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 of

U.S. Patent No. 9,492,559

IPR Trial No. IPR2018-00187

PETITION FOR INTER PARTES REVIEW OF CLAIMS 1-45 OF U.S. PATENT NO. 9,492,559 UNDER 35 U.S.C. § 312 AND 37 C.F.R. § 42.104

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1007	International Patent Publication WO 2007/071711, published on June 28, 2007 ("GSK-711").
1008	U.S. Patent Publication No. 2011/0195086, published on August 11, 2011 ("Merck-086")
1009	[RESERVED]
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1013	U.S. Patent No. 7,955,605, issued on June 7, 2011 ("Pfizer-605")
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I. INTRODUCTION

Sanofi Pasteur Inc. and SK Chemicals Co., Ltd. (collectively, "Petitioner" or "Sanofi") request *inter partes* review of claims 1–45 of U.S. Patent No. 9,492,559 ("the '559 patent"), a post-AIA patent assigned to Pfizer Inc. ("Patent Owner" or "Pfizer"). For the reasons set forth below and in the accompanying Declaration of Dr. Andrew Lees, a leading expert in the glycoconjugation field (the "Lees Declaration"), there is a reasonable likelihood that Petitioner will prevail in establishing that claims 1–45 are unpatentable as obvious over the prior art.

The challenged claims are directed to immunogenic compositions comprising glycoconjugates of *S. pneumoniae* serotype 22F polysaccharide and a carrier protein. During prosecution, Pfizer added two additional limitations to sole independent claim 1, in order to overcome the prior art: (1) a ratio (w/w) of the polysaccharide to the carrier protein "between 0.4 and 2"; and (2) a glycoconjugate molecular weight range of "between 1000 kDa and 12,500 kDa." As explained below and in the Lees Declaration, there is nothing inventive to the claimed 22F glycoconjugate.

22F glycoconjugates had already been made before Pfizer's earliest possible priority date (*i.e.*, January 21, 2014) as part of multivalent polysaccharide conjugate vaccine ("PCV") compositions developed by at least two other major vaccine companies, GSK and Merck, and were shown to be immunogenic.

The primary reference, GSK-711, discloses a 22F polysaccharide-carrier protein conjugate that induces immune responses in well-established animal models and has a ratio of polysaccharide to carrier protein falling within the claimed range of "between 0.4 and 2." GSK-711 does not characterize the size of the 22F glycoconjugate, but it does disclose the molecular weights of ten (10) other different glycoconjugates. All of them have molecular weights falling within the range of "between 1000 kDa and 12,500 kDa" as recited in claim 1. Thus, a person of skill in the art would have reasonably expected that the size of the 22F glycoconjugate 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. At a minimum, a POSA would have been motivated to make 22F glycoconjugates falling within the claimed molecular weight range with a reasonable expectation of success, in view of the teachings in GSK-711 and general knowledge in the art.

Likewise, all of the dependent claims recite various well-known features and well-established methods of making and using the composition of claim 1. None of them reflect anything inventive over the prior art. In fact, many of them had already been specifically disclosed in GSK's, Merck's and Pfizer's own earlier filings.

Indeed, the conjugation chemistry, purification process and analytical methods described in the ’559 patent are standard methods that had been routinely used in generating pneumococcal polysaccharide conjugates well before 2014. In obtaining the ’559 patent, Pfizer merely practiced prior art methods and quantified the molecular weights and other features of the naturally resulting 22F glycoconjugates. This is not inventive.

Petitioner therefore requests that this Petition be granted and that claims 1–45 be found unpatentable and canceled.

II. MANDATORY NOTICES

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are: Sanofi Pasteur Inc., Sanofi, and SK Chemicals Co., Ltd.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner is concurrently filing one additional Petition for IPR of the ’559 patent on other grounds (IPR2018-00188).

Petitioner is aware of the following IPRs filed against U.S. Patent No. 9,492,559 filed by a different petitioner: IPR2017-02131, IPR2017-02132, IPR2017-02136, and IPR2017-02138.

Petitioner is unaware of any other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel: Fangli Chen, Ph.D. (Reg. No. 51,551)

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D. Service Information (37 C.F.R. § 42.8(b)(3))

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III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

The undersigned authorizes the Director to charge the fee set forth in 37 C.F.R. § 42.15(a), as required by 37 C.F.R. § 42.103, to Deposit Account No. 50-3081. The undersigned further authorizes payment for any additional fees that

might be due in connection with this Petition to be charged to the above-referenced deposit account.

IV. CERTIFICATION OF GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner certifies pursuant to Rule 42.104(a) that the '559 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review on the grounds identified in this Petition.

V. IDENTIFICATION OF CHALLENGE (37.C.F.R. § 42.104(b))

Petitioner requests cancellation of claims 1–45 of the '559 patent as unpatentable under post-AIA 35 U.S.C. §103 based on the following grounds.

Ground I: Claims 1, 3–19, 23–37, 41–42 and 45 are obvious over GSK-711 in view of Merck-086 and general knowledge in the art.

Ground II: Claims 2, 40 and 43 are obvious over GSK-711 in view of Merck-086, Lees-2008, PVP-2013, Pfizer-605 and general knowledge in the art.

Ground III: Claims 20–22 are obvious over GSK-711 in view of Merck-086, GSK-531 and general knowledge in the art.

Ground IV: Claims 38 and 39 are obvious over GSK-711 in view of Merck-086, Pfizer-605 and general knowledge in the art.

Ground V: Claim 44 is obvious over GSK-711 in view of Merck-086, Hsieh-2000 and general knowledge in the art.

VI. OVERVIEW OF THE '559 PATENT

A. The Claims of the '559 Patent

The '559 patent issued with 45 claims. Ex. 1001, 141–144. Claim 1 is the sole independent claim. Claim 1 recites the following:

> 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*.

Remaining claims 2–45 all depend directly or indirectly from claim 1 and recite standard features of pneumococcal glycoconjugates and methods of making and using the same. Lees (Ex. 1005) ¶¶20-21.

B. Brief Overview of the Specification of the '559 Patent

The specification of the '559 patent states that a purported object of the invention is "to provide for appropriate protection against *S. pneumoniae* serotypes not found in PREVNAR® (heptavalent vaccine), SYNFLORIX® and/or

PREVNAR®13 while maintaining an immune response against serotypes currently covered by said vaccines." Ex. 1001, 2:18–23.

Of particular relevance to claim 1 (and all dependent claims), Example 13 of the '559 patent describes the synthesis of glycoconjugates comprising serotype 22F. *Id.*, 114-117. The 22F polysaccharides are conjugated to CRM_{197} using reductive amination methods. *Id.* The resulting glycoconjugates were then purified using tangential flow filtration (TFF) followed by diafiltration and then sterile filtration using a 0.22 μm filter (*Id.*, 116:12-20). The immunogenicity of the 22F-CRM_{197} glycoconjugates were measured using opsonophagocytic activity (OPA) assays to detect functional antibodies and ELISA to detect IgG antibodies specific for *S. pneumoniae* serotype 22F. *Id.*, Tables 17, 21, 22; *see also* 117:26–35.

C. The File History of the '559 Patent

The '559 patent issued on November 15, 2016 from U.S. Patent Application No. 14/597,488 ("the '488 application", Ex. 1003). The '488 application was filed January 15, 2015 and claims priority to U.S. Provisional Application No.

61/929,547 (Ex. 1002), filed January 21, 2014.[1] In the only substantive Office Action, the Examiner rejected the claims under 35 U.S.C. § 102(a)(1) as anticipated by US2004/0202668 and US2012/0052088. Ex. 1004, 33-34. In its Response, Applicant amended claim 1 to add the glycoconjugate molecular weight and polysaccharide-to-carrier protein ratio limitations:

> 1. (Currently amended) An immunogenic composition comprising ~~at least one glycoconjugate selected from the group consisting of a glycoconjugate from *S. pneumoniae* serotype 15B,~~ a ~~glycoconjugate from *S.*~~ *Streptococcus pneumoniae* serotype 22F glycoconjugate, ~~a glycoconjugate from *S. pneumoniae* serotype 33F, a glycoconjugate from *S. pneumoniae* serotype 12F, a glycoconjugate from *S. pneumoniae* serotype 10A, a glycoconjugate from *S. pneumoniae* serotype 11A and a glycoconjugate from *S. pneumoniae* serotype 8~~ 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.

Id., 17.

Pfizer further argued that "this combination of glycoconjugate molecular weight and saccharide-to-protein ratio produced sera having opsonophagocytic activity," and that the cited references did not disclose 22F glycoconjugates having this "particular combination" of characteristics or "that such glycoconjugates

[1] For purposes of this Petition, Petitioner has assumed that the claims are entitled to the January 21, 2014 date. Petitioner concurrently filed a Petition to challenge this priority date.

produce functional antibodies." *Id.*, 24. Notably, Pfizer relied solely on attorney arguments and did not submit any comparison data to demonstrate any unique properties of this particular combination. *Id.*

A Notice of Allowance was mailed August 12, 2016. *Id.*, 9.

The arguments for unpatentability presented in this Petition, including the motivation for achieving the claimed size range based on SEC column purification and the expectation-of-success based on the reactive sites (the "column arguments"), have never been addressed before the Patent Office by Pfizer during prosecution or by any third party in other proceedings.

VII. STATE OF THE ART

Well before 2014, glycoconjugates of different serotypes had been routinely used in multivalent vaccines to prevent, treat, or ameliorate infectious diseases or conditions caused by pathogens such as *Streptococcus pneumoniae* of different origins, and the glycoconjugation technology was mature and well-developed. Lees ¶¶33-37.

1. Pneumococcal polysaccharide based vaccines

Pneumococci, like many other bacteria, are covered by a capsule of polysaccharides (PS), which are primarily responsible for the pathogenicity of the bacteria. Lees ¶28; Ex. 1033, 1. The immune system often targets the

polysaccharides. *Id.* This makes the polysaccharides particularly suitable as vaccines. *Id.*; Ex. 1021, 1.

These polysaccharides are carbohydrates with a number of repeating sugar units bonded together. Lees ¶29. They are classified as "serotypes" based on individual reactivities to collections of antisera drawn from patients infected with *S. pneumoniae* bacteria with different epidemic origins. Lees ¶29.

A multivalent vaccine includes different serotypes of isolated polysaccharides to induce protective antibodies against different serotypes of Pneumococci. Lees ¶¶29-30. Merck's Pneumovax®23 product is a multivalent polysaccharide-only vaccine that includes 23 polysaccharide serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. Lees ¶30; Ex. 1017, 1. It was first licensed in the U.S. in 1983. Lees ¶30; Ex. 1018, 1.

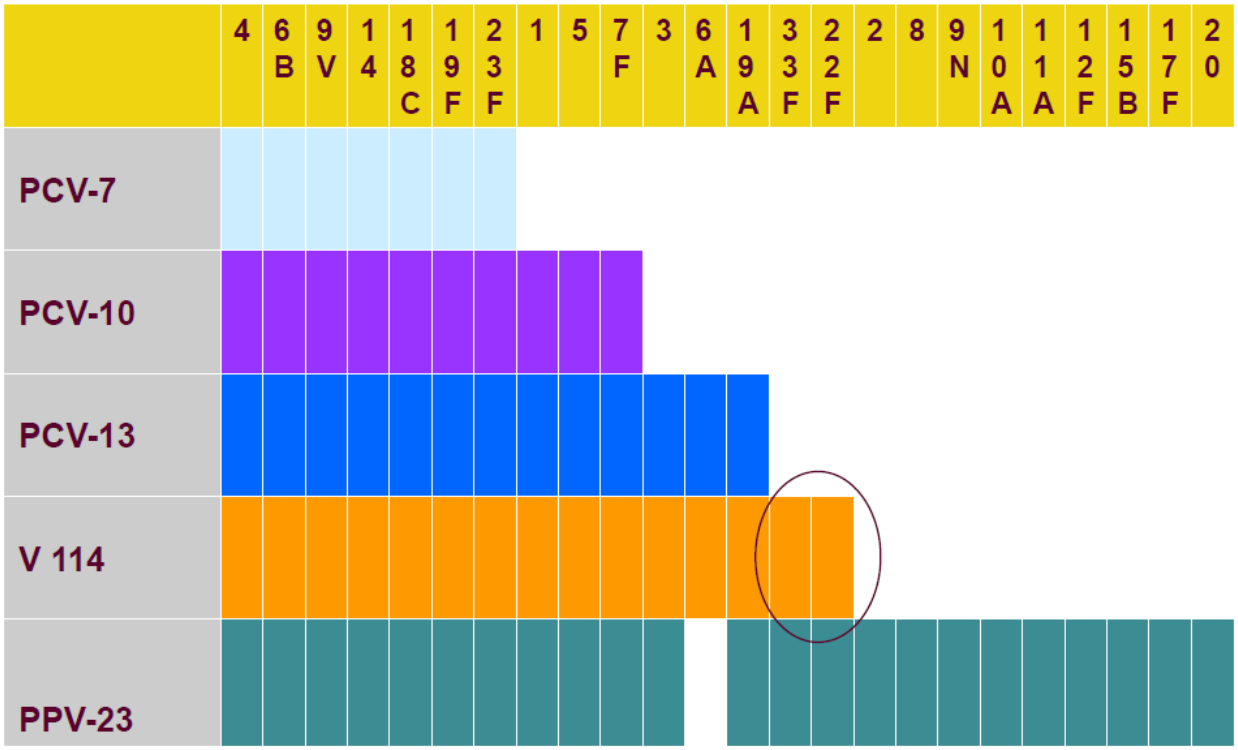
2. Multivalent pneumococcal conjugate vaccines (PCVs) Prevnar® (PCV7), Synflorix® (PCV10) and Prevnar®13 (PCV13) were licensed by 2013

Glycoconjugate vaccines were developed to overcome limitations of polysaccharide-only vaccines. Lees ¶¶27-32. Polysaccharides induce an immune response largely via B-cells. Lees ¶31; Ex.1034, 2. T-cells do not respond to polysaccharides. *Id.*; Ex. 1019, 103. As a result, polysaccharide-only vaccines do not provide protective immunity in infants, the elderly and other immunologically

compromised patients because their B cells are underdeveloped or otherwise diminished. Lees ¶31; Ex. 1019, 103; Ex. 1020, 4-5.

