

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER INC.
Petitioner

v.

POGONA, LLC
Patent Owner

IPR2026-00189
U.S. Patent No. 11,058,757

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,058,757**

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LIST OF EXHIBITS

Exhibit	Short Name	Document
EX1001	'757 patent	U.S. Patent No. 11,058,757
EX1002	Musey Dec.	Declaration of Luwy Musey, M.D.
EX1003		Curriculum Vitae of Luwy Musey, M.D.
EX1004	Goldblatt	Goldblatt, <i>Conjugate Vaccines</i> , CLIN. EXP. IMMUNOL. Vol. 119, pp. 1-3 (2000)
EX1005	Veeramachineni	Veeramachineni et al., <i>Bacterial Capsular Polysaccharides of Pathogens – A Toolbox for Vaccines and Therapeutics</i> , IN: GLYCOME: THE HIDDEN CODE OF BIOLOGY, ed. Dipak K. Banerjee (Nova Science Publishers, Inc., 2021)
EX1006	Ravenscroft	Ravenscroft et al., <i>Genetic and Structural Elucidation of Capsular Polysaccharides from Streptococcus Pneumoniae Serotypes 23A and 23B, and Comparison to Serotype 23F</i> , 450 CARBOHYDRATE RES. 19-29 (October 2017)
EX1007	Deng	Deng et al., <i>Antibody Enhanced HPLC for Serotype-Specific Quantitation of Polysaccharides in Pneumococcal Conjugate Vaccine</i> , NPJ VACCINES (2023)
EX1008	Alexander	International Patent Application WO 2005/120563
EX1009	Gu	International Patent Application WO 2015/121783
EX1010	Porro	International Patent Application WO 2014/118201
EX1011	Al-Sherikh	Al-Sherikh et al., <i>Distribution of Serotypes and Antibiotic Susceptibility Patterns Among Invasive Pneumococcal Diseases in Saudi Arabia</i> , ANNALS OF LABORATORY MEDICINE, Vol. 34, 210-15 (2014)
EX1012	<i>Reserved</i>	<i>Reserved</i>

EX1013	Richter	Richter et al., <i>Changes in Pneumococcal Serotypes and Antimicrobial Resistance after Introduction of the 13-Valent Conjugate Vaccine in the United States</i> , ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Vol. 58, No. 7, 6486-89 (2014)
EX1014	Wagenvoort	Wagenvoort et al., <i>Risk and Outcomes of Invasive Pneumococcal Disease in Adults with Underlying Conditions in the Post-PCV7 Era, The Netherlands</i> , VACCINE, Vol. 34, 334-40 (2016)
EX1015	Kaplan	Kaplan et al., <i>Multicenter Surveillance of Streptococcus pneumoniae Isolates from Middle Ear and Mastoid Cultures in the 13-Valent Pneumococcal Conjugate Vaccine Era</i> , CLINICAL INFECTIOUS DISEASES 60:1339-1345 (2015)
EX1016	Pilishvili	Pilishvili et al., <i>Sustained Reductions in Invasive Pneumococcal Disease in the Era of Conjugate Vaccine</i> , JOURNAL OF INFECTIOUS DISEASE, No. 201, 32-41 (2010)
EX1017	Waight	Waight et al., <i>Effect of the 13-valent Pneumococcal Conjugate Vaccine on Invasive Pneumococcal Disease in England and Wales 4 Years After Its Introduction: An Observational Cohort Study</i> , LANCET INFECTIOUS DISEASES, Vol. 15, 535-43 (2015)
EX1018	ECDC	European Centre for Disease Control and Prevention, <i>Surveillance of Invasive Bacterial Diseases in Europe, 2012</i> (Stockholm: ECDC, 2015)
EX1019	PHAC	Public Health Agency of Canada, Streptococcus and STI Unit, <i>National Laboratory Surveillance of Invasive Streptococcal Disease in Canada: Annual</i>

