teaching by Hsieh-2000 directs a POSA away from the assumptions made by Sanofi throughout its Petition, *i.e.*, assuming that molecular weights or polysaccharide to protein ratios are interchangeable between different serotype glycoconjugates.

Prelim. Resp. 61.

On the current record, we find Petitioner has the better position. Claim 44 requires the "degree of conjugation of said glycoconjugate is between 2 and 15." Ex. 1001, 144:32–34. Dr. Lees states "Hsieh-2000 teaches that a typical degree of conjugation of a successful polysaccharide-CRM_{197} conjugate is 6–9, entirely within the claimed range of "between 2 and 15" in claim 44." Ex. 1005 ¶ 251–252 (citing Ex. 1015, 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. 1015, 8. Thus, the only evidence of record, Hsieh 2000, teaches a degree of conjugation between 6 and 9. Ex. 1015, 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 GSK-711 and Merck-086 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. 1015, 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 claim 44 as obvious over GSK-711, Merck-086, 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 1–45 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 of claims 1–45 of the '559 patent is instituted with respect to all grounds set forth in the Petition;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '559 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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