Conjugating polysaccharides to proteins has been effective in overcoming the limitations of polysaccharide immunogenicity because proteins are T-cell dependent antigens and are immunogenic in infants, the elderly and other immunologically compromised human patients. Lees ¶32.

After the approval of Pneumovax®23, vaccine companies developed PCVs based on many of the same serotypes for the obvious benefits discussed above. Lees ¶33. By 2013, three multivalent PCVs—Prevnar® (PCV7), Synflorix® (PCV10) and Prevnar®13 (PCV13)—were licensed and each includes a subset of the 23 polysaccharide serotypes used in Pneumovax®23, but conjugated to carrier protein(s). Lees ¶34; Ex. 1034, Table 1; Ex. 1037, Table 1. A chart summarizing subsets of the serotypes included in Prevnar® (PCV7), Prevnar®13 (PCV13), Synflorix® (PCV10), Pneumovax®23 (PPV-23), and Merck's V114 (PCV15 currently in clinical trials) is shown below. Ex. 1022, 10 (circle in original).

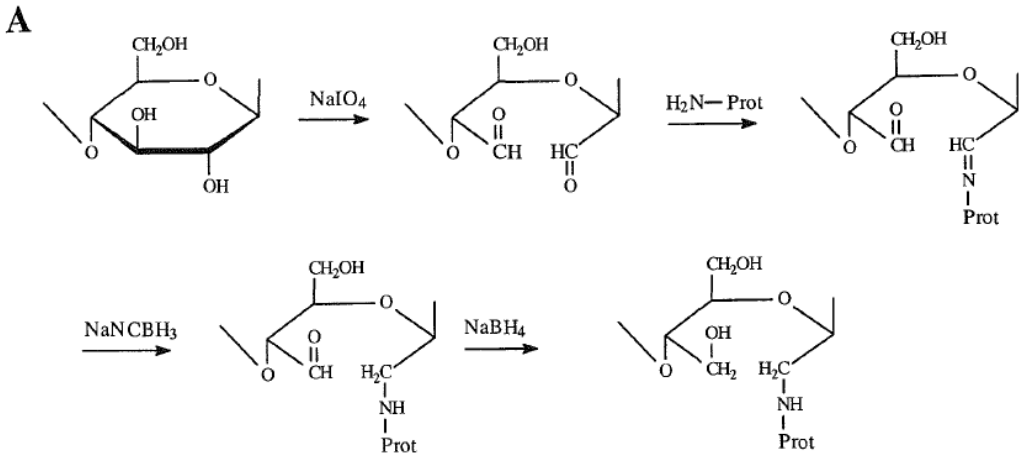


Specifically, Pfizer's Prevnar® contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, each conjugated to a single carrier protein, CRM_{197}. Lees ¶35; Ex. 1023, 1. GSK's Synflorix® includes all seven serotypes found in Prevnar® and three additional serotypes, 1, 5, and 7F. Lees ¶36; Ex. 1024, 6, 8. Three carrier proteins were used in Synflorix® to conjugate polysaccharides of the different serotypes. *Id.* Pfizer's successor product Prevnar®13 includes six additional serotypes, 1, 3, 5, 6A, 7F, and 19A in addition to the 7 serotypes in Prevnar®, all of which were found in Merck's Pneumovax®23 except serotype 6A. Lees ¶37; Ex. 1025 1, 23. All 13 serotypes in Prevnar®13 are conjugated to a single carrier protein, CRM_{197}. *Id.*, 23-24.

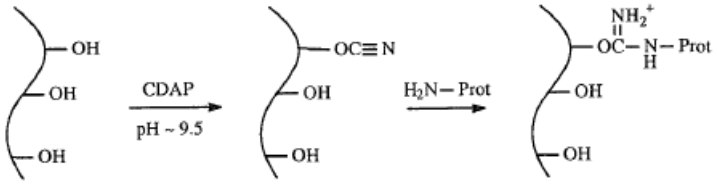
3. Glycoconjugation technology was well established as of 2014

Conjugation chemistry for synthesis of pneumococcal glycoconjugates was established well before 2014. Lees ¶¶40-42, 47. Reductive amination and CDAP are the most commonly used methods. *Id.*, ¶47; Ex. 1011, 7-8. Both involve activating hydroxyl groups on polysaccharides and reacting them with the amino groups on carrier proteins (typically from lysine residues) to form covalent bonds. Lees ¶¶47-49; Ex. 1011, 7-8, 10, Figure 2A-B.

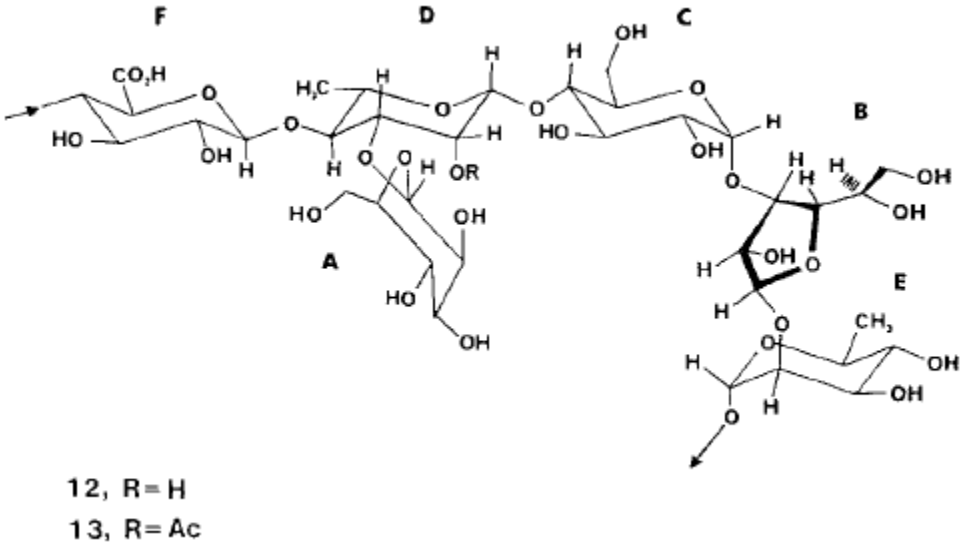
The general scheme of the reductive amination process is illustrated below. *Id.*, Figure 2A.



The general scheme of the CDAP process is illustrated below. *Id.*, Figure 2B.



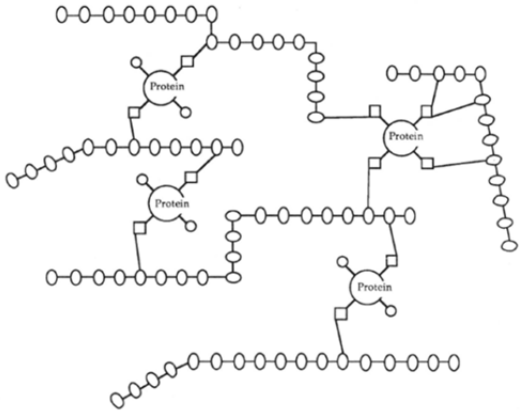
Polysaccharides contain numerous hydroxyl groups. Lees ¶51. Below is an illustrative diagram of a repeating unit of the 22F polysaccharide. *Id.*; Ex. 1026, 7.



Each repeating unit of a 22F polysaccharide has about 14 free hydroxyl groups, excluding the hydroxyl that is acetylated in 80% of the repeating units. Lees ¶52; Ex. 1026, 7, 9.

Likewise, carrier proteins typically have multiple lysines with reactive amino groups. Lees ¶53. For example, each CRM_{197} protein molecule contains at least 29 lysines available for conjugation. Lees ¶53; Ex. 1063, 8. As a result, both

reductive amination and CDAP conjugation chemistry naturally result in highly crosslinked lattice structures with multiple saccharides and carrier protein molecules in each lattice structure. Lees ¶¶50-54; Ex. 1054, 8. A representative glycoconjugate lattice structure is shown below. Lees ¶54; Ex. 1027, 32, Figure 2.



Due to the nature of this chemistry, glycoconjugates synthesized using reductive amination and CDAP tend to have large sizes. Lees ¶55; Ex. 1011, 7, 10-11. For example, the size of a glycoconjugate synthesized using CDAP chemistry is typically in the multimillion Dalton range. Lees ¶55; Ex. 1007, Table 2. However, extremely large conjugates, such as those with molecular weights well above 10 million Dalton, can be difficult to purify. Lees ¶55; Ex. 1011, 9-11. Extremely large conjugates can also precipitate or form a gel. *Id.*; Ex. 1011, 7. To avoid extremely large conjugates, real-time monitoring is routinely performed during conjugation. *Id.*; Ex. 1067, 9. Once the desired size and other

characteristics such as polysaccharide-to-protein ratio are achieved, the conjugation reaction is quenched using standard methods. Lees ¶55.

The ratio of polysaccharide to carrier protein also reflects the crosslinking chemistry in glycoconjugates. Lees ¶57. For pneumococcal conjugates, while the particulars may differ for a specific serotype, the WHO guidelines specifically recommend the ratio "in the range of 0.3–3.0." Lees ¶58; Ex. 1019, 119. All marketed PCV products generally have ratios within 0.5–1.5. Lees ¶59.

4. 22F and other new glycoconjugates were made and added to SYNFLORIX® and PREVNAR®13 to address emerging serotypes

After the introduction of Prevnar®13, certain serotypes not included in Prevnar®13 such as 22F, 33F, 8, 10A, 11A, 12F, and 15B became more prevalent according to epidemiological studies conducted before 2014. Lees ¶38; Ex. 1028, 11; Ex. 1029, 6; Ex. 1085, Table 1; Ex. 1086, Table 2, Figure 3. To address those emerging serotypes, companies had begun developing new PCV products to include prevalent emerging serotypes. Lees ¶38. For example, Merck had begun developing a new PCV15 vaccine, MK-V114, combining emerging serotypes 22F and 33F with the 13 serotypes from Prevnar®13, while maintaining an immune response against all serotypes in the product. *Id.*; Ex. 1050 at 2; Ex. 1051 at 1; Ex. 1052 at 1. All 15 serotypes in Merck's PCV15 are conjugated to CRM_{197}. Ex.

1029, Abstract. MK-V114 was in human clinical trials as of 2014. Lees ¶38; Ex. 1050 at 2; Ex. 1051 at 1; Ex. 1052 at 1.

GSK had also begun developing a new 13-valent PCV vaccine to add 22F and two other serotypes to SYNFLORIX® and demonstrated that the inclusion of 22F does not negatively impact the immune response against other serotypes in animal models. Lees ¶39; Ex. 1007, Examples 8-10.

VIII. SUMMARY OF RELEVANT PRIOR ART REFERENCES

1. GSK-711 (Ex. 1007)

GSK's International Patent Publication WO 2007/071711 was published on June 28, 2007, and is prior art to the '559 patent under AIA 35 U.S.C. § 102(a)(1). GSK-711 was not cited during prosecution of the '559 patent.

GSK-711 is directed to "a multivalent *Streptococcus pneumoniae* vaccine comprising 2 or more capsular saccharide conjugates from different serotypes, wherein the composition comprises a serotype 22F saccharide conjugate." Lees ¶¶80-82; Ex. 1007, Abstract.

Specifically, GSK-711 discloses that the multivalent vaccines may include serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, or 33F. Lees ¶82; Ex. 1007, 8:2-3.