		Summary 2013 (Winnipeg, Manitoba: PHAC, 2014)
EX1020	Lee	Lee et al., <i>Immune Response in Infants to the Heptavalent Pneumococcal Conjugate Vaccine Against Vaccine-Related Serotypes 6A and 19A</i> , CLINICAL AND VACCINE IMMUNOLOGY, Vol. 16, No. 3, 376-81 (2009)
EX1021	Anttila	Anttila et al., <i>Contribution of Serotype-Specific IgG Concentration, IgG Subclasses, and Relative Antibody Avidity to Opsonophagocytic Activity Against Streptococcus Pneumoniae</i> , CLINICAL AND EXPERIMENTAL IMMUNOLOGY, Vol. 118, 402-07 (1999)
EX1022	PFL	Prevnar® FDA Label
EX1023	Vesikari	Vesikari et al., <i>Immunogenicity of the 10-Valent Pneumococcal Non-Typeable Haemophilus Influenzae Protein D Conjugate Vaccine (PHiD-CV) Compared to the Licensed 7vCRM Vaccine</i> , THE PEDIATRIC INFECTIOUS DISEASE JOURNAL, Vol. 28, No. 4, S66-S76 (2009)
EX1024	Yeh	Yeh et al., <i>Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine in Infants and Toddlers</i> , PEDIATRICS, Vol. 126, No. 3, e493–e505 (2010)
EX1025	Myers	Myers, <i>Wyeth's 7-valent Vaccine for Pneumococcal Disease Registered In Russia</i> , FIERCE BIOTECH, March 5, 2009, https://www.fiercebiotech.com/biotech/wyeth-s-7-valent-vaccine-for-pneumococcal-disease-registered-russia
EX1026	Pichichero	Pichichero, <i>Protein Carriers of Conjugate Vaccines</i> , HUMAN VACCINES & IMMUNOTHERAPEUTICS, 2505-23 (2013)

EX1027	WHO	World Health Organization, <i>Pneumococcal Conjugate Vaccine for Childhood Immunization</i> , WEEKLY EPIDEMOL. REC. 82(12) 93, 94 (2007)
EX1028	Hu	Hu et al., <i>Approach to Validating an Opsonophagocytic Assay for Streptococcus Pneumoniae</i> , CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Vol. 12, No. 2, 287-95 (2005)
EX1029	Romero-Steiner	Romero-Steiner et al., <i>Use of Opsonophagocytosis for Serological Evaluation of Pneumococcal Vaccines</i> , CLINICAL AND VACCINE IMMUNOLOGY, Vol. 13, No. 2, 165-69 (2006)
EX1030	Costantino	Costantino et al., <i>The Design of Semi-Synthetic and Synthetic Glycoconjugate Vaccines</i> , EXPERT OPINIONS IN DRUG DISCOVERY, Vol. 6, No. 10, 1045-66 (2011)
EX1031	Wessels	Wessels et al., <i>Structural Properties of Group B Streptococcal Type III Polysaccharide Conjugate Vaccines that Influence Immunogenicity and Efficacy</i> , INFECTION AND IMMUNITY, Vol. 66, No. 5, 2186-92 (1998)
EX1032	Baker	Baker et al., <i>Safety and Immunogenicity of Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccines for Group B Streptococcal Types Ia and Ib</i> , JOURNAL OF INFECTIOUS DISEASES, Vol. 179, 142-50 (1999)
EX1033	Whitney 2003	Whitney et al., <i>Decline in Invasive Pneumococcal Disease after the Introduction of Protein-Polysaccharide Conjugate Vaccine</i> , N. ENGL. J. MED. 1737-1746 (2003)

EX1034	Jakobsen	Jakobsen et al., <i>Intranasal Immunization with Pneumococcal Conjugate Vaccines with LT-K63, a Nontoxic Mutant of Heat-Labile Enterotoxin, as Adjuvant Rapidly Induces Protective Immunity Against Lethal Pneumococcal Infections in Neonatal Mice</i> , INFECTION AND IMMUNITY, Vol. 70, No. 3, 1443-52 (2002)
EX1035	Sogaard	Søgaard, <i>The Clinical Use of Adjuvants in Pneumococcal Vaccination</i> , HUMAN VACCINES, Vol. 7, No. 2, 276-80 (2011)
EX1036	Giudice	Giudice and Rappuoli, <i>Genetically Derived Toxoids for use as Vaccines and Adjuvants</i> , VACCINE, Vol. 17, S44-S52 (1999)
EX1037	Lees	Lees et al., <i>Versatile and Efficient Synthesis of Protein-Polysaccharide Coinjugate Vaccines Using Aminooxy Reagents and Oxime Chemistry</i> , VACCINE 716-729 (2006)
EX1038	Whitney 2014	Whitney et al., <i>Dosing Schedules for Pneumococcal Conjugate Vaccine Considerations</i> , THE PEDIATRIC INFECTIOUS DISEASE JOURNAL, S172-S181 (2014)
EX1039	Nunes	Nunes et al., <i>The Impact of Private Use of PCV7 in 2009 and 2010 on Serotypes and Antimicrobial Resistance of Streptococcus Pneumoniae Carried by Young Children in Portugal: Comparison with Data Obtained Since 1996 Generating a 15-year Study Prior to PCV13 Introduction</i> , VACCINE 1648-1656 (2016)
EX1040	Jefferies	Jefferies et al., <i>13-Valent Pneumococcal Conjugate Vaccine (PCV13)</i> , HUMAN VACCINES 1012-1018 (2011)
EX1041	Reserved	Reserved
EX1042	Malley	U.S. Patent Application Publication No. 2015/0374811

