

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

PFIZER INC.,
Patent Owner.

Case IPR2018-00187
Patent 9,492,559 B2

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

FREDMAN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION AND RELATED ORDERS

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

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

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

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

I. INTRODUCTION

A. Background

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

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

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

On February 12, 2019, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 58 (“Tr.”).

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–45 of the ’559 patent are unpatentable. *See* 35 U.S.C. §316(e). Additionally, the Motions to Exclude Evidence by Petitioner and Patent Owner have been decided below in Sections IV and V and the Motion to Amend has been decided below in Section III.

B. Related Proceedings

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

C. The ’559 Patent (Ex. 1001)

The ’559 patent involves vaccines for “vaccination of human subjects, in particular infants and elderly, against pneumococcal infections” Ex. 1001, 1:21–22. “Pneumonia, febrile bacteraemia and meningitis are the most common manifestations of invasive pneumococcal disease, whereas bacterial spread within the respiratory tract may result in middle-ear infection, sinusitis or recurrent bronchitis.” *Id.* at 1:28–32. “Pneumonia is by far the most common cause of pneumococcal death worldwide.” *Id.* at 1:46–48.

The '559 patent teaches the “etiological agent of pneumococcal diseases, *Streptococcus pneumoniae* (pneumococcus), is a Gram-positive encapsulated coccus,^[1] surrounded by a polysaccharide capsule.^[2]

Differences in the composition of this capsule permit serological differentiation between about 91 capsular types.” *Id.* at 1:49–53.

“Pneumococcal conjugate vaccines (PCVs) are pneumococcal vaccines used to protect against disease caused by *S. pneumoniae* (pneumococcus).” *Id.* at 1:59–61. “There are currently three PCV vaccines^[3] available on the global market: PREVNAR® (called PREVENAR® in some countries) (heptavalent vaccine), SYNFLORIX® (decavalent vaccine) and PREVNAR 13® (tridecavalent vaccine).” *Id.* at 1:61–65.

The '559 patent teaches “there is a need to address remaining unmet medical need for coverage of pneumococcal disease due to serotypes not found in PREVNAR 13® and potential for serotype replacement over time.” *Id.* at 2:3–6.

¹ A “coccus” is defined as “a spherical bacterium.” *See* <https://www.merriam-webster.com/dictionary/coccus>.

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

³ The valency of a vaccine refers to the number of different serotypes of bacteria to which the vaccine induces immune response (e.g., a tridecavalent vaccine protects against thirteen different bacterial strains).

D. Illustrative Claims

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

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

Ex. 1001, 141:28–34.

E. The Instituted Grounds of Unpatentability

We instituted trial based on each challenge to the patentability of the '559 patent presented in the Petition (Pet. 4, 15, 17):

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

⁴ Biemans et al., WO 2007/071711 A2, published June 28, 2007 (“GSK-711,” Ex. 1007).

⁵ Caulfield et al., US 2011/0195086 A1, published Aug. 11, 2011 (“Merck-086,” Ex. 1008).

⁶ Lees et al., “Chapter 11. Conjugation Chemistry,” In: *Pneumococcal Vaccines: The Impact of Conjugate Vaccine* (Ed. George R. Siber et al.); pp. 163–174 (2008) (“Lees-2008,” Ex. 1011).

⁷ “*Pneumococcal Vaccine Polyvalent*” revision to Japan’s “*Minimum Requirements for Biological Products*” published on the website of Japan’s National Institute of Infectious Diseases (as of March 2, 2013) (“PVP 2013,” Ex. 1012).

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

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

ANALYSIS

A. Claim Interpretation

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

⁸ Prasad, A.K., US 7,955,605 B2, issued June 7, 2011 (“Pfizer-605,” Ex. 1013).

⁹ Biemans et al., WO 2011/110531 A2, published Sept. 15, 2011 (“GSK-531,” Ex. 1014).

¹⁰ Hsieh, *Characterization of Saccharide-CRM₁₉₇ Conjugate Vaccines*, In: *Physico-Chemical Procedures for the Characterization of Vaccines* (Eds. Brown F., Corbel M., and Griffiths E.); Vol. 103, pp. 93–104; Basel; Karger, 2000 (“Hsieh 2000,” Ex. 1015).

¹¹ A recent amendment to this rule does not apply here because the Petition was filed before November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018).

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

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

1. “*immunogenic*”

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

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

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

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

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

Next we turn to the Specification of the ’559 patent. When the ’559 patent uses the term “immunogenic,” the ’559 patent identifies “a need for immunogenic compositions that can be used to induce an immune response against additional *Streptococcus pneumoniae* serotypes.” Ex. 1001, 2:10–13. The ’559 patent states that multiple serotypes ranging from 7 to 25 may be included in the “immunogenic composition.” Ex. 1001, 3:4–6. The ’559 patent teaches the “pneumococcal opsonophagocytic assay (OPA), which measures killing of *S. pneumoniae* cells by phagocytic effector cells

in the presence of functional antibody and complement, is considered to be an important surrogate for evaluating the effectiveness of pneumococcal vaccines.” Ex. 1001, 88:52–56. The ’559 patent supports an interpretation of “immunogenic” which requires elicitation of functional antibody for each component in the composition, consistent with the interpretation of Patent Owner.

During prosecution of the ’559 patent, the Examiner cited art that disclosed both the 22F conjugate and other conjugates to address the claimed compositions for dependent claims. See Ex. 1004, 33–34. The Examiner allowed the claims after amendment to include the ranges for molecular weight and ratio of polysaccharide to carrier protein. See Ex. 1004, 11. The Examiner did not address the claim construction issue.

Accordingly, upon review of the parties’ arguments and the evidence before us, including the claims, specification, and prosecution history of the ’559 patent, we conclude that the term “immunogenic,” as it is used in that patent, is reasonably construed as requiring that functional antibody be elicited against each immunogen contained in the composition.

Consequently, to meet the limitations of claim 1 of the ’559 patent, which recites a single immunogen, serotype 22F, only functional antibodies to serotype 22F would be required. However, for claim 3 of the ’559 patent that requires serotypes 22F, 15B, and 33F, functional antibodies against all three serotypes would be required. Similarly for other claims, the term “immunogenic” requires functional antibodies be elicited against any immunogens specifically recited and required.

B. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art;¹² and (4) where in evidence, objective indicia of nonobviousness.¹³ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

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

¹² Petitioner states that a person with the level of skill in the art at the time of the invention “would have had a Ph.D. or equivalent degree in chemistry, immunology, or other biological sciences or an MD and at least 2 years of experience in glycoconjugate vaccine research and development, or would have an M.S. degree and at least 4 years of relevant experience.” Pet. 26, citing Ex. 1005 ¶ 77. Patent Owner “does not dispute Sanofi’s proposed level of skill for the person having ordinary skill in the art.” PO Resp 8. We agree with both parties regarding the level of ordinary skill in the art. *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. See *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

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

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

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

KSR, 550 U.S. at 421. “*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

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

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

C. Obviousness over GSK-711 and Merck-086

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

and the general knowledge of an ordinary artisan. Pet. 30–66. The thrust of Patent Owner’s position is that the cited prior art does not teach or suggest compositions with 22F glycoconjugates that are immunogenic, within the claimed molecular weight ranges, and within the claimed polysaccharide to carrier protein conjugate ratios. PO Resp. 1–5, 18–55. Based on our review of the arguments and the evidence of record, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of claims 1, 3–19, 23–37, 41, 42, and 45 would have been obvious over GSK-711, Merck-086, and the general knowledge of an ordinary artisan. After providing a discussion of the prior art and Petitioner’s position, we will address Patent Owner’s arguments.

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

GSK-711 teaches a *Streptococcus pneumoniae* vaccine comprising “capsular saccharide antigens (preferably conjugated), wherein the saccharides are derived from at least ten serotypes of *S. pneumoniae*” that may include an “*S. pneumoniae* saccharide conjugate of 22F.” Ex. 1007, 6:4, 24–26.¹⁴ GSK-711 teaches “*Streptococcus pneumoniae* capsular saccharides . . . may be conjugated to a carrier protein independently selected from the group consisting of . . . CRM197. . . .” Ex. 1007, 8:18–20. GSK-711 teaches “saccharide conjugates present in the immunogenic compositions of the invention may be prepared by any known coupling technique” and specifically, conjugates “can also be prepared by direct reductive amination methods. . . .” Ex. 1007, 15:9–10; 16:1. GSK-711 teaches “22F-PhtD administered within the 13-valent conjugate vaccine

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

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

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

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

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

2. Merck-086 (Ex. 1008)

Merck-086 teaches “a multivalent immunogenic composition having 15 distinct polysaccharide-protein conjugates. Each conjugate consists of a capsular polysaccharide prepared from a different serotype of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F or 33F) conjugated to a carrier protein, preferably CRM₁₉₇.” Ex. 1008 ¶ 2.

Merck-086 teaches “conjugates containing serotypes 22F and 33F provide[] robust antibody responses demonstrat[ing] the feasibility of expanding coverage of pneumococcal serotypes. . . .” Ex. 1008 ¶ 15. Merck-086 teaches the pneumococcal conjugate vaccine (PCV) with “induced high OPA^[15] GMTs to each serotype and a 100% OPA response rate for all 15 serotypes contained in the vaccine.” Ex. 1008 ¶ 114.

Merck-086 teaches “purified polysaccharides are chemically activated to make the saccharides capable of reacting with the carrier protein. . . .

Coupling to the protein carrier (*e.g.*, CRM₁₉₇) 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 CRM₁₉₇ carrier protein in a 0.2 – 2 to 1 charge ratio. The blended saccharide-CRM₁₉₇ 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 CRM₁₉₇ carrier protein with the total polysaccharide being composed of 2 µg of 14 serotypes including 22F and 4 µg of serotype 6B. Ex. 1008 ¶ 104.

¹⁵ Opsonophagocytosis.

3. Analysis

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

Petitioner asserts “GSK-711 demonstrate[s] that a 13-valent vaccine formulation containing the 22F-PhtD glycoconjugate induced anti-22F immune response in old mice, young mice, and guinea pigs, respectively. . . .” Pet. 31 (citing Ex. 1005 ¶¶ 125–128; Ex. 1007, 68–73). Petitioner also asserts “Merck-086 discloses a PCV15 composition containing a 22F-CRM₁₉₇ 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 CRM₁₉₇.” Pet. 34 (citing Ex. 1005 ¶ 134; Ex. 1007, 9:18–22, 11:4–27). Petitioner asserts the “22F-PhtD conjugate disclosed in Table 2 has the ratio of carrier protein to polysaccharide of 2.17. Lees [Ex. 1005] ¶137; Ex. 1007, Table 2. When converted to a polysaccharide to carrier protein ratio, this equals 0.46, which falls within the range claimed in claim 1.” Pet. 34. Petitioner asserts:

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

Pet. 36 (citing Ex. 1005 ¶ 140).

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

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

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

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

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

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

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

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

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

Having reviewed the cited evidence, and the record as a whole, we find that Petitioner has accurately described the above stated teachings of GSK-711 and Merck-086, which we adopt as our own. See Pet. 30–50. We focus our remaining analysis on Patent Owner’s arguments that the cited combination fails to teach or suggest an immunogenic composition including: (1) a serotype 22F glycoconjugate having a molecular weight of between 1000 kDa and 12,500 kDa; and (2) a polysaccharide to carrier protein ratio (w/w) of between 0.4 and 2.

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

Patent Owner asserts: “Claim 1 and each of the challenged dependent claims require that the recited serotype 22F glycoconjugate ‘has a molecular weight of between 1,000 kDa and 12,500 kDa. . . .’ GSK-711, Merck-086 and the general knowledge do not alone or in combination teach or suggest this limitation.” PO Resp. 19 (internal citation omitted).

i. Optimization of molecular weight

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

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

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

Patent Owner asserts:

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

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

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

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

Patent Owner asserts “Lees-2008 cautions that ‘careful control’ over numerous factors (*e.g.*, pH, temperature, ratio of protein and polysaccharide and concentration of each) is ‘key to successful conjugation.’” PO Reply 25 (citing Ex. 1011, 8). Patent Owner concludes that the “teachings of Lees-2008 show that more than routine experimentation would be needed to determine the appropriate molecular weight (or polysaccharide to protein ratio) of any given serotype glycoconjugate. . . .” PO Reply 26.

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

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

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

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

Merck-086 teaches that “[c]apsular polysaccharides from *Streptococcus pneumoniae* can be prepared by standard techniques known to those skilled in the art. For example, polysaccharides can be isolated from bacteria and may be sized to some degree by known methods (see, e.g., European Patent Nos. EP497524 and EP497525) and preferably by microfluidisation.” Ex. 1008 ¶ 17. Merck-086 teaches “[p]olysaccharides can be sized in order to reduce viscosity in polysaccharide samples and/or to improve filterability for conjugated products. In the present invention, capsular polysaccharides are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, **22F**, 23F and 33F of *S. pneumoniae*.” Ex. 1008 ¶ 17 (emphasis added). Merck-086 teaches that:

The different serotype saccharides are individually conjugated to the purified CRM₁₉₇ carrier protein using a common process flow. In this process the saccharide is dissolved, sized to a target molecular mass, chemically activated and buffer-exchanged by ultrafiltration. The purified CRM₁₉₇ is then conjugated with the activated saccharide and the resulting conjugate is purified by ultrafiltration prior to a final 0.2 µm membrane filtration.