It also teaches that the saccharides in the immunogenic composition may be conjugated to a carrier protein independently selected from CRM_{197}, diphtheria toxoid (DT), tetanus toxoid (TT), pneumococcal pneumolysis (Ply), polyhistidine triad proteins (PhtX proteins such as PhtD proteins), or *Haemophilus influenzae* protein D (PD). Lees ¶83; Ex. 1007, 9:18-22 and 11:4-27.

Example 2 describes working examples of different pneumococcal glycoconjugates synthesized using CDAP methods. Lees ¶84; Ex. 1007, Table 1. Table 2 (reproduced below) describes characteristics of 14 different examples, including two 22F glycoconjugates. Lees ¶84; Ex.1007, 54 (highlight added).

TABLE 2 – characteristics of the conjugates

Conjugates	PS size ($Dax10^3$)	Carrier/PS Ratio	Free PS (Elisa)	Free Carrier	PS Antigenicity (Elisa)	Conj. Size (kDa)
PS1-PD	349-382*	1.5-1.6	1.0%-1.2%	3.9%-4.8%	87%-95%	1499 - 1715
PS4-PD	93-100*	1.5-1.6	4.7-6.5%	3.2%-4.0%	90%-96%	1303 - 1606
PS5-PD***	367-443	0.80	8.7-11.2%	2.2%-3.8%	93%-108%	1998-2352
PS6A-PD	1100-1540	0.61	4.5%	Not done	45.9%	Not done
PS6B-PD***	1069-1391	0.7-0.8	1.3-1.6%	<2.0%	68%-75%	4778-5235
PS7F-PD	255-264*	1.1-1.2	<1%	<1.4%	58%	3907-4452
PS9V-PD	258-280*	1.3-1.5	<1%	<1.3%	67%-69%	9073-9572
PS14-PD	232-241*	1.4	<1%	<1.5%	70%	3430-3779
PS18C-TT*	89-97*	2.2-2.4	1.5-2.2%	<4%	46%-56%	5464-6133
PS19A-Ply*	151	3.2	<1%		29%	
PS19F-DT	133-143*	1.4-1.5	4.1%-5.9%	<1.2%-<1.3%	82%-88%	2059-2335
PS22F-PhtD*	159-167	2.17	5.8	Not done	37%	Not done
PS22F-AHPhtD*	159-167	3.66-4.34	<1%	Not done	28-31%	Not done
PS23F-PD***	914-980	0.5	1.4-1.9%	3.7%-4.9%	137%-154%	2933-3152

* PS size following microfluidization of the native PS

Multivalent vaccine formulations using combinations of the glycoconjugates shown in Table 2 were also prepared and were shown to be immunogenic in various animal models (young mice, old mice and guinea pigs). Lees ¶¶87-91; Ex. 1007, Examples 8–10.

GSK-711 further teaches that the inclusion of 22F glycoconjugates in a PCV could be useful for inducing herd immunity and eliciting a (protective) immune

response in infants (defined as 0–2 years old**)** and in elderly patients (***e.g.***, over 50, 55, or 60 years of age) and can protect elderly patients from diseases such as pneumonia, invasive pneumococcal disease (IPD), and/or chronic obstructive pulmonary disease (COPD). Lees ¶93; Ex. 1007, 5:16-38 and 42:29-35.

2. Merck-086 (Ex. 1008)

Merck's U.S. Publication No. 2011/0195086 was published on August 11, 2011 and is prior art to the '559 patent under AIA 35 U.S.C. § 102(a)(1). Merck-086 was not cited during prosecution of the '559 patent.

Merck-086 discloses an immunogenic composition comprising fifteen different glycoconjugates. Lees ¶95; Ex. 1008, Abstract. Each glycoconjugate includes a polysaccharide prepared from *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to a carrier protein such as CRM_{197}. Lees ¶95; Ex. 1008, Abstract, Examples 2, 3. Example 2 describes the preparation of various CRM_{197} glycoconjugates using reductive amination. Lees ¶96; Ex. 1008, 11.

Example 3 describes adjuvanted and non-adjuvanted formulations for the 15-valent composition. Lees ¶¶97-98; Ex. 1008, Table 1. Table 1 shows the final composition of the two clinical liquid formulations for the PCV-15 composition (reproduced below).

TABLE 1

Composition of Adjuvanted and Non-Adjuvanted 15 - valent Pneumococcal Conjugate Vaccine Formulations

Description of Ingredients		Clinical Formulations, unit/0.5 mL dose: Adjuvanted PCV-15	Clinical Formulations, unit/0.5 mL dose: Non-adjuvanted PCV-15
Active Ingredients	Pneumococcal polysaccharide antigens	32 µg of total polysaccharide (2 µg of each of the following polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F; 4 µg of serotype 6B polysaccharide)	32 µg of total polysaccharide (2 µg of each of the following polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F; 4 µg of serotype 6B polysaccharide))
	Carrier protein CRM_{197}	~32 µg	~32 µg
Other Ingredients	Aluminum (µg)[a]	125	0
	Polysorbate-80 (µg)	0	2.5
	L-histidine (mM)	20	20
	Sodium Chloride (mM)	150	150
	Water for Injection	Q.S.[b]	Q.S.[b]

[a]Quantity of elemental aluminum in APA.
[b]Quantify sufficient to 0.5 mL.

Example 4 describes the immunogenicity of PCV-15 in two animal models—infant rhesus monkeys and New Zealand White Rabbits—as measured by opsonophagocytosis (OPA) functional antibodies and/or IgG titers, including a comparative study between PCV-15 and Prevnar®. Lees ¶ 99; Ex. 1008, Tables 2-6.

In addition, Merck-086 teaches detailed pharmaceutical excipients that can be used to formulate PCV-15 and dosage forms. Lees ¶¶100-102; Ex. 1008, 9-10.

3. GSK-531 (Ex. 1014)

GSK's WO 2011/110531 was published on September 15, 2011 and is prior art to the '559 patent under AIA 35 U.S.C. § 102(a)(1). GSK-531 was not cited during prosecution of the '559 patent.

GSK-531 is directed to an improved reductive amination process for conjugating a polysaccharide (including 22F) to a carrier protein that leads to retention of size and/or the retention of epitopes. Lees ¶104. Ex. 1014, 2:5-6, 32-33.

Among other things, GSK-531 teaches that pneumococcal glycoconjugates can be mixed with other antigens such as diphtheria toxoid (DT), tetanus toxoid (TT), and pertussis components such as detoxified Pertussis toxoid (PT) and filamentous haemagglutinin (FHA) with optional pertactin (PRN) and/or agglutinin 1 +2, and Hepatitis B surface antigen (HepB). Lees ¶105; Ex. 1014, 20:25-31. It also teaches that pneumococcal glycoconjugates can be mixed with other antigens such as conjugates of a capsular saccharide from *N. meningitidis* A, C, W or Y. Lees ¶105; Ex. 1014, 21:1-3.

4. Lees-2008 (Ex. 1011)

"Chapter 11. Conjugation Chemistry" in the book *Pneumococcal Vaccines: The Impact of Conjugate Vaccine* was published by ASM Press in 2008,

and is prior art to the '559 patent under AIA 35 U.S.C. § 102(a)(1). Lees-2008 was not cited during prosecution of the '559 patent.

Lees-2008 discusses many aspects of *S. pneumoniae* polysaccharide and carrier protein conjugation and resultant glycoconjugates. In particular, Lees-2008 teaches that O-acetyl groups on polysaccharides were considered important epitopes and could be useful for immunogenicity. Lees ¶107; Ex. 1011, 5.

5. PVP-2013 (Ex. 1012)

"Pneumococcal Vaccine Polyvalent" is a revision to the document "Minimum Requirements for Biological Products" (MRBP), which is dated March 1, 2006 and published by the Japanese National Institute of Infectious Diseases ("NIID"). PVP-2013 was archived on March 2, 2013 by the Internet Archive's "Wayback Machine" service and is prior art to the '559 patent under AIA 35 U.S.C. § 102(a)(1). PVP-2013 was not cited during prosecution of the '559 patent.

Among other things, PVP-2013 sets forth permitted O-acetate content (O-acetyl/polysaccharide unit molar ratio) of acetylated serotypes such as serotype 22F. Lees ¶110; Ex. 1012, 3-4. For 22F polysaccharides, PVP-2013 teaches that the permitted range for O-acetate content is "0.5–1.5." Lees ¶110; Ex. 1012, 4.

6. Pfizer-605 (Ex. 1013)

Pfizer's earlier U.S. Patent No. 7,955,605 issued on June 7, 2011 and is prior art to the '559 patent under AIA 35 U.S.C. § 102(a)(1). Pfizer-605 was not cited during prosecution of the '559 patent.

Pfizer-605 is directed to immunogenic compositions comprising 13 distinct pneumococcal polysaccharide-protein conjugates. Lees ¶112; Ex. 1013, 2:7–13. The patent discloses methods of preparing the conjugates using reductive amination in DMSO (an aprotic solvent) or in water. Lees ¶112; Ex. 1013, Examples 2-17.

Among other things, Pfizer-605 also describes the use of size exclusion chromatography, specifically a CL-4B column, to profile the relative molecular size distribution of the conjugates. Lees ¶113; Ex. 1013, 15:26-28. Example 17 (reproduced below) describes the characterization of 19A-CRM_{197} conjugates using a CL-4B column, specifically teaching that a preferred value for conjugate molecular size is about 70% 0.3 K_d, with a preferred free saccharide level of below about 20–25%. Lees ¶113; Ex. 1013, Example 17, 36:58–61.

Table 7

Comparisons of Key Conjugate Characteristics for Serotype 19A Co-lyophylization in DMSO vs. Discrete Lyophylization

	Co-Lyophylization (n = 6)		Discrete Lyophylization (n = 6)	
Characteristic	Mean	Standard Deviation	Mean	Standard Deviation
%0.3 Kd (CL-4B) saccharide	67	7.2	58	13.0
Free Saccharide (%)	<18	<3.5	31	9.2

7. Hsieh-2000 (Ex. 1015)

The chapter authored by C.L. Hsieh entitled "Characterization of Saccharide-CRM_{197} Conjugate Vaccines" in the book *Physico-Chemical Procedures for the Characterization of Vaccines* (Eds. F. Brown et al.) was published by Dev Biol. Basel, Karger in 2000, and is prior art to the '559 patent under AIA 35 U.S.C. § 102(a)(1). Hsieh-2000 was not cited during the prosecution of the '559 patent.

Hsieh-2000 characterizes saccharide-CRM_{197} conjugate vaccines, including pneumococcal vaccines successfully developed by Wyeth. Lees ¶115; Ex. 1015, 2. Hsieh-2000 teaches that for saccharide-CRM_{197} conjugates, the loss of lysine can be indicative of covalent bonding and has been relatively consistent in the range of 6–9. Lees ¶115; Ex. 1015, 8. Hsieh-2000 also teaches that "a percent value of less

than 0.3 K_d reflects the quantity of high molecular weight fraction of the glycoconjugate." Lees ¶116; Ex. 1015, 6.

IX. PERSON OF ORDINARY SKILL IN THE ART

As of the earliest possible priority date of the '559 patent, a person of ordinary skill in the art ("POSA") 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. Lees ¶77. Such a person would be generally familiar with conjugation chemistry, regulatory and WHO guidelines for glycoconjugate vaccines, manufacturing and quality control considerations for such vaccines, and relevant analytical techniques such as SEC-MALLS, NMR and others. *Id.*

X. CLAIM CONTRUCTION

In an *inter partes* review, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification. 37 C.F.R. §42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2146 (2016). Claim terms are also "generally given their ordinary and customary meaning," which is the meaning that

the term would have had to a POSA at the time of the invention in view of the specification. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007).

A. "immunogenic"

Under the broadest reasonable construction standard, the preamble of a claim is not limiting. "[A]s a general rule preamble language is not treated as limiting." *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc*., 672 F.3d 1335, 1347 (Fed. Cir. 2012). A preamble is "not limiting 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.'" *Braintree Labs., Inc. v. Novel Labs., Inc*., 749 F.3d 1349, 1357 (Fed. Cir. 2014) (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)). Here, the claim body defines a structurally complete invention. The term "immunogenic" in the preamble only states an intended use or an inherent property. It does not further limit the scope of the claims. *See Braintree Labs*, 749 F.3d at 1357.

Should the Board determine that the preamble is limiting, Petitioner proposes the following construction.

The '559 patent specification does not define "immunogenic." Both ELISA and OPA assays were used. Ex. 1001, Tables 17-18, 21-22. OPA titers as low as 10 and as high as 4335 for a 22F-CRM_{197} glycoconjugate in a murine immunogenicity model were considered immunogenic. Ex. 1001, 117:26–35,

Tables 17-18; *see also* 102:38–43, Table 8 (for an 8-CRM_{197} glycoconjugate, OPA titers ranging from 4 to 17 for a 0.001 μg sample was considered "good"). This suggests that any opsonophagocytic activity above 0 is considered immunogenic. Two leading dictionaries define "immunogenic" as "relating to or producing an immune response" or "capable of eliciting an immune response." Ex. 1030 at 3; Ex. 1091 at 1. Accordingly, Petitioner proposes that the term be construed as "capable of producing an immune response as determined by an immunogenic assay known in the art by a POSA including an OPA assay."