EX1043		File History of U.S. Patent No. 11,058,757 - Application 16/089040 File History (Excerpts)
EX1044		File History of U.S. Provisional Application 62/316555
EX1045	Daniels	Daniels et al., <i>A Review of Pneumococcal Vaccines: Current Polysaccharide Vaccine Recommendations and Future Protein Antigens</i> , J. PEDIATRIC PHARMACOLOGY AND THERAPEUTICS, Vol. 21, No. 1, 27-35 (2016)
EX1046	<i>Reserved</i>	<i>Reserved</i>
EX1047	Pogona Complaint	<i>Pogona, LLC v. Merck Sharp & Dohme LLC</i> , 2-25-cv-15294 (D.N.J. September 5, 2025) (D.I. 1, Complaint)
EX1048	CDC	Centers for Disease Control and Prevention, <i>Invasive Pneumococcal Disease in Children 5 Years After Conjugate Vaccine Introduction – Eight States, 1998-2005</i> , MORBIDITY AND MORTALITY WEEKLY REPORT, Vol. 57, No.6, 144-48 (2008)
EX1049	SDD	Pfizer’s Search Disclosure Declaration (Protective Order Material – Filing Party & Board Only)
EX1050	Merck Study	A Study to Evaluate the Safety, Tolerability and Immunogenicity of V114 in Healthy Adults and Infants (V114-005) (Version 5, 2015-11-03)

I. INTRODUCTION

U.S. Patent No. 11,058,757 (“the ’757 patent,” EX1001) claims a purportedly new implementation of a well-known technology: the selection of particular *Streptococcus pneumoniae* serotypes, which are strains of the *S. pneumoniae* bacteria, for use in a vaccine against pneumococcal disease. The ’757 patent issued without a single rejection, following an Examiner interview in which the Examiner stated that the recited serotypes “appear to be free of prior art.” EX1043 at 21. But the prior art, including art cited in an information disclosure statement during prosecution (and apparently overlooked by that Examiner), taught precisely the serotypes the Examiner said it did not. Without this oversight, the ’757 patent never would have issued; all claims are anticipated, or alternatively obvious, over an abundance of prior art that teaches the relevant serotypes and their inclusion in pneumococcal vaccines.

Streptococcus pneumoniae causes a variety of harmful and potentially deadly infections. Vaccines against *S. pneumoniae*—including the specific type of vaccines the ’757 patent claims, known as pneumococcal conjugate vaccines (PCVs)—have been widely used for decades. And for many of those decades, Petitioner has been at the forefront of efforts to develop and distribute vaccines to prevent these diseases. Wyeth (acquired by Petitioner in 2009) developed the first PCV, Prevnar®, which is “7-valent,” meaning it covers seven pneumococcal serotypes; it was licensed in

the United States in 2000. EX1004 at 2; EX1045 at 28 & tbl.1. Petitioner later developed and introduced Prevnar 13® (a 13-valent PCV) in the United States in 2010, expanding protection against a larger number of *S. pneumoniae* serotypes. EX1045 at 28 & tbl.1. The prevalence and distribution of *S. pneumoniae* serotypes can vary over time and geography. Consequently, formulating a pneumococcal vaccine depends in large part on selecting and expanding the number of serotypes in the vaccine.