Ex. 1008 ¶ 86.

Thus, Merck-086 disclosed methods to optimize the size of the polysaccharides using known techniques, including the serotype 22F polysaccharide, and taught to couple to known carrier proteins such as

CRM₁₉₇, while limiting the upper size range using membrane filtration. Ex. 1008 ¶¶ 17, 86. Thus, rather than fabricating desired sizes, Merck 2011 specifically provides methods to constrain polysaccharide sizes within a particular size range. Ex. 1006 ¶ 86.

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

GSK-711 teaches the “saccharide conjugates present in the immunogenic compositions of the invention may be prepared by any known coupling technique” including “direct reductive amination methods as described in US 4365170 (Jennings) and US 4673574 (Anderson). Other methods are described in EP-0-161-188, EP-208375 and EP-0-477508.” Ex. 1007, 15:9–16:3. GSK-711 is replete with suggestions to conjugate pneumococcal polysaccharides of various serotypes to CRM₁₉₇. See, e.g., Ex. 1007, 6.

GSK-711 teaches an “immunogenic composition of the invention may thus comprise one or more saccharide conjugates wherein the average size (e.g. weight-average molecular weight; Mw) of each saccharide before conjugation is above . . . 1000kDa.” Ex. 1007, 13:5–8. GSK-711 exemplifies a range of conjugate sizes where the lowest reported value is 1303 kDa and the highest reported value is 9572 kDa, both values falling within the range of 1000 kDa to 12,500 kDa required by claim 1. Ex. 1007, 53 (Table 2).

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

Thus, GSK-711 demonstrates that the artisan preferred a range of conjugated polysaccharide sizes overlapping that recited by the ’559 claims, disclosed methods to optimize the size of the polysaccharides as well as to couple to known conjugates such as CRM₁₉₇. Ex. 1007, 13–15, 54–55.

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

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

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

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

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

Ex. 1005 ¶ 151.

Dr. Lees’ position is supported by Dr. Kasper’s¹⁶ statement that “[g]iven that routine conjugation techniques and conditions readily achieved those disclosed molecular weights (as well as polysaccharide to protein ratios falling within the claimed range), a POSITA would have understood such molecular weights to be typical of immunogenic conjugates.” Ex. 2037 ¶ 101.

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

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

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

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

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

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

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

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

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

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

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

The evidence of record, therefore, shows that optimization of polysaccharide conjugate size was well known to the person of ordinary skill in the art, as even Patent Owner's expert Dr. Wang acknowledged that with regard to conjugation conditions, that "you can really control [them]." Ex. 1106, 157:2–5. This is also supported by Dr. Lees' statements and testimony that optimization of conjugate sizes was routine. Ex. 1005 ¶ 151,

Ex. 2054, 88:11–22. This evidence supports a determination that routine optimization of conjugate size would have been obvious within the size range of Table 2 of GSK-711 (Ex. 1007, 54) and the express 50–1600 kilodalton range of GSK-711. Ex. 1007, 82. This routine optimization would have been particularly obvious when combined with the teachings of Merck-086 to optimize the size of the polysaccharides using known techniques, including the serotype 22F polysaccharide; with teachings of GSK-711 of methods to optimize the size of the polysaccharides as well as to couple to known conjugates such as CRM₁₉₇; and with Dr. Kasper’s statement that “routine conjugation techniques and conditions readily achieved those disclosed molecular weights.” Ex. 2037 ¶ 101.

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

Lees-2008 notably teaches that serotype 22F vaccines are used in formulations, teaching “the currently available licensed 23-valent pneumococcal PS vaccine is formulated with PSs from the 23 most prevalent strains: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F.” Ex. 1011, 5. Lees-2008 teaches that “[s]ize fractionation is usually necessary” (Ex. 1011, 7) and that “[c]areful control over the factors relevant to the particular chemistry is key to successful conjugation. These factors include pH, temperature, the ratio of the protein and PS, and the concentration of each.” Ex. 1011, 8. Thus, Lees-2008 demonstrates that the factors necessary to obtain particular glycoconjugates are results optimizable variables, noting “[s]ince each

capsular serotype has a different structure, reaction conditions, including concentrations, molar ratios of periodate, oxidation times, and pH, must be optimized. . . .” Ex. 1011, 9. Lees-2008 explains that after the reaction has been completed, particular desired sizes of glycoconjugates can be obtained because “purification of the conjugate is usually performed by size exclusion, by using either size exclusion chromatography or membranes with appropriate molecular weight cutoffs.” Ex. 1011, 8.

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

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

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

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

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

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

We find that a preponderance of the evidence of record demonstrates that conjugate size is a results effective variable associated with improved stability of conjugates and good immune response, limited only by filter size, thereby rendering “optimization within the grasp of one of ordinary skill in the art.” *In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012). “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

We, therefore, conclude that a preponderance of the evidence of record supports Petitioner's position that the 1,000 to 12,500 kDa size range in claim 1 of the '559 patent, which overlaps with the 1303 and 9572 kDa in GSK-711, would have been consistent with the ranges optimized and used to generate multivalent vaccines. Pet. 40–44; Ex. 1007, 55:2–10. “In cases involving overlapping ranges, we and our predecessor court have

consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). *See also E.I. DuPont de Nemours & Company v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (reaffirming this obviousness doctrine).

ii. *CDAP conjugation and serotype 22F glycoconjugate molecular weight*

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

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

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

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

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

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

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

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

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

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

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

iii. *GSK-711 table 2 molecular weight calculations*

Patent Owner asserts that Petitioner

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

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

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

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

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

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

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

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

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

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

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

iv. Serotype 22F glycoconjugate size relative to polysaccharide

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

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

Patent Owner asserts that:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

v. *Merck-086 and molecular weight*

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

We agree with Patent Owner that Merck-086 has very limited disclosure regarding the size of glycoconjugates, only teaching that polysaccharides such as 22F can be conjugated to carrier proteins such as CRM₁₉₇. Ex. 1008, ¶¶ 17–18. However, the obviousness analysis is based on the combination of the disclosures of Merck-086 with GSK-711, not Merck-086 alone. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981) (“The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.”)