XI. LEGAL STANDARD

In obviousness cases, *Graham v. John Deere Co.* requires an evaluation of any differences between the claimed subject matter and the asserted prior art. 383 U.S. 1, 17–18 (1966). As noted in *KSR International Co. v. Teleflex Inc*., the obviousness inquiry may account for the inferences and creative steps that would be employed by a person of ordinary skill in the art. 550 U.S. 398, 418 (2007).

If a patent claims a range of values for a variable, a *prima facie* case of obviousness is established where the prior art discloses examples or ranges of values for the same variable that overlap with the claimed range, even at the endpoints. *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997); *see also In re Woodruff*, 919 F.2d 1575, 1577–78 (Fed. Cir. 1990). *Prima facie* cases of

obviousness can also be established where the prior art discloses values for the same variables claimed but where there is no overlap at all with the claimed range. *Gentiluomo v. Brunswick Bowling & Billiards Corp.*, 36 F. App'x 433, 437–39 (Fed. Cir. 2002); *In re Huang*, 100 F.3d 135, 136–39 (Fed. Cir. 1996).

Even if ranges are not explicitly disclosed in the prior art, obviousness is properly found where the claimed range is a "mere quantification of the results of a known process." *Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1312 (Fed. Cir. 2017) (the Board's finding of obviousness in an *inter partes* reexamination was upheld where there was no indication that a range limitation was "anything other than mere quantification of the results of a known process"). Similarly, a *prima facie* case of obviousness may be established where the prior art "inherently" discloses values within the claimed range. *K-Swiss Inc. v. Glide N Lock GmbH*, 567 F. App'x 906, 913 (Fed. Cir. 2014) (*prima facie* case of obviousness established where a claimed range for material deformation above 20% or above 50% were not explicitly disclosed in the prior art and an expert testified that the prior art would have inherently achieved deformation above 50% given the structural and material properties disclosed).

A *prima facie* case of obviousness raised in a petition is sufficient to establish a "reasonable likelihood" of success for purposes of instituting review under 35 USC § 314. *See*, *e.g.*, *Otter Prods., LLC v. Speculative Prod. Design,*

LLC, IPR2014-01450, 2015 WL 1090310, at *6 n.7 (PTAB Mar. 11, 2015); *Ford Motor Co. v. Paice LLC and the Abell Found., Inc.*, IPR2014-01416, 2015 WL 1201879, at *6 n.6 (PTAB Mar. 12, 2015).

XII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

Ground I: Claims 1, 3–19, 23–37, 41–42 and 45 Are Obvious over GSK-711 in view of Merck-086 and General Knowledge in the Art

i. Claim 1

Claim 1 is directed to (1) an immunogenic composition comprising a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the glycoconjugate has (2) an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a carrier protein; (3) a ratio (w/w) of the polysaccharide to the carrier protein between 0.4 and 2; and (4) the glycoconjugate has a molecular weight between 1000 kDa and 12,500 kDa.

As explained more fully below, the claimed subject matter is obvious because each claim element is disclosed in the prior art and a POSA would have had a motivation to combine the prior art teachings with a reasonable expectation of success.

(1) The 22F glycoconjugates taught in GSK-711 and Merck-086 are immunogenic

As discussed above, the term "immunogenic" in the preamble only states an intended use or an inherent property. *See* Sec. X. It does not further limit the scope of the claims. *Id.* In any event, the 22F glycoconjugates taught in both GSK-711 and Merck-086 are immunogenic. Lees ¶¶124-133.

Specifically, Examples 8, 9 and 10 of GSK-711 demonstrate that a 13-valent vaccine formulation containing the 22F-PhtD glycoconjugate induced anti-22F immune response in old mice, young mice, and guinea pigs, respectively, measured by anti-22F antibodies in the serum using ELISA assays. Lees ¶¶125-128; Ex. 1007, 68-73. For example, ELISA data disclosed in Table 15 of Example 8 shows that after immunizing the elderly C57BI mice with the 13-valent vaccine, the serum GMC (geometric mean concentration) of anti-22F antibodies was 5.81 µg/mL (group 2) and 3.76 µg/mL (Group 3), respectively. Lees ¶126; Ex. 1007, Table 15. Similarly, the serum GMC of anti-22F antibodies in young BalbC mice was 3.99 µg/mL (group 2) and 3.76 µg/mL (Group 3), respectively. Lees ¶126; Ex. 1007, Table 16. The serum GMC of anti-22F antibodies in guinea pigs was 2.51 µg/mL (group 2) and 3.67 µg/mL (group 3), which are more than 20 and 30 fold higher than the negative control of 0.12 µg/mL, respectively. Lees ¶126; Ex. 1007, Table 17. Additional 22F glycoconjugates, 22F-PhtD-E and 22F-PD, induced even higher serum GMC of anti-22F antibodies in guinea pigs (*i.e.*, 45.74

μg/mL and 30.68 μg/mL induced by 22F-PhtD-E in Groups 4 and 5, respectively, and 96.38 μg/mL induced by 22F-PD in Group 6). *Id.*

ELISA is one of the only two assays recommended by WHO to demonstrate immunogenicity against a particular polysaccharide serotype.[2] Lees ¶127; Ex. 1019, 105. Pfizer itself used it to measure immunogenicity of many of the pneumococcal conjugates disclosed in the '559 patent. Ex. 1001, 87-88, Tables 21-22.

OPA, which measures functional antibodies, is the other assay recommended by WHO. Lees ¶127; Ex. 1019, 106-107. GSK-711 demonstrates that both 22F-PhtD and 22F-AH-PhtD glycoconjugates are immunogenic measured by both anti-22F IgG GMC and OPA functional antibodies GMT (geometric mean titer). Lees ¶128; Ex. 1007, Figures 5-6.

Furthermore, Merck-086 discloses a PCV15 composition containing a 22F-CRM_{197} glycoconjugate that induced 22F specific immune response in animal

[2] The WHO guidelines indicate that the antibody concentration of 0.35 μg/mL in human sera measured by ELISA is a "benchmark" for immunogenicity. Ex. 1019, 105; Lees at FN6.

models measured by both IgG antibody titer[3] and functional antibody OPA GMTs. Lees ¶¶129-131; Ex. 1008, Tables 2-6. Specifically, Merck-086 shows that its PCV15 induced high OPA GMTs in infant rhesus monkeys to each serotype including 22F and a 100% response rate for all serotypes contained in the composition after 3 doses. Lees ¶130; Ex.1008, Table 2. It also shows that PCV15 induced high IgG GMTs to all serotypes including 22F after 1 or 2 doses in New Zealand White Rabbits. Lees ¶131; Ex. 1008, Table 5. Moreover, Merck's PCV15 was in clinical trials and showed 22F-specific immunogenicity in human patients before 2014. Lees ¶132; Ex. 1050 at 2; Ex. 1051 at 1; Ex. 1052 at 1.

Undoubtedly, immunogenic 22F glycoconjugates existed well before 2014. Lees ¶133.

(2) GSK-711 teaches a 22F glycoconjugate comprising "an isolated capsular polysaccharide from S. pneumoniae serotype 22F and a carrier protein"

GSK-711 describes two working examples of 22F glycoconjugates, "PS22F-PhtD" and "PS22F-AHPhtD".[4] Lees ¶135; Ex. 1007, Table 2. Both glycoconjugates include an isolated polysaccharide form *S. pneumoniae* serotype

[3] Merck-086 uses electrochemiluminescence (ECL) assay to measure IgG antibody, which is similar to the ELISA assay. Lees ¶131; Ex. 1008, Tables 5-6.

[4] In this Petition, "PS22F" and "22F" are used interchangeably.

22F and the carrier protein PhtD conjugated either directly or via an adipic acid dihydrazide linker. Lees ¶135; Ex. 1007, Table 2.

In addition, GSK-711 teaches that isolated polysaccharides from *S. pneumoniae* including 22F may be conjugated to a carrier protein independently selected from CRM_{197}, diphtheria toxoid (DT), tetanus toxoid (TT), pneumococcal pneumolysis (Ply), polyhistidine triad proteins (PhtX proteins such as PhtD proteins), or *Haemophilus influenzae* protein D (PD). Lees ¶134; Ex. 1007, 9:18-22, 11:4-27.

(3) GSK-711 teaches, "a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2"

The 22F-PhtD conjugate disclosed in Table 2 has the ratio of carrier protein to polysaccharide of 2.17. Lees ¶137; Ex. 1007, Table 2. When converted to a polysaccharide to carrier protein ratio, this equals 0.46,[5] which falls within the range claimed in claim 1. *Id.*

GSK-711 further teaches, among preferred ratios, a carrier protein to polysaccharide weight ratio of between 1:2 and 2.5:1. Lees ¶136; Ex. 1007, 20:1-6. This equals a weight ratio of polysaccharide to carrier protein between 0.4 and

[5] 0.46 is the inverse of the ratio of carrier protein to polysaccharide of 2.17 disclosed in GSK-711 Table 2. Lees ¶¶85, 137.

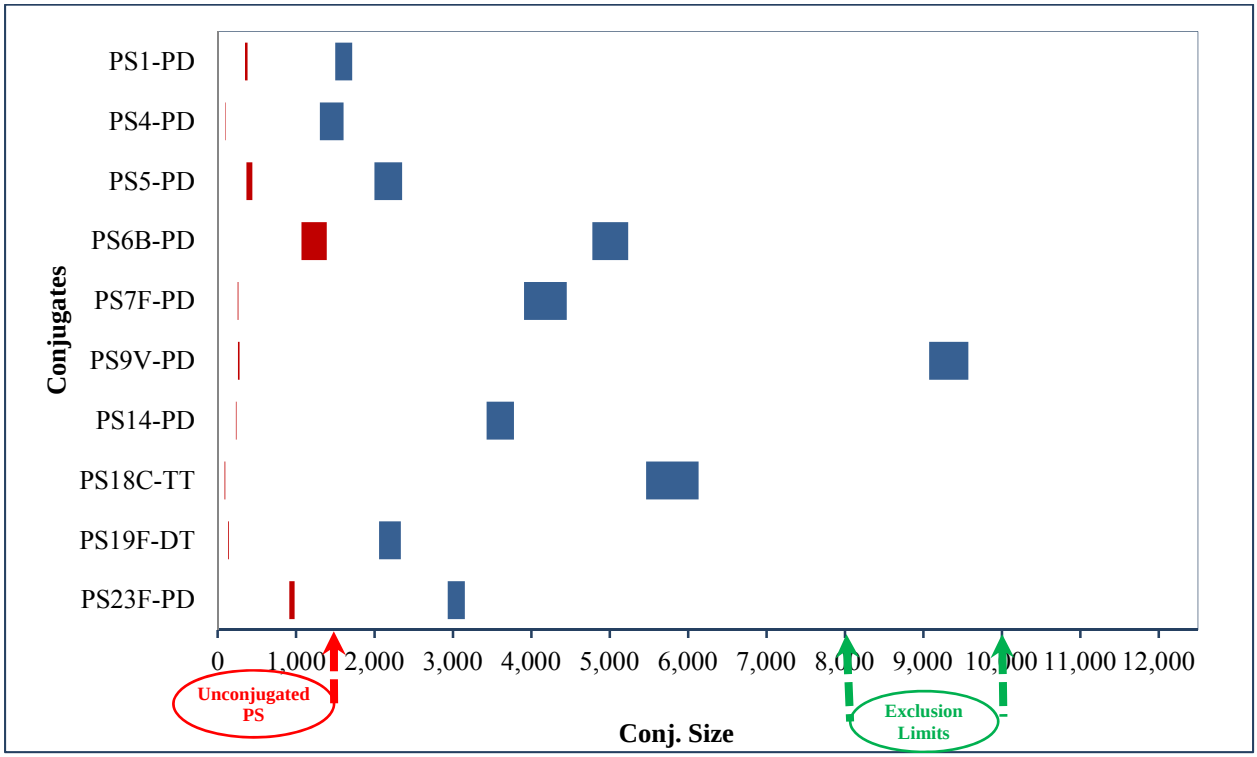
2, the same range required by claim 1. *Id.* GSK-711 also teaches weight ratios of polysaccharide to carrier protein between 0.4 and 0.67, and between 0.5 and 1. *Id.* Both of these ratios fall within the range claimed in claim 1. *Id.*

(4) GSK-711 renders the claimed MW range of "between 1000 kDa and 12,500 kDa" obvious

The only limitation not explicitly described in GSK-711 is the molecular weight range "*between 1000 kDa and 12,500 kDa*." The molecular weights of the two 22F glycoconjugates in Table 2 (PS22F-PhtD and PS22F-AHPhtD) are not explicitly disclosed (marked as "Not done"). Lees ¶138; Ex. 1007, Table 2. However, Table 2 explicitly discloses the molecular weights for 10 different pneumococcal glycoconjugates with different serotypes and carrier protein combinations, all of which fall within the range of 1,000 kDa and 12,500 kDa and span most of that range as illustrated in the table and diagram below:

Conjugates	Conj. Size (kDa)
PS1-PD	1499–1715
PS4-PD	1303–1606
PS5-PD	1998–2352
PS6B-PD	4778–5235
PS7F-PD	3907–4452
PS9V-PD	9073–9572
PS14-PD	3430–3779
PS18C-TT	5464–6133
PS19F-DT	2059–2335
PS23F-PD	2933–3152

Lees ¶139; Ex. 1007, Table 2.