The '757 patent added nothing new or non-obvious to the field of PCVs. Filed by former Pfizer/Wyeth vaccine developers, EX1047, ¶21—who presumably were familiar with the prior art in the field—the patent is directed to a supposedly novel selection of known *S. pneumoniae* serotypes for inclusion in vaccines. Essentially, the claims recite the well-known structure of conjugates included in PCVs, various common variations on PCVs, and a handful of known serotypes added to the vaccine. All the recited serotypes were disclosed in the prior art and reflected in publicly available epidemiological data, and specifically identified for inclusion in a PCV. There are no working examples in the '757 patent, no suggestion that vaccines including the claimed serotypes presented any particular technical challenge, and no purported solution to such a challenge. It merely claims including well-known serotypes in a PCV. Its claims are independently anticipated by at least two prior art patent applications (Alexander and Gu) and/or are obvious. The Board

should institute *inter partes* review based on Alexander, Gu, and the additional grounds herein, and cancel all claims.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner identifies the following as real parties-in-interest: Pfizer Inc.

Related matters: The '757 patent is asserted in *Pogona, LLC v. Merck Sharp & Dohme LLC*, 2-25-cv-15294 (D.N.J.). Petitioner is not a party to this litigation.

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Petitioner consents to electronic service.

III. STANDING AND PROCEDURAL STATEMENTS

Petitioner certifies under 37 C.F.R. § 42.104(a) that the '757 patent is available for review and Petitioner is not barred or estopped from requesting review on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Petitioner is submitting a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e), and all required fees pursuant to § 42.15(a),

concurrently with this Petition. If additional fees are due at any time during this proceeding, the PTO is authorized to charge such fees to Deposit Account No. 50-6403.

IV. RELIEF REQUESTED AND GROUNDS RAISED

Petitioner respectfully requests cancellation of all claims of the '757 patent as unpatentable, on the following grounds:

Ground I: Alexander anticipates claims 1-2, 4-8, 11, and 15-19.

Ground II: Alexander renders obvious claims 1-9, 11-12, and 15-19.

Ground III: Gu anticipates claims 1, 3-6, 9, 11-12, 15, and 18-19.

Ground IV: Gu renders obvious claims 1, 3-6, 9, 11-12, 15, and 18-19.

Ground V: Claims 1-9 and 11-19 are obvious over Alexander or Gu, in view of the Serotype Prevalence References—Kaplan, Pilishvili, Waight, ECDC, and/or PHAC—and/or the Vaccine Recommendation References—Porro, Al-Sherikh, Richter, and/or Wagenvoort.

Ground VI: Claim 6 is obvious over Alexander or Gu, in view of Lee and/or Anttila.

Ground VII: Claims 7 and 10 are obvious over Alexander or Gu, in view of PFL.

Ground VIII: Claims 2, 16, and 17 are obvious over Alexander in view of Vesikari and/or PFL.

V. BACKGROUND

A. Technology Overview

1. *Streptococcus pneumoniae* and its serotypes

As Dr. Luwy Musey, Petitioner's expert witness, explains, *Streptococcus pneumoniae* causes a variety of harmful infections, including invasive pneumococcal disease (IPD) (e.g., meningitis, sepsis, bacteremic pneumonia) and non-invasive pneumococcal disease (non-IPD) (e.g., otitis media (OM), non-bacteremic pneumonia, sinusitis) associated with a significant healthcare burden, morbidity, and mortality. Infections caused by *S. pneumoniae* are referred to as "pneumococcal," and collectively cause more than one million deaths per year. EX1002 (Musey Dec.), ¶14.

Many strains of *S. pneumoniae* are encapsulated in a polysaccharide that plays an important role in virulence and immune evasion. *Id.*, ¶15. That capsular polysaccharide can take different forms, called serotypes, which are used to classify variations of the bacterium. *Id.*, ¶16. Serotypes are typically referenced using a standardized designation system that allocates each a number and sometimes a letter, for example "20" or "23A." *Id.*; EX1006 at 2.

The prevalence of different serotypes varies both geographically and temporally; a given serotype may become unusually prevalent for a period of time or in a particular region. EX1002, ¶17. Monitoring pneumococcal serotype

prevalence and identifying newly emerging serotypes is essential for designing new pneumococcal vaccines. *Id.* This is particularly important after the introduction of a pneumococcal vaccine to a population when the prevalence of vaccine-type (VT) serotypes (*i.e.*, serotypes included in the vaccine) is reduced and the prevalence of non-VT serotypes (*i.e.*, serotypes not included in the vaccine) increases correspondingly. *Id.*, ¶¶17-18.