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

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

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

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

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

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

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

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

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

GSK-711 discloses a range of ratios of polysaccharide to carrier protein that includes and fully overlaps the range claimed. Ex. 1007, 19:1–6. *Peterson*, 315 F.3d at 1329. GSK-711 teaches “the majority of the conjugates, for example 6, 7, 8, 9 or more of the conjugates have a ratio of carrier protein to saccharide that is greater than 1:1, for example 1.1:1.” Ex. 1007, 19:1–6. Dr. Lees further explains that “[f]or pneumococcal conjugate vaccines, while the particulars may differ for a specific serotype, the WHO guidelines specifically recommend a ratio ‘in the range of 0.3–3.0.’” Ex. 1005 ¶ 58 (citing Ex. 1019, 119 (“For pneumococcal conjugate vaccines the ratio is typically in the range 0.3–3.0 but varies with the serotype.”)). Patent Owner also acknowledges that GSK-711 teaches an example of a final

conjugate of serotype 22F that has a polysaccharide to protein ratio of 0.46, within the range required by claim 1. See PO Resp. 43. Dr. Lees supports the obviousness of the claimed range, noting that:

It is desirable to avoid very low or very high polysaccharide-to-carrier protein ratios. Glycoconjugates having a very low polysaccharide-to-carrier protein ratio would require administration of large amounts of the conjugates in order to provide an effective amount of the polysaccharide. Ex. 1054 at 13. By contrast, glycoconjugates with a very high polysaccharide-to-carrier protein ratio may interfere with the immunogenic role of the carrier protein.

Ex. 1005 ¶ 57.

The exemplary serotype 22F-PhtD conjugate with a 0.46 ratio, along with the overlapping ranges disclosed and claimed by GSK-711, the overlapping Merck-086 0.2–2 to 1 charge ratio, and the statement by Dr. Lees that this range substantially overlaps the World Health Organization’s recommended ratios for pneumococcal conjugate vaccines, all provide reasonable motivation for the ordinary artisan to have selected ratios for the serotype 22F conjugate within the range required by claim 1 of the ’559 patent. Ex. 1007, 19:1–6; Ex. 1008, 11 ¶ 94; Ex. 1005 ¶ 58; Ex. 1019, 119.

We recognize that Figure 6 of GSK-711 shows what Patent Owner states to be a 12 fold lower level of antibody titer for serotype 22F-PhtD with a 0.46 ratio relative to serotype 22F-AH-PhtD with a 3.66 to 4.34 ratio. See PO Resp. 46 (citing Ex. 1007, 93). We also recognize that Dr. Wang states that “a POSA would have focused on the glycoconjugate having the significantly superior immunogenicity, *i.e.*, PS22FPhtD.” Ex. 2058 ¶ 81.

However, GSK-711 expressly teaches that either conjugate may be used, noting a “13 valent vaccine was made by further adding the serotypes

19A and 22F conjugates above (with 22F either directly linked to PhtD, or alternatively through an ADH linker).” Ex. 1007, 54:12–14. Thus, the plain text of GSK-711 teaches that either conjugate may be used. Therefore, even if the GSK-711 teaching were interpreted as a preference for the higher polysaccharide to protein ratio rather than simply a preference for the ADH linker, it is well settled that disclosed examples, and even preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971). “[A] given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine.” *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). *See also In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (“The prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the [claimed] solution.”).

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

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

overlapping amounts to those recited in the claims of the '559 patent. Table 1 of Merck 2011 discloses an example that would reasonably have been expected to result in a 1:1 w/w ratio of the 22F polysaccharide to the CRM₁₉₇ carrier protein. Ex. 1008, ¶ 104. This expectation is supported by Dr. Kasper's statement that the ratios "resulted in an average polysaccharide to protein ratio in the conjugates of approximately 1." Ex. 2037 ¶ 115.

ii. *GSK-711 suggests overlapping polysaccharide to protein ratios*

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

Patent Owner compares these facts to *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853 (Fed. Cir. 2015), and asserts, "[s]imilar to the facts of *Insite*, the challenged patent claims recite a combination of features (*e.g.*, polysaccharide to protein ratios and molecular weights), and the cited prior art reference does not disclose one of the recited claim features (*i.e.*, molecular weight) in that combination." PO Resp. 52 (citing Ex. 1054, 13 "[t]he optimal [polysaccharide-protein] ratio has to be determined by experiment in pre-clinical studies or clinical trials.")

We do not find these arguments persuasive. In *Insite*, the Federal Circuit relied on District Court findings that "it would not have been obvious to a person of ordinary skill in the art to formulate a topical azithromycin formulation for ophthalmic treatment of any infection" because "there were

‘innumerable’ options for ophthalmic treatments” and concerns that azithromycin “might not penetrate ocular tissue based on its high molecular weight, charge and insolubility in water.” *Insite*, 783 F.3d at 861.

In contrast, here, both of the cited prior art references, GSK-711 and Merck-086, specifically direct the ordinary artisan to incorporate serotype 22F conjugates into pneumococcal vaccines. *See* Ex. 1008, ¶15 (“[T]he addition of new polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses demonstrates the feasibility of expanding coverage of pneumococcal serotypes not covered by existing pneumococcal vaccines.”). *See also* Ex. 1007, 4:12–15 (“The present invention provides an immunogenic composition . . . [that] comprises a 22F saccharide conjugate.”).

Moreover, as discussed above, the GSK-711 and Merck-086 together suggest molecular weights and polysaccharide to carrier protein ratios that overlap and fall within the ranges recited in claim 1 of the ’559 patent. *See, e.g.,* Ex. 1007, 19:1–6; Ex. 1008, 11–12; Ex. 1005 ¶ 58. In addition, the ordinary artisan was aware of desirable ranges of polysaccharide to carrier protein. Ex. 1019, 119. As Dr. Kasper noted “the acceptable range of ‘Saccharide content/protein ratio’ . . . for each of the seven disclosed conjugates,” though not including 22F, “overlaps to a large extent with the claimed ratio of 0.4 to 2, consistent with the general understanding in the art as of January 21, 2014 that such ratios are typical for immunogenic conjugates.” Ex. 2035 ¶¶ 112–113.

Therefore, unlike *Insite*, we conclude that the evidence of record directly suggests incorporation of a serotype 22F glycoconjugate into a pneumococcal vaccine and suggests selection of molecular weight and

polysaccharide to carrier protein ratio from a limited series of optimizable ranges disclosed in the prior art. We also conclude that the prior art provides a reasonable expectation of success in doing so, particularly in light of the disclosure in the prior art of functional glycoconjugates. Specifically, GSK-711 demonstrates an immunogenic serotype 22F glycoconjugate with an overlapping polysaccharide to carrier protein ratio and Merck-086 demonstrates an immunogenic serotype 22F glycoconjugate in a 1:1 polysaccharide to carrier protein ratio. Ex. 1007, 19:1–6; Ex. 1008, 11–12, Table 1. Patent Owner provides no evidence showing that any serotype 22F glycoconjugate fails to result in an immunogenic response.

Therefore, a preponderance of the evidence of record supports the obviousness of selecting polysaccharide to carrier protein ratio values for the serotype 22F polysaccharides within the 0.4 and 2 range recited in claim 1 of the '559 patent based on the disclosures of GSK-711, Merck-086, and the knowledge of the ordinary artisan, including the WHO guidelines.