As explained below, 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. Lees ¶140.

(i) There was a reasonable expectation that the 22F glycoconjugates disclosed in Table 2 had molecular weights that also fall within the claimed range

Given that the same conjugation and purification methods were used to produce all the glycoconjugates in Table 2, there would have been a reasonable

expectation 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. Lees ¶141.

First, all the glycoconjugates described in Table 2 were made by the CDAP chemistry, which is likely to produce a 22F-PhtD conjugate with an average molecular weight above 1000 kDa. Lees ¶142. The CDAP chemistry activates the hydroxyl groups on polysaccharides to form reactive groups, which then react with the amino groups on the carrier protein to form covalent linkages, resulting in crosslinked lattice structures. *See* Sec. VII(3); Lees ¶142. 22F, like other pneumococcal polysaccharides disclosed in Table 2, has numerous hydroxyl groups in each repeating unit. ***Id.*** As discussed in the State of the Art section, each unit of 22F has at least 14 hydroxyl groups. ***Id.*** Table 2 discloses that the starting size of 22F is 159–167 kDa, which corresponds to approximately 160 units.[6] Lees ¶142. Thus, each starting 22F polysaccharide molecule contains, on average, about 2240 hydroxyl groups. ***Id.*** The carrier protein PhtD contains about 59 lysines with the amino groups potentially available for crosslinking with the hydroxyl groups on 22F polysaccharides. Lees ¶142. As a result, a 22F-PhtD

[6] The molecular weight of each repeating unit of 22F is just under about 1000 Dalton. Lees, FN4.

conjugate synthesized using CDAP would naturally result in highly crosslinked lattices with each lattice containing multiple saccharide molecules and multiple carrier protein molecules. Lees ¶¶50, 142; Ex. 1027, 32. For illustration purposes, it can be reasonably assumed that the "smallest" lattice includes 2 molecules of a 22F polysaccharide. Lees ¶143. The total weight of polysaccharides in this "smallest" lattice conjugate would therefore be 320 kDa.[7] *Id.* Because Table 2 discloses that the carrier protein to polysaccharide ratio is 2.17, the total weight of PhtD in the lattice would be 694.4 kDa (about 7 molecules of PhtD[8]). *Id.* As a result, the molecular weight of the "smallest" 22F-PhtD conjugate would be 1014.4 kDa (320 kDa +694.4 kDa). *Id.*, FN12. Given the numbers of potential reactive sites on both 22F polysaccharides (on average, 2240 hydroxyl groups per molecule) and the carrier protein PhtD (59 lysines per molecule), it can also be reasonably assumed that majority of the lattices would be much larger and contain significantly more numbers of polysaccharide molecules in each lattice. Lees ¶143. In fact, it would be highly unlikely that a 22F-PhtD lattice would only contain 2 molecules of 22F polysaccharides. *Id.* Thus, the average molecular

[7] 160 kDa is used as MW for starting polysaccharide, which is within the range disclosed in Table 2. Ex. 1007, Table 2.

[8] The molecular weight of PhtD is about 94 kDa. Ex. 1079, 3.

weight of all lattices in the 22F-PhtD conjugate should be well above 1000 kDa. *Id.*

Second, all except one of the glycoconjugates described in Table 2 were purified using Sephacryl S400HR gel filtration, which has a size exclusion limit under 8,000 kDa. Lees ¶144; Ex. 1007, 51:15-18; Ex. 1060, Tables 1-2. The size distribution of all the conjugates was analyzed using the TSK5000-PWXL SEC column, which has a separation limit under 10,000 kDa. Lees ¶144; Ex.1061, Tables 4.6, 4.11. The size distribution is a key indicator of process consistency and was routinely used as an important lot release assay. Lees ¶¶65, 144; Ex. 1067, 9; Ex. 1019, 120; Ex. 1015, 6, 10; Ex. 1073, 12. Typically, the size distribution of glycoconjugates is characterized by percentages of different K_d values corresponding to the different sized conjugates in fractions collected from a specified SEC column (in this case, the TSK5000-PWXL column). Lees ¶144. In order to meaningfully demonstrate size distribution and ensure lot-to-lot consistency, it is important to use an SEC column with a sufficiently high size exclusion or separation limit such that a majority of the fractions will be under the limit. Lees ¶144; Ex. 1069, 1; Ex. 1015, 6-7. It was therefore desirable to use an SEC column with a size exclusion limit above the average molecular weight of the conjugates. *Id.* In addition, high molecular weight fractions may not be properly recovered from the column, which can negatively impact the yield of the

conjugates and the accurate characterization of size distribution. Lees ¶144; Ex. 1015, 7; Ex. 1073, 30. Thus, a POSA would have understood that, by using a Sephacryl S400HR column (exclusion limit below 8,000 kDa) to purify the conjugates and the TSK5000-PWXL column (exclusion limit below 10,000 kDa) to analyze the size distribution, the GSK inventors would have been targeting a molecular weight well below 12,500 kDa, and would have monitored the conjugation reaction and quenched it before the average size reached 12,500 kDa. *Id.* This is consistent with the sizes achieved for the 10 different glycoconjugates shown in Table 2. *Id.* The same would likely have been achieved for the two 22F-glycoconjugates.

Taken to its logical conclusion, even though molecular weights for the 22F glycoconjugates were not expressly disclosed in Table 2, there was a reasonable expectation that the two 22F-glycoconjugates would have had molecular weights within the required range of "between 1,000 kDa and 12,500 kDa." Lees ¶145.

(ii) A POSA would have been motivated to make 22F glycoconjugates that fall within the claimed range with a reasonable expectation of success

At a minimum, in view of the teachings of GSK-711 and general knowledge in the art, a POSA would have been motivated to make 22F glycoconjugates that fall within the claimed MW range with a reasonable expectation of success. Lees ¶146.

As shown above, GSK-711 discloses 10 different pneumococcal glycoconjugates with molecular weights ranging from 1,303–9,572 kDa, entirely within the claimed range of 1000–12,500 kDa. Ex. 1007, Table 2. A POSA would have concluded that this range is a desirable range for pneumococcal conjugates, including 22F glycoconjugates. Lees ¶147.

Furthermore, a POSA would also have understood that this range (1000–12,500 kDa) was desirable 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. Lees ¶148. Because unconjugated polysaccharides are less immunogenic in infants, elderly and immunocompromised patients and may also inhibit the immune response to conjugated polysaccharide, it was desirable to minimize the level of unconjugated polysaccharides in the purified glycoconjugates. Lees ¶148; Ex. 1019, 103. Typically, unconjugated polysaccharides have sizes ranging from about several kDa to several thousand kDa (*e.g.*, 10–2,000 kDa). *See, e.g.*, Ex. 1014, 8:21-24; Lees ¶148. For example, the starting polysaccharide sizes for all the conjugates disclosed in Table 2 of GSK-711 range from 89–1540 kDa. Lees ¶148; Ex. 1007, Table 2. In particular, the starting size for 22F polysaccharides ranges from 159–167 kDa. *Id.* In addition, GSK-711 and Merck-086 also disclose that unconjugated starting 22F saccharides can be above 300 kDa, 500 kDa or 1000 kDa, about 500±300 kDa, or

between $1X10^5$ and $1X10^6$ Daltons. Lees ¶151; Ex. 1007, 14:5-11; Ex. 1008, 6. To effectively separate conjugates from unconjugated polysaccharides using an SEC column (such as Sephacryl S400HR as used in GSK-711) or tangential flow filtration (TFF), the size of the conjugates needs to be preferably at least 3–5 fold larger than the unconjugated polysaccharides because, as Dr. Lees explained, a glycoconjugate behaves more like a ball, whereas a polysaccharide runs like a string—so they "appear" much bigger than they are. Lees ¶148. Therefore, in view of the starting size range for 22F polysaccharides routinely used in the art (see above), a POSA would have been motivated to generate a 22F glycoconjugate with a minimum size above approximately 1000 kDa to facilitate effective separation from unconjugated polysaccharides. *Id.*

On the other hand, large glycoconjugates with molecular weights above 12,500 kDa are difficult to purify and difficult to analyze using the Sephacryl S400HR column and TSK5000-PWXL column disclosed in GSK-711 because both have size exclusion limits well below 12,500 kDa. Lees ¶¶55, 149; Ex. 1011, 7, 9-11; Ex. 1060, Tables 1-2; Ex. 1061, Tables 4.6, 4.11. Furthermore, large glycoconjugates are undesirable also because they were known to precipitate or form a gel, which makes them difficult to purify by any column, TFF, or even sterile filtration. Lees ¶¶55, 149; Ex. 1011, 7-8. Overconjugation may also result

in the reduction or elimination of T-cell epitopes required for eliciting an immune response. Lees ¶149; Ex. 1011, 12.

Therefore, a POSA would have been motivated to make a 22F glycoconjugate with a molecular weight between 1000 kDa and 12,500 kDa. Lees ¶150.

Furthermore, a POSA would also have had a reasonable expectation of success that a 22F glycoconjugate with a size between 1,000 kDa and 12,500 kDa can be made using routine CDAP or reductive amination methods available prior to 2014. Lees ¶151. As explained above, CDAP or reductive amination chemistry naturally results in glycoconjugates with large lattice structures including multiple saccharide molecules linked to multiple carrier protein molecules in each lattice. Lees ¶¶50, 54, 151. Based on the starting size of 22F (*e.g.*, 159–167 kDa) and the carrier protein PhtD disclosed in Table 2 of GSK-711, the size of even the "smallest" lattice conjugates can easily go above 1000 kDa. Lees ¶¶144, 151. In addition, as discussed above, unconjugated starting 22F saccharides with sizes above 300 kDa, 500 kDa or 1000 kDa, about 500±300 kDa, or between $1X10^5$ and $1X10^6$ Daltons were also routinely used. Lees ¶151; Ex. 1007, 14:5-11; Ex. 1008, 6. In addition to PhtD (~94 kDa), GSK-711 and Merck-086 also disclose other carrier proteins with known molecular weights such as CRM_{197} (~58 kDa), diphtheria toxoid (~58 kDa), tetanus toxoid (~150 kDa), and Protein D (~42 kDa).

Lees ¶151. A POSA would 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 synthesize 22F glycoconjugates with molecular sizes above 1000 kDa. Lees ¶151. A POSA could also have quenched the conjugation reaction at a desired time before the average conjugate size reached 12,500 kDa to facilitate purification, characterization and to avoid precipitation or forming a gel. *Id.* GSK-711 teaches 10 different pneumococcal glycoconjugates with molecular weights all falling within the claimed range of 1,000 kDa and 12,500 kDa, further confirming a POSA's reasonable expectation of success. Lees ¶152. Moreover, the '559 patent only used the standard reductive amination chemistry that existed before 2014 to make the 22F conjugates within the claimed range. Lees ¶153.