2. Pneumococcal conjugate vaccines (PCVs)

Vaccines generally work by introducing an antigen that stimulates the body's immune system to identify and neutralize the antigen and thereby protect against disease. EX1002, ¶¶19-20. PCVs contain capsular polysaccharide antigens from isolated serotypes of *S. pneumoniae* conjugated to a carrier protein or polypeptide, which increases the immunogenic effect. *Id.*, ¶¶21-23. The most common carrier proteins used with PCVs are toxoids (*i.e.*, toxins that have been rendered less toxic), such as CRM₁₉₇, which is a non-toxic mutant of diphtheria toxin. *Id.*, ¶¶24, 26; EX1026 at 2506. It is well known that PCVs induce a more robust and durable immune response compared to unconjugated pneumococcal polysaccharide vaccines, especially in children and young adults. EX1045 at 29-31.

In 1983, a pneumococcal polysaccharide vaccine (Pneumovax 23[®]; PPSV23) vaccine was licensed in the United States containing unconjugated capsular polysaccharides from 23 pneumococcal disease-causing serotypes. EX1045 at 27-

28 & tbl.1. To elicit a more protective immune response in infants and young children, Prevnar® (PCV7), a 7-valent PCV (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to CRM₁₉₇), was licensed in the United States in 2000. *Id.* Subsequently, hospitalization rates due to diseases caused by the specific serotypes of PCV7 significantly decreased in immunized children and the elderly. *Id.* at 29; EX1002, ¶26.

But only five years after PCV7 was introduced, pneumococcal diseases caused by non-PCV7 serotypes had increased. EX1045 at 29. This led to the development of Prevnar 13® (PCV13), a 13-valent PCV (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F conjugated to CRM₁₉₇ protein), which was licensed in 2010 in the United States. *Id.* at tbl.1. PCV13 was introduced to cover all seven serotypes in PCV7 as well as six of the most prevalent serotypes that were not included in PCV7. *Id.* at 27, 29. After PCV13 implementation, pneumococcal disease rates from these new serotypes added to PCV13 dropped. *Id.*; EX1002, ¶27.

After the introduction of PCV13, extensive surveillance of the epidemiology of pneumococcal diseases and the serotype distribution was conducted to identify serotypes to include in a future pneumococcal vaccine. EX1002, ¶¶29-30. This included public health agencies (such as the U.S. Centers for Disease Control and Prevention (CDC), the European Centre for Disease Control and Prevention (ECDC) and the Public Health Agency of Canada (PHAC)) regularly monitoring the evolving

pneumococcal serotype prevalence after pneumococcal vaccine implementation. This serotype distribution data was (and is) published and/or provided by request to enable serotype selection when designing future pneumococcal vaccines. *Id.*

Before the alleged priority date of the '757 patent (March 31, 2016), PCVs comprising at least two *S. pneumoniae* capsular polysaccharides from serotypes 23A, 23B, and 35B were specifically disclosed in published patent applications. *See infra* §IX. Further, before the priority date of the '757 patent, there was a clear trend toward including additional serotypes in subsequent generations of PCVs based on the prevalence of emerging serotypes not covered by previous vaccines; there also was a direct recommendation to include serotypes 23A, 23B, and 35B, which were among the top most common non-PCV13 serotypes isolated. *See infra* §IX; EX1002, ¶¶29-30. Methods of making and administering PCVs, moreover, were well-known in the art. EX1002, ¶¶31-33.

B. '757 Patent Overview

The '757 patent issued on July 13, 2021, from U.S. Application No. 16/089,040, filed on March 31, 2017. EX1001 at cover page, (22), (45). Its earliest priority claim is to March 31, 2016. *Id.*, (60).

The '757 patent relates to vaccines against *S. pneumoniae*. Claim 1, the only independent claim, recites:

1. A pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides [sic] conjugated to a polypeptide, wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B.

Id. at 70:35-41.