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

Patent Owner asserts a “POSA reading claims 3 or 4 (or claims 5–8) would understand that all of the serotype glycoconjugates recited in these claims would be required to be immunogenic, not just serotype 22F glycoconjugates.” PO Resp. 53–54 (citing Ex. 2058 ¶ 88). Patent Owner asserts that “[n]either GSK-711 nor Merck-086 exemplifies the generation of a serotype 15B glycoconjugate (as required by claim 3) or a serotype 12F, 10A, 11A or 8 glycoconjugate (as required by claim 4).” PO Resp. 55 (citing Ex. 2058 ¶ 89). Patent Owner asserts Lees-2008 teaches that “multivalent pneumococcal glycoconjugate compositions ‘present additional complexities’ due to each serotype being chemically distinct, requiring

optimization of each glycoconjugate within the compositions.” PO Resp. 55 (citing Ex. 2058 ¶ 89).

While we agree, as noted above, that Patent Owner correctly construes the claims to require the term “immunogenic” to apply to all of the serotypes present in the composition, we are not persuaded that claims 3 and 4 are unobvious over the disclosures in GSK-711, Merck-086, and the knowledge of the person of ordinary skill in the art.

GSK-711 teaches a “multivalent pneumococcal vaccine of the invention will be selected from the following serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.” Ex. 1007, 7:1–3. Thus, GSK-711 expressly suggests a vaccine containing serotypes 10A, 11A, and 15. Just as we agreed with Patent Owner that the construction of the word “immunogenic” in claim 1 reasonably requires each serotype contained in a vaccine to induce an immune response, we also find that the disclosure of a vaccine by GSK-711 containing multiple serotypes also requires induction of an immune response, otherwise there would be no need to include a serotype unable to induce such a response. And indeed, GSK-711 uses the same term, immunogenic, to describe the pneumococcal vaccine composition. See Ex. 1007, 4:12.

We recognize that Dr. Wang correctly notes that “[n]either GSK-711 nor Merck-086 exemplifies the generation of a serotype 15B glycoconjugate (as required by claim 3) or a serotype 12F, 10A, 11A or 8 glycoconjugate (as required by claim 4).” Ex. 2058 ¶ 89. However, “[a]ll the disclosures in a reference must be evaluated . . . and a reference is not limited to the

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

We note that Dr. Kasper stated that at the time of invention, the ordinary artisan was aware of serotype 15B, that PVP 2013 discloses inclusion of serotype 15B in a pneumococcal vaccine, and that based on the prior art disclosures “a POSITA would have been motivated with a reasonable expectation of success to additionally include a serotype 15B conjugate.” Ex. 2037 ¶¶ 44, 88, 120. Dr. Kasper also noted that the “claimed serotypes were well-known to be prevalent and had already been included in the Pneumovax® 23 polysaccharide vaccine.” Ex. 2037 ¶ 122.

This is consistent with Dr. Lees’ statement that “[c]laims 3–8 [of the ’559 patent] collectively recite 20 additional serotypes. However, . . . all 20 of the recited serotypes were already included in multivalent pneumococcal vaccines on the market in 2014” and, therefore, “[o]ne would also have reasonably expected success because, as shown in GSK-711 and Merck-086, 22F and other new serotypes were successfully included in multivalent PCV compositions while maintaining the immunogenicity to all serotypes in the compositions.” Ex. 1005 ¶¶ 158–59.

We, therefore, conclude that incorporation of known immunogenic serotypes such as 10A, 11A, 15B, and 33F into the vaccine suggested by GSK-711, Merck-086, and the knowledge of the ordinary artisan would have been obvious in order to increase the coverage of serotypes of pneumococcal vaccines.

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

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

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

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

Patent Owner asserts “23-valent free unconjugated polysaccharide vaccine referred to in PVP2013 is not the same as the glycoconjugate compositions that are claimed” because “[t]here is no carrier protein in the PVP-2013 free polysaccharide compositions.” PO Resp. 58. Patent Owner

asserts “[b]ecause carrier proteins or glycoconjugates are not mentioned in PVP-2013, this document would not have taught a POSA how to arrive at the specific polysaccharide to protein ratio (w/w) recited in the ’559 patent claims.” PO Resp. 58. Patent Owner asserts “Pfizer-605 does not refer to any serotype 22F glycoconjugates, and, therefore, does not teach an appropriate molecular weight or polysaccharide to protein ratio for a serotype 22F glycoconjugate.” PO Resp. 59.

1. *Lees-2008 (Exhibit 1011)*

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

2. *PVP-2013 (Exhibit 1012)*

PVP-2013 is titled “Pneumococcal Vaccine Polyvalent” and was published on the website of Japan’s National Institute of Infectious Diseases (see Pet. 68). PVP-2013 discusses starting materials used to make vaccines including serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. See Ex. 1012, 1. PVP-2013 teaches various tests used to analyze polysaccharides used in the vaccines including, among others, an O-acetate content test. Ex. 1012, 3, 4. PVP-2013 provides a range of O-acetate for a variety of serotypes including a range of 0.5 – 1.5 for serotype 22F. Ex. 1012, 4.

3. *Pfizer-605 (Exhibit 1013)*

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

4. *Analysis*

We find Patent Owner’s arguments unpersuasive. Claim 2 requires “at least 0.1 mM acetate per mM polysaccharide” and claims 40 and 43 require a mM ratio that “is at least 0.6.” Ex. 1001, 141:35–37, 144:15–18, 27–30. Dr. Kasper stated “PVP 2013 specifies that, for a pneumococcal polysaccharide vaccine, serotype 22F capsular polysaccharide must contain an ‘O-acetyl/ polysaccharide unit molar ratio’ of ‘0.5 - 1.5’; that entire specified range meets the claimed ratio of ‘at least 0.1.’” Ex. 2037 ¶ 142 (citing Ex. 1009, 4). Consistent with Dr. Kasper’s statement, PVP 2013 states the “O-acetate content (O-acetyl/polysaccharide unit molar ratio) shall be within the range of the following specification” where the range for serotype 22F is given as “0.5–1.5.” Ex. 1012, 3, 4. Dr. Lees further performs a calculation on the PVP-2013 analysis, finding that “the permitted minimum ratio of O-acetylation level . . . is at least 0.625.” Ex. 1005 ¶ 229.

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

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

Indeed, Dr. Kasper explained that the prior art evidences “that O-acetyl groups can contribute to the immunogenicity of pneumococcal polysaccharides.” Ex. 2037 ¶ 143. This teaching evidencing that O-acetyl groups are associated with immunogenicity, in combination with the teaching of PVP-2013 to incorporate acetate into serotype 22F in particular at levels within the scope of the claims of the ’559 patent, demonstrates that the evidence of record better supports Petitioner’s position that use of acetate in the molar ratios suggested by PVP 2013 would have been expected to improve vaccine activity.