(5) There was no indication that the claimed combination of polysaccharide-to-carrier protein ratio and MW range is anything other than mere quantification of the resulting conjugates of prior art processes

Pfizer added the limitations of polysaccharide-to-protein ratio of "between 0.4 and 2" and the glycoconjugate molecular weight range of "between 1000 kDa and 12,500 kDa" in order to overcome the cited prior art during prosecution. Lees ¶154; Ex. 1004, 17, 23-24. Pfizer asserted that this combination induced antibody responses and that the prior art does not disclose an immunogenic 22F

glycoconjugate having this "particular combination" of characteristics. Lees ¶154; Ex. 1004, 24. However, Pfizer did not submit any evidence to show that this combination is surprising. Lees ¶154. For example, Pfizer did not submit any data to compare the immunogenicity of 22F glycoconjugates with a polysaccharide-to-carrier protein ratio or molecular weight *outside* the claimed ranges with those *inside* the ranges. *Id.* No such data was disclosed in the original specification. *Id.* In fact, Table 18 of the '559 patent shows that 22F glycoconjugates *within* the claimed ranges exhibited wide variations of immunogenicity (from OPA GMT 10 to 235 at dose level 0.001 μg and from OPA GMT 252 to 4335 at dose level 0.01 μg). Lees ¶154; Ex. 1001, Table 18. Indeed, Pfizer disclosed the claimed ranges among laundry lists of different ranges in the original specification without any particular focus. Lees ¶155; Ex. 1001, 25-27. Pfizer appears to have simply chosen *two of the broadest ranges* to add to the claims in an attempt to avoid the prior art. Lees ¶155. As Dr. Lees pointed out, these ranges are so broad that the majority, if not all, of pneumococcal glycoconjugates made using routine CDAP or reductive amination methods available well before 2014 would fall within the claimed ranges. *Id.*

Recently, in *Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1312 (Fed. Cir. 2017), the Federal Circuit held that a range limitation of "30% reduction in pulling force" was obvious over the prior art because there was no indication that

the range limitation was "anything other than mere quantification of the results of a known process." The court specifically noted that the range limitation was added to the claims during reexamination in order to overcome the prior art, with seemingly no focus on that limitation in the original specification. *Id.* The court further observed that none of the steps in the patent differed in any material way from the process disclosed in the prior art and there was no evidence that the claimed 30% reduction in pulling force would have been unexpected or unattainable from the process disclosed in the prior art. *Id.* The court stated that simply because the prior art never quantified the reduction in pulling force by its disclosed embodiments does not preclude the possibility, or even likelihood, that its process achieved at least a 30% reduction. *Southwire Co.* at 1311-12.

Applying the same analysis here, the limitations of polysaccharide-to-protein ratio of "between 0.4 and 2" and the glycoconjugate molecular weight range of "between 1000 kDa and 12,500 kDa" were added during prosecution to avoid the prior art, with no focus on these limitations in the original specification. Lees ¶154; Ex. 1001, 25-27. None of the conjugation methods disclosed in the '559 patent differ in any material way from the prior art methods and there was no evidence that the claimed polysaccharide-to-carrier protein ratio and molecular weight range would have been unexpected or unattainable from the prior art process such as the CDAP process disclosed in GSK-711 or the reductive

amination disclosed in Merck-086. Lees ¶155. In fact, the '559 patent appears to have only used the standard reductive amination chemistry that existed before 2014 to make the 22F conjugates within the claimed ranges. *Id.* There is simply no indication that the claimed combination is anything other than mere quantification of the resulting conjugates of prior art processes. *Id.*

For at least all of the reasons stated above, claim 1 is obvious over the prior art.

ii. Claims 3–9

Claims 3–9 are directed to multivalent compositions including the 22F-carrier protein glycoconjugate of claim 1.

Specifically, claim 3 requires that the claimed composition further includes *S. pneumoniae* serotypes 15B and 33F glycoconjugates.

Claim 4 requires that the claimed composition further includes *S. pneumoniae* serotypes 12F, 10A, 11A and 8 glycoconjugates.

Claim 5 requires that the claimed composition further includes *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F glycoconjugates.

Claim 6 requires that the claimed composition further includes *S. pneumoniae* serotypes 1, 5 and 7F glycoconjugates.

Claim 7 requires that the claimed composition further includes *S. pneumoniae* serotypes 6A and 19A glycoconjugates.

Claim 8 requires that the claimed composition further includes *S. pneumoniae* serotype 3 glycoconjugate.

Claim 9 requires that the claimed composition is an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20-valent pneumococcal conjugate composition.

Thus, claims 3–8 collectively recite 20 additional serotypes. However, as shown in the chart below and in the Lees Declaration, all 20 of the recited serotypes were already included in multivalent pneumococcal vaccines on the market including Prevnar®, Prevnar®13, Synflorix®, Pneumovax®23, and Merck's MK-V114 (PCV15), which was known to be in the clinical trials as of the earliest possible priority date. Lees ¶¶30, 34-37, 158.

Claim	Recited Serotype	PCV7 Prevnar® Pfizer	PCV10 Synflorix® GSK	PCV13 Prevnar®13 Pfizer	PCV15 MK-V114 Merck	Pneumovax®23
3	15B					x
	33F				x	x
4	8					x
	10A					x
	11A					x
	12F					x
5	4	x	x	x	x	x
	6B	x	x	x	x	x
	9V	x	x	x	x	x
	14	x	x	x	x	x
	18C	x	x	x	x	x
	19F	x	x	x	x	x
	23F	x	x	x	x	x
6	1		x	x	x	x
	5		x	x	x	x
	7F		x	x	x	x
7	19A			x	x	x
	6A			x	x	
8	3			x	x	x
9	22F in 8-20 valent conjugate composition				x	

In particular, Pneumovax®23, which was first marketed 30 years ago as a polysaccharide-only vaccine, contains all valences recited except for serotype 6A, and starting with Prevnar® in 2000, vaccine makers steadily released multivalent PCV products with greater inclusion of serotypes so as to approach all those included in Pneumovax®23. Lees ¶¶30, 34-37, 159. Most recently, Prevnar®13 expanded its valences to include 6A (among other serotypes), and Merck was developing a PCV15 product with even more valences, including 22F. Lees ¶¶37-

38, 159; Ex. 1050 at 2; Ex. 1051 at 1; Ex. 1052 at 1. It is no surprise, then, that the serotypes recited in claims 3–8 are all taught by GSK-711, since there was a clear motivation to make ever-higher valent glycoconjugate vaccines approaching the portfolio of serotypes contained in Pneumovax®23 as those serotypes became more epidemiologically relevant. Lees ¶¶34-37, 159. One would have had a reasonable expectation of success, as well, 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. *Id.*

(1) GSK-711 teaches multivalent immunogenic compositions (specifically, up to 23 valent as recited in claim 9) comprising a pneumococcal 22F-glycoconjugate and various additional serotypes recited in claims 3–8

GSK-711 teaches multivalent immunogenic compositions comprising a pneumococcal 22F glycoconjugate and specifically contemplates a range of serotype valences up to 23, including all of the serotypes recited in the claims of the ’559 patent. Lees ¶¶160-161; Ex. 1007, 5:12-14, 7:26-28. Specifically, GSK-711 teaches that the multivalent compositions may include all or subsets of the following serotypes including the 20 serotypes recited in claims 3–8 of the ’559

patent in **bold**: **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**. Lees ¶¶160-161; Ex. 1007, 8:1-3.

(2) There was a motivation to make multivalent vaccines against the emerging serotypes recited in claims 3 and 4

As discussed in the State of the Art section and in the Lees Declaration, after the introduction of Prevnar®13, certain serotypes that were not included in Prevnar®13 became more epidemiologically prevalent. Lees ¶¶38, 162; Ex. 1028, 11; Ex. 1029, 6 (citing Ex. 1049). Those emerging serotypes included 22F as recited in claim 1, serotypes 33F and 15B as recited in claim 3, and serotypes 12F, 10A, 11A and 8 as recited in claim 4. *Id.* Therefore, a POSA would have been motivated to make multivalent vaccines against the emerging serotypes recited in claims 3 and 4. *Id.*

(3) There was a motivation to combine emerging serotype 22F with serotypes from Prevnar® (PCV7), Synflorix® (PCV10), and Prevnar®13 (PCV13) recited in claims 5-8

The serotypes recited in claim 5—serotypes 4, 6B, 9V, 14, 18C, 19F and 23F—are all included in Prevnar®, Synflorix® and Prevnar®13. Lees ¶¶36-37. These are among the most successful pneumococcal glycoconjugate vaccines, and thus a POSA would have been motivated to combine the valences recited in

dependent claim 5 with the emerging 22F serotype in independent claim 1. Lees ¶¶163-164.

Similarly, the serotypes recited in claim 6—serotypes 1, 5 and 7F—were common to Synflorix® and Prevnar®13, and thus a POSA would have been motivated to incorporate these serotypes as well. Lees ¶¶36-37, 165.

Additionally, the serotypes recited in claims 7 and 8—serotypes 6A, 19A and 3—were found in Prevnar®13, and were also known to be included in Merck's PCV15 (MK-V114) prior to the earliest possible priority date of the '559 patent. Lees ¶¶37, 166; Ex. 1008, [0007]. Thus, a POSA would have been motivated to incorporate these serotypes as well. Lees ¶166.

(4) There was a reasonable expectation-of-success to make multivalent glycoconjugate vaccine compositions as recited in claims 3-9

From PCV7 (Prevnar®) to PCV10 (Synflorix®) and to PCV13 (Prevnar®13), vaccine manufactures had consistently found success as they increased the valences of pneumococcal glycoconjugate vaccines while maintaining the immunogenicity against all serotypes in the compositions. Lees ¶¶30, 35-37, 167. In particular, Pfizer admitted that it had previously solved the issue of high valency with single carrier CRM_{197} in Prevnar®13. Ex. 1059, 2:25-29; *see also Merck Sharp & Dohme Corp. v. Siber Hausdroff et al.*, 2017 WL

3160412, IPR2017-01215, paper 8 at 28-36 (PTAB Mar. 30, 2017). In the '559 patent, Pfizer used the same single carrier protein CRM_{197} to generate multivalent compositions. Ex. 1001, Examples 1-20.

Merck also successfully developed its PCV15 MK-V114 by adding serotypes 22F and 33F to PCV13 (Prevnar®13) using single carrier CRM_{197} without undermining the immune response induced against other serotypes in the product. Lees ¶169; Ex. 1008, Tables 1-6; Ex. 1029, 6-7; Ex. 1051, 1; Ex. 1052, 1.

Additionally, GSK-711 demonstrated that adding 22F and 19A conjugates to an 11-valent composition (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, the same serotypes included in Synflorix®, with the addition of serotype 3) did not negatively impact the immune response induced against other polysaccharides in the composition. Lees ¶171; Ex. 1007, Examples 8–10, Tables 15-17. An immune response was shown against all serotypes. *Id.*

Therefore, a POSA would have had a reasonable expectation of continued success in combining a 22F conjugate with those serotypes recited in claims 3–8 and as PCV valence approached 20 as recited in claim 9. Lees ¶172.

iii. Claims 10, 16 and 17

Claim 10 recites a carrier protein selected from the group consisting of DT (Diphtheria toxin), TT (tetanus toxoid), CRM_{197}, other DT mutants, PD

(*Haemophilus influenzae* protein D), and immunologically functional equivalents thereof. Claim 16, which depends from claim 10, specifically recites CRM_{197}. Claim 17, which depends from claim 16, further requires that the polysaccharide is individually conjugated to CRM_{197}.

Well before 2014, carrier proteins CRM_{197}, tetanus toxoid (TT), diphtheria toxoid (DT), *H. influenzae* protein D (protein D), and variants of these proteins were known in the art and used in pneumococcal glycoconjugates. Lees ¶174; Ex. 1019, 117; Ex. 1036, 2. GSK-711 specifically teaches that any saccharide present in the glycoconjugate, including 22F, may be conjugated to a carrier protein independently selected from the group consisting of TT, DT, CRM_{197}, and PD. Lees ¶175; Ex. 1007, 9:18-22. These are the same carrier proteins recited in claims 10, 16 and 17. Lees ¶175.

CRM_{197}, in particular, is one of the most commonly used carrier proteins, partly because of its non-toxicity and the abundance of lysine residues available for conjugation. Lees ¶46; Ex. 1036, 2. Prevnar® and Prevnar®13 both use CRM_{197} as the sole carrier protein, which is individually conjugated to all the serotypes in the products. Lees ¶¶35, 37, 46; Ex. 1065, 2. Merck-086 also teaches that the different serotypes in its PCV-15, including 22F, are individually conjugated to CRM_{197}. Lees ¶176; Ex. 1007, Example 2.

Thus, claims 10, 16 and 17 are not inventive.

iv. Claims 11–13

Claim 11 depends from claim 1 and requires that the claimed immunogenic composition further includes a buffer, a salt, a divalent cation, a non-ionic detergent, a cryoprotectant, an anti-oxidant, or a combination thereof.

Claim 12 depends from claim 11 and specifically requires that the claimed immunogenic composition further includes a buffer.

Claim 13 depends from claims 12 and specifies that the buffer is phosphate, succinate, histidine or citrate.

All these excipients recited in claims 11–13 are conventional and were routinely used in pharmaceutical compositions, including vaccines well before 2014. Lees ¶179. For example, Example 11 in GSK-711 provides various formulations for the 13-valent immunogenic composition including a 22F glycoconjugate. Lees ¶179; Ex. 1007, 73-75. Formulation (d) includes a non-ionic detergent (Tween 80), salts (*e.g.*, KCl and NaCl), and a phosphate buffer (KH_2PO_4/Na_2HPO_4), as recited in claims 11–13. Lees ¶179; Ex. 1007, 75.