The claim recites three broad features: (1) a pharmaceutical composition (*i.e.*, a vaccine); (2) at least two capsular polysaccharides conjugated to a polypeptide (*i.e.*, the known structure of a conjugate in a multivalent PCV); and (3) a list of three known *S. pneumoniae* serotypes that appear, together and separately, in the prior art. The “comprising” and “at least” language mean that the claim encompasses pharmaceutical compositions including conjugates with any two of serotypes 23A, 23B, and 35B, with any number of any additional serotypes.

The dependent claims (all depending from claim 1) recite various attributes that add nothing to patentability. *Id.* at 70:42-72:29. For example, claim 3 lists known polypeptides used as a carrier. Claim 4 recites known formulation components. Claims 5 and 15-16 recite known ways of administering a vaccine. Claim 18 recites administering a vaccine to a human. And claim 6 recites the well-known immune response elicited by pneumococcal vaccines. Still others, such as claims 12-14, recite additional serotypes that also appear in the prior art.

C. The Prosecution History

During prosecution, the Examiner overlooked art disclosing conjugates including the serotypes recited in the claims. The '757 patent issued without any rejections; the only office action was a requirement for restriction/election. EX1043 at 8-12. The Examiner's only substantive discussion of patentability in the prosecution history was in the summary of a March 4, 2021 interview included with the Notice of Allowance. It states:

The examine [sic] and the attorney discussed the allowable subject matter of pharmaceutical composition comprising polysaccharide conjugates 35B, 23A and 23B from *Streptococcus pneumoniae*. ***These serotypes*** along with 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34 or 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B ***appear to be free of prior art*** and the specification table 2 has support doe [sic] said composition.

Id. at 24 (emphasis added).

That statement was wrong. First, the lead patent prior art references asserted in this Petition, Alexander and Gu, *infra* §IX, disclose pharmaceutical compositions comprising conjugates comprising *S. pneumoniae* serotypes 23A, 23B, and 35B. Further, numerous secondary prior art references asserted in this Petition directly recommend including *S. pneumoniae* serotypes 23A, 23B, and 35B in future PCVs. The Examiner failed to conduct an adequate search that led to these references or overlooked key aspects of these references during prosecution.

Second, several prior art references cited in information disclosure statements (IDSes) also disclose conjugates including the serotypes recited in the interview summary and the importance of including them in PCVs. For example, the IDS submitted on March 10, 2020, listed Malley and Jefferies and both references disclosed or studied several of these serotypes. EX1043 at 1-3. Malley explicitly disclosed *S. pneumoniae* capsular polysaccharide conjugates that could include any of serotypes 8, 9N, 10A, 11A, 12 F, 15B, 20, 22F, 23A, or 34—a list that overlaps with the serotypes the Examiner wrongly concluded were “free of prior art.” EX1042, ¶¶134, 203; EX1043 at 24. The Examiner made this error, moreover, despite noting correctly in the restriction that the technical feature of the invention groups—polysaccharides—was taught by Malley. EX1043 at 10, ¶4.

Likewise, Jefferies disclosed that several non-PCV13 serotypes, including 6C, 8, 11A, 12F, 15B/C, 22F, and 35B, were “reported as increasing in prevalence in a number of carriage and disease studies” and that “antibiotic resistant pneumococci of serotypes 15A and 35B . . . have also increased in prevalence in the US since PCV7 introduction.” EX1040 at 1014.

More than two months after the first notice of allowance was mailed on March 10, 2021, EX1043 at 13-43, Patent Owner submitted another IDS for the Examiner to consider on May 14, 2021, listing Nunes. *Id.* at 44-54. Nunes disclosed that non-

vaccine “serotypes 6C, 15A, 15B/C, 16F, 21, 23A, 23B” were among “the most frequently carried in 2009 and 2010.” EX1039 at 1650.

Third, a prior art reference cited in the provisional application also discloses the interview summary’s serotypes and the importance of including them in PCVs. EX1044, ¶4. The Public Health Agency of Canada’s 2013 Report (“PHAC”) discussed the need for “[c]ontinued vigilance . . . to recognize possible increases in other non-PCV13 serotypes circulating in Canada, such as serotype[s] 22F, 23A and 23B.” EX1019 at 57; *see infra* §V.