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

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

We therefore conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by GSK-711, Merck-086, and the knowledge of the ordinary artisan with the acetate ratios suggested by PVP-2013 in order to retain immunogenic activity as disclosed by PVP-2013 and Lees-2008 using known methods such as those of Pfizer-605.

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

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

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

1. GSK-531 (Exhibit 1014)

GSK-531 discusses forming a vaccine through conjugation of bacterial capsular saccharides, including *Streptococcus pneumoniae* serotype 22F, by reductive amination to proteins including CRM₁₉₇. Ex. 1014, 2:35–3:17, 7:34, 9:21. GSK-531 teaches including additional antigens in the

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

2. Analysis

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

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

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

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

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

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

1. *Pfizer-605 (Exhibit 1013)*

Pfizer-605 discusses “a multivalent immunogenic composition, wherein the capsular polysaccharides are from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9v, 14, 18C, 19A, 19F and 23E of *Streptococcus pneumoniae*, the carrier protein is CRM₁₉₇, and the adjuvant is an aluminum-based adjuvant.” Ex. 1013, 2:24–28. Pfizer-605 teaches “[c]haracterization of the conjugate . . . include[ed] use of size exclusion chromatography media (CL-4B) to profile the relative molecular size distribution of the conjugate.” Ex. 1013, 36:50–53. Pfizer-605 teaches “a preferred value for conjugate molecular size is about 70% 0.3 Kd, with a preferred free saccharide level below about 20–25%.” Ex. 1013, 24.

2. *Analysis*

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

further agree with Petitioner that claims 38 and 39 would have been obvious because Pfizer-605 discloses that size exclusion chromatography (SEC) with CL-4B sepharose is used to assess molecular size and Pfizer-605 teaches preferred values for conjugate size and free saccharide levels that overlap those of claims 38 and 39. “In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1329, 1330 (Fed. Cir. 2003).

Dr. Lees stated that, based on Pfizer-605, a POSA would have had motivation to prepare a 22Fglycoconjugate that meets the minimum percentage value “at least 30%” as measured by a K_d value below or equal to 0.3 in a CL-4B column as recited in claim 39 and would also have had a reasonable expectation of success that such a minimum threshold may be achieved by routine optimization of the conjugation process available in 2014.

Ex. 1005 ¶ 244.

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

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

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

characterized saccharide-CRM₁₉₇ conjugates included in *Hib*, pneumococcal and meningococcal vaccines successfully

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

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

Patent Owner asserts Petitioner “has not demonstrated that claim 1 is obvious over GSK-711, Merck-086, GSK-531 and the ‘general knowledge.’” Therefore, Sanofi has likewise not met its burden in showing that claim 44 is obvious.” PO Resp. 62. Patent Owner asserts “Hsieh 2000 does not refer to serotype 22F glycoconjugates. Ex. 2058, ¶102. Hsieh 2000 also does not contain any guidance about targeting any particular molecular weight or polysaccharide to protein ratio for a serotype 22F glycoconjugate.” PO Resp. 56 (citing Ex. 2040 ¶ 102).

1. *Hsieh-2000 (Exhibit 1015)*

Hsieh-2000 discusses the characterization of vaccines composed of polysaccharides conjugated to CRM₁₉₇, including a 7-valent pneumococcal saccharide-CRM₁₉₇ conjugate vaccine. Ex. 1015, 1. Hsieh-2000 teaches that “CRM₁₉₇ is a mutant of diphtheria toxin” and “lists the methods that have been used to characterize CRM₁₉₇” including “High Performance Size-exclusion Liquid Chromatography . . . [that] is adequate to control the consistency and purity of the product.” Ex. 1015, 2. Hsieh 2000 teaches that important parameters for conjugate vaccines include molecular size and polysaccharide to protein ratio among others. See Ex. 1015, 6. Hsieh

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

2. Analysis

We have already concluded that a preponderance of evidence supports the obviousness of claim 1 for the reasons discussed. We further agree with Petitioner that claim 44 would have been obvious because Hsieh-2000 discloses that size exclusion chromatography (SEC) with either CL-2B or CL-4B sepharose is used to assess molecular size and Hsieh-2000 discloses the typical extent of conjugation for CRM₁₉₇ conjugates, and how to measure it. Ex. 2035 ¶¶ 94–96. Claim 44 requires the “degree of conjugation of said glycoconjugate is between 2 and 15.” Ex. 1001, 144:32–34.

Dr. Kasper stated “[b]ased on Hsieh 2000, a POSITA would have been motivated with a reasonable expectation of success to construct the conjugate of claim 1 with a ‘degree of conjugation’ between 2 and 15.” Ex. 2035 ¶ 153. Dr. Lees similarly states that “Hsieh-2000 teaches that a typical degree of conjugation of a successful polysaccharide-CRM₁₉₇ conjugate is 6–9, entirely within the claimed range of ‘between 2 and 15’ in claim 44.” Ex. 1005 ¶ 252. Hsieh-2000 teaches “[f]or saccharide-CRM₁₉₇ conjugates, there is a limited number of exposed lysines on surface CRM₁₉₇, which can participate in the conjugation reaction. The loss of lysine has been relatively consistent in the range of 6-9.” Ex. 1015, 8. Thus, the only evidence of record, Hsieh 2000, teaches a degree of conjugation between 6 and 9. Ex. 1015, 8.

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

the statements of Dr. Kasper and Dr. Lees and the specific teachings of Hsieh-2000 do not persuade us that the specific conjugation degree of claim 44 would have been unobvious because the requirement is not an absolute expectation of success, but rather a reasonable expectation of success based on the teachings of the prior art. “Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success.*” *Kubin*, 561 F.3d at 1360 (internal quotation marks and citation omitted).

We, therefore, conclude that a preponderance of the evidence supports the obviousness of modifying the vaccine suggested by GSK-711, Merck-086, and the knowledge of the ordinary artisan with purification and conjugation techniques of Hsieh 2000 to obtain quality conjugates.

III. PATENT OWNER’S MOTION TO AMEND

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

A. Threshold Requirements

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

The Board must assess the patentability of the proposed substitute claims “without placing the burden of persuasion on the patent owner.” *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1328 (Fed. Cir. 2017) (en banc).

Patent Owner's proposed substitute claims, however, must still meet the statutory requirements of 35 U.S.C. § 316(d) and the procedural requirements of 37 C.F.R. § 42.121 as a threshold matter. See USPTO's Memorandum, GUIDANCE ON MOTIONS TO AMEND IN VIEW OF AQUA PRODUCTS (Nov. 2017), available at https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf. Accordingly, Patent Owner must demonstrate: (1) the amendment proposes a reasonable number of substitute claims; (2) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter; (3) the amendment responds to a ground of unpatentability involved in the trial; and (4) the original disclosure sets forth written description support for each proposed claim. See 35 U.S.C. § 316(d)(1)(B),(3); 37 C.F.R. § 42.121; *Hospira, Inc. v. Genentech, Inc.*, Case IPR2017-00737, slip op. at 47 (PTAB Oct. 3, 2018) (Paper 108).