Furthermore, Merck-086 details a variety of pharmaceutical excipients that can be used to formulate its PCV15 composition. Lees ¶180. Excipients include, *inter alia*, buffers (such as phosphate, succinate, histidine or citrate) (Ex. 1008, ¶¶ [0066]-[0067]), surfactants (*i.e.*, non-ionic detergent) (*Id.*, ¶¶[0070]-[0071]), and

salts [*Id.*, ¶[0065]). Lees ¶180. In Example 3, Merck-086 discloses two clinical formulations of PCV-15 containing polysorbate-80 (for non-adjuvanted), L-histidine, and sodium chloride. Lees ¶180; Ex. 1008, Table 1.

Thus, claims 11, 12 and 13 are not inventive.

v. Claims 14, 15 and 29

Claim 14 is directed to a syringe or a container filled with the immunogenic composition of claim 1.

Claim 15 depends from claim 14 and further specifies that the syringe is siliconized or made of glass.

Claim 29 is directed to a container filled with the immunogenic composition of claim 1.

Before 2014, a syringe or other type of container, such as a vial, had been routinely used to package vaccine compositions to facilitate storage, shipping and administration. Lees ¶183.

For example, GSK-711 teaches the use of "conventional" syringes and vials for containing and administering its claimed vaccine compositions. Lees ¶183; Ex. 1007, 41:15–16, 40:20–21.

Merck-086 specifically teaches that its PCV15 composition containing a 22F conjugate can be formulated in single dose vials, multi-dose vials or as pre-filled

syringes. Ex. 1008, [0061]; Lees ¶183. Furthermore, pre-filled glass syringes were already used for Prevnar®13 and Synflorix® for intramuscular injection. Lees ¶184; Ex. 1045, 5–6; Ex. 1024, 8, 14.

Therefore, claims 14, 15 and 29 are not inventive.

vi. Claim 18

Claim 18 recites that each dose of the immunogenic composition in claim 1 comprises 0.1 μg to 100 μg of the polysaccharide. This range encompasses standard doses and dose ranges for a polysaccharide included in PCV products. Lees ¶186.

For example, GSK-711 teaches immunogenic compositions that contain pneumococcal polysaccharide at a dose of between 0.1–20 μg, 0.5–10 μg, 0.5–5 μg, or 1–3 μg. Lees ¶187; Ex. 1007, 20:16-17. In Example 2, GSK-711 describes that a 13-valent vaccine was made by further adding the serotypes 19A and 22F conjugates at a dose of 3 μg each of polysaccharide per human dose. Lees ¶188; Ex. 1007, 54:12-15. Similarly, the clinical formulations of Merck's PCV-15 disclosed in Merck-086 contain 32 μg of total polysaccharide, with 2 μg each of 14 serotypes (including 22F) and 4 μg of serotype 6B polysaccharide per dose. Lees ¶189; Ex. 1008, Table 1.

Thus, claim 18 is not inventive.

vii. Claim 19

Claim 19 recites that each dose of the immunogenic composition in claim 1 comprises 10 μg to 150 μg of carrier protein. This is a common dose range for the carrier protein in PCV products. Lees ¶191.

For example, each dose of Prevnar®13 includes 32 μg of carrier protein and Synflorix® includes approximately 17–32 μg of carrier proteins in total. Lees ¶191; Ex. 1045, 5–6; Ex. 1024, 13–14; Ex. 1044, 2.

GSK-711, moreover, discloses dosages with amounts of carrier protein within the claimed range. Lees ¶192; Ex. 1007, 54:9-15. In particular, the 13-valent composition disclosed in Example 2 contains a total amount of carrier protein of at least 38.7 μg and almost certainly below 150 μg, according to Dr. Lees' calculation. Lees ¶193.

Additionally, the clinical formulations of Merck's PCV-15 contain approximately 32 μg of total carrier protein per dose. Lees ¶194; Ex. 1008, Table 1.

Thus, claim 19 is not inventive.

viii. Claims 23–26

Claim 23 depends from claim 1 and requires that the immunogenic composition further includes at least one adjuvant.

Claim 24 depends from claim 23 and specifies that "said at least one adjuvant is selected from the group consisting of aluminum, calcium phosphate, a liposome, an oil-in-water emulsion, and poly(D,L-lactide-co-glycolide) (PLG) microparticles or nanoparticles."

Claim 25 depends from claim 24 and recites that said adjuvant is aluminum phosphate, aluminum sulfate or aluminum hydroxide.

Claim 26 depends from claim 23 and recites that at least one adjuvant is a CpG oligonucleotide.

All of the adjuvants recited in claims 23–26 had been routinely used in PCV compositions before 2014. Lees ¶196. For example, aluminum phosphate was used as an adjuvant in Prevnar®, Prevnar®13, and Synflorix®. *Id.* Ex. 1042, 1; Ex. 1045, 5; Ex. 1024, 15. Both GSK-711 and Merck-086 teach various adjuvants suitable for specific use in vaccine compositions containing a 22F glycoconjugate, including aluminum salts (such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc.); oligonucleotides containing CpG; and others. Lees ¶¶197-199; Ex. 1007, 27:21-24, 28:20-30, 30:9-35; Ex. 1008, [0032]-[0047]. More specifically, GSK-711 describes adjuvanted 13-valent PCV formulations which include a liposome based adjuvant and an oil-in-water emulsion. Lees ¶¶197-198;

Ex. 1007, Example 11, formulation (c). Merck-086 teaches a specific clinical formulation of PCV-15 containing aluminum as an adjuvant. Lees ¶199; Ex. 1008, Table 1.

Thus, claims 23–26 are not inventive.

ix. Claims 27–28

Claims 27 and 28 depend on claim 1 and recite formulations in liquid form and in lyophilized form, respectively.

Liquid and lyophilized forms of glycoconjugate vaccines had been known and used well before 2014. Lees ¶201. For example, Prevnar®13 and Synflorix® were both provided as liquid preparations, and the WHO guidelines specifically suggested that pneumococcal glycoconjugate vaccines may be formulated in lyophilized form. Lees ¶201; Ex. 1045, 5–6; Ex. 1024, 13, 15; Ex. 1019, 123. GSK-711 specifically teaches that a vaccine composition containing a 22F glycoconjugate may be stored in solution or lyophilized. Lees ¶202; Ex. 1007, 40:13. Therefore, claims 27 and 28 are not inventive.

x. Claims 30–34 and 37

Claim 30 depends from claim 1 and is directed to a method of preventing, treating or ameliorating an infection, disease or condition associated with *S.*

pneumoniae in a subject by administering to the subject an effective amount of the claimed immunogenic composition.

Claim 31 depends from claim 1 and is specifically directed to a method of preventing an infection caused by *S. pneumoniae* in a subject by administering to the subject an effective amount of the claimed immunogenic composition.

Claim 32 depends from claim 30 and specifies that the subject is a human being less than 2 years of age.

Claim 33 depends from claim 30 and specifies that the subject is a human adult 50 years of age or older.

Claim 34 depends from claim 30 and specifies that the subject is an immunocompromised human.

Claim 37 depends from claims 1 and is directed to a method of inducing an immune response to *S. pneumoniae* serotype 22F in a subject by administering an effective amount of the claimed immunogenic composition.

The claimed therapeutic use of an immunogenic 22F conjugate has been specifically taught and demonstrated in GSK-711 and Merck-086. Lees ¶205. For example, GSK-711 teaches that the inclusion of 22F glycoconjugates in a pediatric pneumococcal glycoconjugate vaccine could be useful for inducing herd immunity in the population such that the onset of serious disease caused by this serotype (such as pneumonia, invasive pneumococcal disease, and/or chronic obstructive

pulmonary disease) may be prevented or reduced in severity. Lees ¶206; Ex. 1007, 5:17-28. It also teaches that vaccines containing a 22F glycoconjugate may be administered in a safe and effective amount to elicit an immune response in infants (aged 0–2) and in the elderly population over the age of 50, 55 or 60. Lees ¶207; Ex. 1007, 42:21-35. GSK-711 specifically demonstrated that administering a 13-valent vaccine containing a 22F glycoconjugate to elderly C57BI mice and young Balb/c mice induced an immune response to 22F and all other serotypes. Lees ¶208; Ex. 1007, Examples 8, 9.

Similarly, Merck-086 showed that its PCV-15 composition containing a 22F glycoconjugate induced immune response against 22F and all other serotypes in infant rhesus monkeys and New Zealand White Rabbits animal models. Lees ¶209; Ex. 1008, Examples 4-5. Thus, Merck states that its PCV-15 provides broad coverage against pneumococcal disease, particularly, in infants and young children. Lees ¶209; Ex. 1008, Abstract.

Moreover, as discussed in the State of the Art section, glycoconjugate vaccines were developed to overcome limitations of polysaccharide-only vaccines and induce protective immunity when administered to infants under the age of 2, the elderly and other immunocompromised patients. Lees ¶¶31-32, 210. Prevnar®13 is indicated for active immunization for the prevention of invasive disease caused by the *S. pneumoniae* serotypes in children 6 weeks through 5 years

of age, and in adults 50 years of age and older. Lees ¶210; Ex. 1025, 1. In Canada, Prevnar®13 was recommended by the National Advisory Committee on Immunization for use in immunocompromised patients, such as hematopoietic stem cell transplant recipients or HIV-positive patients. Lees ¶210; Ex. 1084, 19.

In view of the above, a POSA would have been motivated to practice the therapeutic methods of claims 30–34 and 37 and would have had a reasonable expectation that such methods would be successful in preventing, treating or ameliorating a pneumococcal infection, disease or condition, particularly in infants, the elderly or immunocompromised patients. Lees ¶211.

xi. Claims 35 and 36

Claims 35 and 36 depend on claim 30 and specify that the claimed administration of the claimed immunogenic composition is in a single dose schedule or in a multiple dose schedule, respectively.

Single and multiple dose schedules are standard dose schedules for vaccines such as Prevnar®. Lees ¶212. More specifically, GSK-711 and Merck-086 both teach single dose and multiple dose schedules for administering a pneumococcal vaccine containing a 22F glycoconjugate. Lees ¶213; Ex. 1007, 40:2-3; Ex. 1008, [0057].

Therefore, claims 35 and 36 are not inventive.

xii. Claims 41 and 42

Claim 41 depends from claim 1 and specifies that the claimed glycoconjugate is prepared using reductive amination.

Claim 42 depends from claim 41 and further specifies that the reductive amination includes (a) oxidation of the polysaccharide to form an activated polysaccharide and (b) reduction of the activated polysaccharide and a carrier protein to form the glycoconjugate.

Claims 41 and 42 are product-by-process claims and should be analyzed for patentability in the same way as claim 1. *See* claim 1, *supra*. In any event, GSK-711 teaches that its claimed glycoconjugates, including the 22F glycoconjugate, can be prepared by reductive amination methods. Lees ¶217; Ex. 1007, 17:1. To carry out reductive amination, GSK-711 specifically teaches that (a) aldehyde groups can be generated on a polysaccharide by oxidation to form an activated polysaccharide, and (b) glycoconjugates can be formed by reduction of the activated polysaccharide (*i.e.*, the "saccharide-aldehyde") and a carrier protein. Lees ¶217; Ex. 1007, 18:23-31.

Similarly, Merck-086 specifically describes reductive amination methods for the preparation of a 22F-CRM_{197} glycoconjugate. Lees ¶218; Ex. 1008, Example 2.

Moreover, as discussed in the State of the Art section, reductive amination had been routinely used to make glycoconjugates before 2014. Lees ¶¶48, 216. Prevnar®13, for instance, was synthesized using reductive amination. Lees ¶47; Ex. 1045, 3. Typically, a reductive amination process involves the steps of (a) oxidation of the polysaccharide to form an activated polysaccharide and (b) reduction of the activated polysaccharide and a carrier protein to form the glycoconjugate. Lees ¶¶48, 216.

Therefore, claims 41 and 42 merely recite routine and conventional reductive amination methods which had already been used to generate 22F glycoconjugates before the earliest possible priority date. Lees ¶219.

xiii. Claim 45

Claim 45 depends from claim 1 and specifies that the polysaccharide in the claimed glycoconjugate has a molecular weight of between 10–2,000 kDa.

The molecular weight range recited in claim 45 is a standard target range for preparing starting polysaccharides to be used in glycoconjugates. Lees ¶220. For instance, GSK-711 teaches that the starting polysaccharides (including 22F polysaccharides) for use in glycoconjugation should be between 50 kDa and 1,600 kDa. Lees ¶221; Ex. 1007, 14:8-11. This range falls entirely within the range recited in claim 45. *Id.* Additionally, Table 2 shows that all polysaccharides used

for 14 different glycoconjugates had molecular weights ranging from 93 kDa to 1391 kDa. Lees ¶221; Ex. 1007, Table 2. The two 22F glycoconjugates, in particular, had starting polysaccharide sizes of 159–167 kDa. ***Id.*** All of these sizes fall within the range recited in claim 45. ***Id.*** A *prima facie* case of obviousness is established where the prior art discloses examples or ranges of values that overlap with the claimed range. *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997); *see also In re Woodruff*, 919 F.2d 1575, 1577–78 (Fed. Cir. 1990).