B. Proposed Substitute Claims

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

Claim 46 (substitute for original claim 1): An immunogenic composition comprising:

a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the 22F glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a CRM₁₉₇ carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2;

glycoconjugates from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F all individually conjugated to CRM₁₉₇;

an aluminum salt adjuvant; and

wherein the composition exhibits more than a 2-log increase above baseline in serum IgG levels in New Zealand White Rabbits across all serotypes in the composition following administration of two equal doses of the composition in the form of an initial dose and a booster dose.

Claim 47 (Substitute for original claim 2): The immunogenic composition of claim 46, wherein the glycoconjugate comprises at least ~~0.4~~ 0.8 mM acetate per mM polysaccharide.

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

C. Definiteness, Written Description, and Enablement

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

In particular, we determine that the substitute claims are definite and have adequate written description support.

1. *Claims 46–52 are not indefinite*

i. *Claim 46 and 48–52*

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

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

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

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

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

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

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

As to assays and baselines, the World Health Organization (WHO) guidelines state that “[i]mmune responses to pneumococcal conjugate vaccines can be assessed by . . . Determination of serotype-specific IgG antibody geometric mean concentrations (GMCs) based on measurement of binding to polysaccharides (e.g. using an ELISA method). Appendix 1 provides a detailed consideration of the development and standardization of ELISA methods. . . .” Ex. 1019, 126–127. Goldblatt¹⁷ explains that different assays may be standardized to the WHO guidelines using known bridging techniques, specifically stating:

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

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

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

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

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

ii. Claim 47

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

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

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

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

2. Claim 46–52 have written description support

i. Claims 46 and 48–52

Petitioner asserts that

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

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

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

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

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

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

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

ii. Claim 47

Petitioner asserts that “nothing supports ‘at least 0.8 mM acetate per mM polysaccharide’ recited in claim 47.” Pet. Opp. 21.

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

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

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

3. Claim 46–52 are enabled

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

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

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

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

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

D. Unpatentability

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

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

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

1. *Claims 46 and 48–52 are obvious over Hausdorff, Merck-086, GSK-711, and the knowledge of the ordinary artisan*

a. Hausdorff (Ex. 2027)

Hausdorff teaches “a multivalent immunogenic composition, wherein the capsular polysaccharides are from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9v, 14, 18C, 19A, 19F and 23F of *Streptococcus pneumoniae*, the carrier protein is CRM₁₉₇, and the adjuvant is an aluminum-based adjuvant.” Ex. 2027 ¶ 8. Hausdorff teaches a starting “saccharide/protein ratio of 2:1.” Ex. 2027 ¶ 89. Hausdorff teaches that “[s]ize exclusion chromatography media (CL-4B) was used to profile the relative molecular size distribution of the conjugate.” (Hausdorff ¶ 92).

Hausdorff “examined the ability of the 13vPnC vaccine with AlPO₄ adjuvant to elicit vaccine serotype-specific immune responses. The pneumococcal serotypes represented in the 13vPnC vaccine include types 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.” Ex. 2027 ¶ 230.

Hausdorff teaches:

New Zealand White rabbits were immunized intramuscularly at week 0 and week 2 with the planned human clinical dose of each polysaccharide (2 µg of each PS, except 4 µg of 6B) formulated with or without AlPO₄ (100 µg/dose). Sera were collected at various time points. Serotype specific IgG was

measured by ELISA and functional activity was assessed by OPA.

Ex. 2027 ¶ 230.

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

TABLE 3

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

^aGMTs of pooled sera consisted of equal volumes of serum from each individual rabbit within a group

^bStatistically different (p = 0.022) from treatment group without ALPO₄

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

b. Merck-086 (Ex. 1008)

As discussed above in Section II.C.1, Merck-086 teaches an immunogenic composition composed of serotypes “of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F or 33F) conjugated to a carrier protein, preferably CRM₁₉₇.” Ex. 1008 ¶ 2. Table 1 of Merck-086 shows a vaccine formulation with a 1:1 ratio for 14 serotypes including serotype 22F and a 2:1 ratio for serotype 6B, specifically showing the formulation comprises 32 µg of total polysaccharide and 32 µg of CRM₁₉₇ carrier protein with the total polysaccharide being composed of 2 µg of 14 serotypes including 22F and 4 µg of serotype 6B. Ex. 1008 ¶ 104.

Merck-086 teaches formulations containing 15 serotypes of the pneumococcal conjugate vaccine (PCV-15) “were evaluated in 4 studies in adult New Zealand White Rabbits (NZWRs) using a compressed immunization regimen in which rabbits received a full human dose of vaccine at day 0 and day 14.” Ex. 1008 ¶ 115.

Table 4

Fold-rise (Post-dose 2:Pre-dose 1) in IgG Responses to Non-Prevnar™ Serotypes of PCV-15
Lead Formulations Tested in NZWR

Serotype	NZWR-1	NZWR-2	NZWR-3	NZWR-4
1	14.9	30.5	55.1	59.9
3	33.6	16.2	61.5	28.5
5	12.8	70.2	112.0	134.0
6A	21.3	77.8	143.0	123.0
7F	42.0	83.8	194.0	108.0
19A	40.5	79.1	450.0	314.0
22F	45.7	87.8	243.0	135.0
33F	21.7	47.9	98.8	69.4

Merck 2011 Table 4.

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

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

c. GSK-711 (Ex. 1007)

As discussed above in Section II.C.2, GSK-711 teaches “the multivalent pneumococcal vaccine of the invention will be selected from the following serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.” Ex. 1007, 7:1–3. GSK 2008 teaches conjugation of polysaccharides to the carrier protein CRM₁₉₇ (see Ex. 1007, 10:4–6) and teaches “[p]referably the ratio of carrier protein

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

d. Analysis

i. Claim 46

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

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

Petitioner asserts that “Hausdorff showed that 13vPnPC (Pprevnar13[®]) achieved a 2-Log IgG Increase or higher across all serotypes (at least in one study).” Pet. Opp. 13 (citing Ex. 2027, Table 3). Petitioner asserts that “[b]ecause Pprevnar13[®] has become one of the most successful multivalent PCVs since its approval in 2009, a POSA seeking to add serotype 22F to Pprevnar13[®] in January 2014 would have been motivated to achieve the same.” Pet. Opp. 13 (citing Ex. 1101 ¶¶ 59–64).

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

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

Petitioner also asserts that Dr. Paradiso held the position in a published paper that “CRM₁₉₇-based conjugates made it possible to induce good immunity to new ‘*without negatively affecting the components*

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

Patent Owner asserts Petitioner “has not directed the PTAB to prior art of record that teaches the claimed limitations of “molecular weight” and “ratio (w/w) of the [22F] polysaccharide to the [CRM₁₉₇] carrier protein” required by every proposed substitute claim.” PO Reply 6.

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

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

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

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

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

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

Viewing the evidence as a whole, we determine that a preponderance of the evidence demonstrates that it would have been obvious to incorporate a serotype 22F polysaccharide—conjugated to CRM₁₉₇, with molecular weights and saccharide to protein ratios falling in the claimed ranges as rendered obvious by Merck-086 and GSK-711—into a pneumococcal vaccine with the 13 serotypes and aluminum salt adjuvant disclosed by Hausdorff with a reasonable expectation of success in obtaining a 2-log increase above baseline in serum IgG levels as required by claim 46.

As to reasons to include serotype 22F into such a composition, Merck-086 states “the addition of new polysaccharide-protein conjugates containing serotypes 22F and 33F provides robust antibody responses [and]

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

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

Ex. 1007, 5:18–22. Thus, both Merck-086 and GSK-711 provide specific reasons to incorporate serotype 22F into a pneumococcal vaccine to provide robust antibody responses that will provide herd immunity and reduce disease in human populations. As discussed extensively regarding claim 1 above, these two references also render the specific molecular weight and saccharide to protein ratios obvious and we incorporate that reasoning here.

As to the issue of immune interference and a reasonable expectation of success in obtaining a 2-log increase, Table 3 of Hausdorff shows that a composition with thirteen of the fourteen serotypes that were required by claim 46, conjugated with CRM₁₉₇, produced an immune response with more than a 2-log increase above baseline serum IgG levels in New Zealand White Rabbits after administration of the two equal doses with or without the aluminum salt adjuvant. Ex. 2027 ¶ 231, Table 3.

Thus, the issue resolves to whether there would have been a reasonable expectation of success in the inclusion of serotype 22F in Hausdorff’s pneumococcal vaccine composition while retaining the 2-log increased immune response of the thirteen serotypes and also allowing a 2-log increase in serotype 22F response.

Dr. Van Alphen states that

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

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

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

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

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

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

We recognize Patent Owner correctly notes that Merck-086 only obtained a 2-log increase of serum IgG levels in serotype 22F conjugates in two of the four arms, and annotates Figures 3 and 4 in Merck 2011 to identify particular experimental results that did not satisfy the 2-log increase. PO Reply 7–8. However, “[o]bviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success.*” *Kubin*, 561 F.3d at 1360 (quoting *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). Evidence that all of the Merck-086 experiments showed a greater than 1-log increase in serum IgG levels and half of the experiments shows a greater than 2-log increase supports the

determination that there was a reasonable expectation of success. *See* Ex. 1008 ¶¶ 7, 117, Table 4.

We note that “this is not the case where the prior art teaches merely to pursue a ‘general approach that seemed to be a promising field of experimentation’ or ‘gave only general guidance as to the particular form of the claimed invention or how to achieve it.’” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) (*quoting O’Farrell*, 853 F.2d at 903; *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1167 (Fed. Cir. 2006)). Here, both Merck-086 and GSK-711 specifically suggested incorporation of a serotype 22F conjugate linked to CRM₁₉₇ into a pneumococcal vaccine that was already composed of other known serotypes, including all of the thirteen serotypes disclosed by Hausdorff. Ex. 1008 ¶ 15; Ex. 1007, 5:18–22; Ex. 2027 ¶ 231, Table 3.

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

Paradiso 2009 supports the position that immune interference would not necessarily have been expected with the addition of a serotype 22F-CRM₁₉₇ conjugate to the thirteen serotype composition of Hausdorff because Paradiso 2009 states “[w]ith conjugates on CRM₁₉₇ it has been possible to induce good immunity to new serotypes without negatively affecting the components already in the vaccine.” Ex. 1107, 3.

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

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

Thus, we find that a preponderance of the evidence supports a determination that there would have been a reasonable expectation of success in obtaining a fourteen serotype pneumococcal vaccine composition as required by claim 46 with 2-fold increases in IgG responses in New Zealand White Rabbits because Merck-086 itself exemplifies 2-fold increases in IgG responses in New Zealand White Rabbits for serotype 22F conjugates, and because Paradiso-2009 supports the position that inclusion of an additional serotype 22F-CRM₁₉₇ conjugate into the thirteen serotype composition of Hausdorff would not have been expected to result in immune interference. Ex. 1008 ¶ 15; Ex. 1107, 3.

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

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

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

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

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

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

IV. PATENT OWNER’S MOTION TO EXCLUDE

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

Patent Owner asserts that we should exclude Exhibit 1101 because Dr. Van Alphen “analyzed the proposed amended claims by considering only select limitations and disregarding entirely the limitations reciting molecular weight” and “ratio (w/w) of the [22F] polysaccharide to the [CRM₁₉₇] carrier protein” required by every proposed substitute claim.” Paper 45, 2. Patent Owner asserts that Dr. Van Alphen “failed to apply reliable principles and methods to the facts of the case in contravention of Fed. R. Evid. 702.” Paper 45, 3.

Petitioner asserts that “Dr. Van Alphen carefully considered and addressed each and every limitation recited in the proposed substitute claims, and reliably applied the obviousness legal standard to the facts of this case.” Paper 49, 2. Petitioner asserted that Dr. Van Alphen “specifically explained that he based his opinion also on the *lack of any evidence* provided by Pfizer suggesting that combining a 22F-CRM₁₉₇ conjugate with the recited ‘MW’ and ‘PS-to-protein’ ratio ranges with the 13 serotypes from Prevnar13[®] individually conjugated to CRM₁₉₇ is inventive.” Paper 49, 4.

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

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

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

V. PETITIONER'S MOTION TO EXCLUDE

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

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

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

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

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

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

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

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

V. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that (1) claims 1, 3–19, 23–37, 41, 42, and 45 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, (2) claims 2, 40, and 43 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, Lees-2008, PVP 2013, Pfizer-605; (3) that claims 20–22 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, GSK-531; (4) that claims 38 and 39 of the '559 patent are unpatentable as obvious over the combination of GSK-711, Merck-086, Pfizer-605; and (5) that claim 44 is unpatentable as obvious over the combination of GSK-711, Merck-086, Hsieh 2000.

We deny Patent Owner's Contingent Motion to Amend to replace claims 1–4, 9, 41, and 42 with substitute claims 46–52.

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

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

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

VI. ORDER

For the reasons given, it is

ORDERED, based on a preponderance of the evidence, that claims 1–45 are unpatentable;

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

FURTHER ORDERED, Patent Owner's Motion to Exclude Exhibit 1101 is denied;

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

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

FURTHER ORDERED, because this is a final written decision, the parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2018-00187
Patent 9,492,559 B2

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