Ground II: Claims 2, 40 and 43 Are Obvious over GSK-711 in View of Merck-086, Lees-2008, PVP-2013, Pfizer-605 and General Knowledge in the Art

Claim 2 depends from claim 1 and requires that "the glycoconjugate comprises at least 0.1 mM acetate per mM polysaccharide."

Claim 40 depends from claim 1 and requires that "a ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM isolated polysaccharide is at least 0.6."

Claim 43 depends from claim 42 (which pertains to activating the polysaccharide as part of the reductive amination method of glycoconjugate synthesis) and requires that "a ratio of mM acetate per mM polysaccharide in the glycoconjugate to mM acetate per mM polysaccharide in the activated polysaccharide is at least 0.6."

Restated, claim 2 recites a minimum required threshold O-acetylation level in the 22F glycoconjugate; claim 40 recites a minimum threshold ratio of O-acetylation level in the 22F glycoconjugate as compared to that in the isolated polysaccharide; and claim 43 recites a minimum threshold ratio of O-acetylation level in the 22F glycoconjugate as compared to that in the activated polysaccharide. Lees ¶224.

(1) There was clear motivation to meet the threshold O-acetylation level and ratios recited in claims 2, 40 and 43

Lees-2008 establishes that O-acetyl groups on polysaccharides were considered desired epitopes well before 2014. Lees ¶¶70, 225; Ex. 1011, 5. It was generally known that O-acetyl groups could be important for protective immunogenicity. Lees ¶225; Ex. 1011, 5, 7. Therefore, it was desirable for a POSA to preserve the O-acetylation level found on native 22F polysaccharide during a glycoconjugation process. Lees ¶226; Ex. 1011, 5, 7.

It was also known that in the native 22F polysaccharide, O-acetyl groups are present in approximately 80% (*i.e.*, 0.80) of the repeating units of the polysaccharide. Lees ¶225; Ex. 1026, 9. In other words, it was known that the O-acetylation level on native 22F polysaccharide is 0.8 mM acetate per mM of polysaccharide repeating unit. *Id.* Therefore, a POSA would strive to preserve O-

acetylation to be as close to the level of the native 22F polysaccharide as possible, which is well above the claimed threshold level recited in claim 2. Lees ¶228.

Additionally, PVP-2013, which is a revised version of "Minimum Requirements for Biological Products" ("MRBP") published by the Japanese National Institute of Infectious Diseases ("NIID"), indicates that for 22F polysaccharides, the permitted O-acetylation level by NIID is "0.5–1.5" mM acetate per mM polysaccharide unit, which again is well above the threshold in claim 2. Lees ¶227; Ex. 1012, 3, 4.

Therefore, Lees-2008 and/or PVP-2013 clearly establish a motivation to meet the threshold recited in claim 2. Lees ¶228.

In addition, as Dr. Lees explained, the permitted minimum O-acetylation level of 0.5 (as measured by mM acetate per mM polysaccharide) in PVP-2013 also indicates that the permitted minimum ratio of O-acetylation level (as measured by mM acetate per mM polysaccharide) in the glycoconjugate to that in the isolated or activated polysaccharide (also measured by mM acetate per mM polysaccharide) is at least 0.625,[9] thus establishing a motivation to meet that 0.6 threshold in claims 40 and 43. Lees ¶229.

[9] 0.5/0.8 = 0.625, assuming that the isolation or activation process does not remove the O-acetyl groups on the 22F polysaccharide. If the isolation or activation

(2) There was a reasonable expectation-of-success to achieve the threshold O-acetylation as required by claims 2, 40 and 43

Before the priority date, a POSA would have known that such thresholds could be achieved by using conjugation conditions that do not alter or remove the O-acetyl groups present on the native 22F polysaccharide. Lees ¶231. It was known at the time that protic solvents such as water are required to alter or remove O-acetyl groups on polysaccharides by donating protons. Lees ¶232. Thus "aprotic" solvents such as DMSO (which cannot donate protons) were used instead in the reductive amination process so as to avoid potential loss of O-acetyl groups. Lees ¶232; Ex. 1011, 5, 7, 9. Indeed, as Dr. Lees pointed out, 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. Lees ¶232; Ex. 1013, Examples 2, 4, 6, 8, 10, 12, 14, 17.

Therefore, a POSA would have been motivated to modify the conjugation process disclosed in GSK-711 to use reductive amination in DMSO as disclosed in

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process alters or removes the O-acetyl groups, the permitted minimum ratio of O-acetylation level in the glycoconjugate to the O-acetylation level in the isolated or activated polysaccharide would be greater than 0.625 because the denominator would be less than 0.8. Lees ¶229.

Pfizer-605 and would have had a reasonable expectation that such a modified conjugation process would successfully preserve the O-acetylation level on the native 22F polysaccharide, which is well above the minimum threshold recited in claims 2, 40, and 43. Lees ¶233.

Ground III: Claims 20–22 Are Obvious over GSK-711 in View of Merck-086, GSK-531 and General Knowledge in the Art

Claims 20–22 are directed to combination vaccines. Specifically, claim 20 depends from claim 1 and requires that the claimed immunogenic composition further includes an antigen from other pathogens.

Claim 21 depends from claim 20 and specifies that the antigen may be selected from diphtheria toxoid (D), tetanus toxoid (T), pertussis antigen (P), acellular pertussis antigen (Pa), hepatitis B virus (HBV) surface antigen (HBsAg), hepatitis A virus (HAV) antigen, conjugated *Haemophilus influenzae* type b capsular saccharide (Hib), and inactivated poliovirus vaccine (IPV) antigen.

Claim 22 depends from claim 1 and requires that the claimed immunogenic composition further includes a conjugated *N. meningitidis* serogroup A capsular saccharide (MenA), a conjugated *N. meningitidis* serogroup W135 capsular saccharide (MenW135), a conjugated *N. meningitidis* serogroup Y capsular

saccharide (MenY), or a conjugated *N. meningitidis* serogroup C capsular saccharide (MenC).

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

In fact, Example 3 in GSK-711 demonstrates that inclusion of *Haemphilus influenzae* protein D in an 11-valent PCV composition provides improved protection against acute otitis media (AOM) caused by various pneumococcal serotypes and *H. influenzae* in infants. Lees ¶236; Ex. 1007, Example 3, Table 3.

Although the 11-valent PCV composition used in Example 3 of GSK-711 does not include a 22F serotype, GSK-531 specifically teaches that its disclosed pneumococcal glycoconjugates (including a 22F glycoconjugate) can be mixed with other antigens, including those specifically recited in claim 21, such as diphtheria toxoid (DT), tetanus toxoid (TT), and pertussis components such as detoxified Pertussis toxoid (PT) and filamentous haemagglutinin (FHA) with optional pertactin (PRN) and/or agglutinin 1 +2, and Hepatitis B surface antigen (HepB). Lees ¶237; Ex. 1014, 20:25-31. It also teaches that its pneumococcal glycoconjugates (including a 22F glycoconjugate) can be mixed with other

antigens, including those recited in claim 22, such as conjugates of a capsular saccharide from *N. meningitidis* A, C, W or Y. Lees ¶238; Ex. 1014, 21:1-3.

Furthermore, by the earliest possible priority date, various combination vaccines had been successfully licensed to provide broad coverage including *Infanrix®-hexa* (DTPa, HBV, IPV and Hib), Tritanrix® (which contains a whole cell pertussis component and HepB surface antigen), and various tetravalent meningococcal conjugate vaccines comprising serogroups A, C, W, and Y manufactured by Sanofi-Pasteur, Novartis, and GSK (*see* Ex. 1037, Table 1). Lees ¶239. In addition, the combination of 9-valent PVC with TETRAMUNE (diphtheria toxoid, tetanus toxoid, whole cell pertussis, and CRM_{197}-conjugated *Haemophilus influenzae* type B oligosaccharide) and a combination CRM_{197}-conjugated pneumococcal-meningococcal C vaccine were shown to be safe and immunogenic in human patients. Lees ¶239; Ex. 1082, 1; Ex. 1083, Abstract.

Moreover, Pfizer didn't provide any data in the '559 patent regarding the combination vaccines recited in claims 20–22. Lees ¶240. In fact, Pfizer discloses nothing more than what was already known in the prior art. *Id.*

Therefore, the combination vaccines recited in claims 20–22 are not inventive.

Ground IV: Claims 38 and 39 are Obvious over GSK-711 in View of Merck-086, Pfizer-605 and General Knowledge in the Art

i. Claim 38

Claim 38 depends from claim 1 and specifies that at least 30% of the glycoconjugates in the claimed composition have a K_d below or equal to 0.3 in a CL-4B column.

Although GSK-711 does not specifically teach the limitation recited in claim 38, the percentage of glycoconjugates with a specific distribution coefficient (K_d) value was routinely used as a measure of size distribution before 2014. Lees ¶¶65-68, 242. In particular, it was well known that a percent value of glycoconjugates with a K_d value equal to or less than 0.3 in a CL-4B column reflects the percentage of high molecular weight fraction of the glycoconjugate. Lees ¶242; Ex. 1015, 6.

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

protocols using lyophilization, which is similar to what was used in the '559 patent, to reach the desired percentage of conjugate size 0.3 K_d in a CL-4B column. Lees ¶243. As shown in Table 7, Pfizer achieved the percentage values of 67% and 58% measured by 0.3 K_d in a CL-4B column, respectively, well above the "at least 30%" threshold recited in claim 38. Lees ¶243; Ex. 1013, Table 7.

Therefore, 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 and would have had a reasonable expectation-of-success. Lees ¶244.

ii. Claim 39

Claim 39 depends from claim 1 and specifies that the claimed immunogenic composition contains "less than about 50% of free polysaccharide compared to a total amount of polysaccharide."

It was well known before 2014 that unconjugated polysaccharides do not induce effective immune response when administered to infants, elderly and immunologically compromised patients. Lees ¶246; Ex. 1019, 103. Therefore, it was highly desirable to minimize the free polysaccharide level in a conjugate vaccine composition. *Id.* Pfizer-605 specifically teaches that a preferred free

saccharide level in pneumococcal glycoconjugates below 20–25%. Lees ¶246; Ex. 1013, 36:58–61.

Indeed, all of the percentages of free polysaccharide in the glycoconjugate compositions shown in Table 2 of GSK-711 are below 12%. Lees ¶247; Ex. 1007, 54. Specifically, the PS22F-PhtD glycoconjugate composition contains 5.8% free polysaccharide, and the PS22F-AHPhtD glycoconjugate composition contains less than 1% free polysaccharide. *Id.*

Therefore, it would have been obvious to reduce the amount of free polysaccharide in a glycoconjugate vaccine below 50% as a matter of routine quality control, and this was already achieved using standard methods available before the earliest possible priority date. Lees ¶248.

Ground V: Claim 44 Is Obvious over GSK-711 in View of Merck-086, Hsieh-2000 and General Knowledge in the Art

Claim 44 depends from claim 1 and requires that "the degree of conjugation of said glycoconjugate is between 2 and 15."

As Pfizer stated in the '559 patent, the "degree of conjugation" is typically measured by "the number of lysine residues in the carrier protein (*e.g.*, CRM_{197}) that become conjugated to the saccharide which can be characterized as a range of conjugated lysines." Lees ¶250; Ex. 1001, 26:35-39.

While GSK-711 does not specifically characterize the degree of conjugation in its 22F-glycoconjugates, the degree of conjugation recited in claim 44 had already been achieved in many glycoconjugates before the earliest possible priority date. Lees ¶250. For example, Hsieh-2000 characterized saccharide-CRM_{197} conjugates included in *Hib*, pneumococcal and meningococcal vaccines successfully developed by Wyeth and observed that the formulation of the covalent bonds between lysines and polysaccharides had been "consistent in the range of 6–9," **(**Ex. 1015, 8), which falls entirely within the range of 2–15 as claimed in claim 44. Lees ¶¶251-252.

Thus, 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 by the earliest possible priority date. Lees ¶253.

XIII. CONCLUSION

Based on the foregoing, claims 1–45 of the '559 patent are unpatentable as obvious. Petitioner requests institution of an *inter partes* review to cancel those claims.

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a)(1)(i) because, according to the "word count" function of Microsoft Word Microsoft Office Professional Plus 2010, the Petition contains 13,979 words, excluding the parts of the Petition exempted from the word count by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

I hereby certify that, on November 20, 2017, I caused a true and correct copy of the following materials:

- Petition for Inter Partes Review of U.S. Patent No. 9,429,559
- Exhibits 1001-1005, 1007-1008, 1011-1030, 1032-1045, 1047-1091
- Power of Attorney
- List of Exhibits
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