Lastly, even the Examiner’s searches (“L20” and “L25”) conducted as part of the notice of allowance submitted on March 10, 2021, appear to elicit at least ten results (“L26”) where each of the serotypes 23A, 23B, or 35B in combination with other key concepts (“L17”-“L19”, “L22”-“L24”) are mentioned. EX1043 at 38-39.

Thus, while the Examiner’s rationale for allowance states it was based on the novelty and nonobviousness of the specific serotype combinations, the prior art asserted in this Petition and the prosecution history, including the Patent Owner’s own cited documents, disclosed just those serotypes.

VI. LEVEL OF ORDINARY SKILL

With respect to the ’757 patent, the POSA would include a research team with one or more researchers with an M.D. or Ph.D. in immunology, virology, biochemistry, chemistry, or a related discipline, and several years of work

experience in vaccinology or related fields, and one or more individuals with an advanced degree and experience in drug delivery of vaccines. EX1002, ¶10.

VII. OVERVIEW OF THE PRIOR ART

Copious prior art discloses PCVs, the *S. pneumoniae* serotypes recited in the claims of the '757 patent, and the use of those serotypes in such vaccines.

A. Alexander

WO2005/120563 (“Alexander”), entitled “Induction of an Immune Response Against Streptococcus Pneumoniae Polysaccharides,” published on December 22, 2005. EX1008 at cover page, (43), (54). Alexander is prior art to the '757 patent under 35 U.S.C. § 102(a)(1). Alexander was not before the Examiner.

Alexander describes “compositions comprising a mixture of at least two Streptococcus [sic] *pneumoniae* capsular polysaccharides from different *Streptococcus pneumoniae* serotypes, wherein the capsular polysaccharide from each serotype is conjugated to a separate polypeptide comprising a pan DR binding peptide sequence.” EX1008, ¶9; EX1002, ¶¶50-55.

Alexander also discloses “methods of inducing an immune response in a mammal” by “administering to [it] a mixture of at least two *Streptococcus pneumoniae* capsular polysaccharides from different” serotypes conjugated to a polypeptide, and methods of making vaccines to do so. EX1008, ¶¶10, 11.

Alexander also discloses a set of serotypes from which to draw the mixture:

“In some embodiments, the compositions of the invention comprise a mixture of conjugates . . . with capsular polysaccharides from 2, . . . 30 or more of the following serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F, 6A, 7A, 7B, 7C, 9A, 9L, 12A, 13, 15A, 15C, 16F, 18A, 18B, 18F, 19B, 19C, 21, 22A, **23A**, **23B**, 24F, 25, 27, 29, 31, 34, **35**, 38, 45, or 46.” *Id.*, ¶63 (emphases added); EX1002, ¶¶50-55.

B. Gu

WO2015/121783 (“Gu”), entitled “Immunogenic Glycoprotein Conjugates,” published on August 20, 2015. EX1009 at cover page, (43), (54). Gu is prior art under 35 U.S.C. § 102(a)(1). Gu was not before the Examiner.

Gu describes a vaccine composed of “glycoconjugates comprising a saccharide covalently conjugated to a carrier protein through a spacer.” *Id.* at 1:3-4. Gu sets out a number of ways for “coupling immunogenic molecules, such as saccharides . . . to peptide or protein carriers,” including the use of “cross-linking or coupling reagents.” *Id.* at 1:21-25.

Gu also discloses several carrier proteins that can be used to “increas[e] immunogenicity of poorly immunogenic molecules,” including *S. pneumoniae* capsular polysaccharides. *Id.* at 1:12-13, 11:17-18. Specifically, Gu lists toxoids of “tetanus, diphtheria, pertussis, *Pseudomonas*, *E. coli*, *Staphylococcus*, and

Streptococcus” as preferred carriers, and a “particularly preferred carrier [being] of diphtheria toxoid CRM₁₉₇.” *Id.* at 36:14-19.

The disclosure of Gu further details several specific pneumococcal (or Pn) serotypes intended for inclusion in a vaccine formulation. It lists specific embodiments in which “the Pn capsular polysaccharide is selected from the group consisting of Pn-serotype 2, 9N, 15A, 17F, 20, **23A**, **23B** and **35B** capsular polysaccharides.” *Id.* at 11:23-25, 22:31-23:1 (emphases added); EX1002, ¶¶56-59.

C. The Serotype Prevalence References

1. Kaplan

Kaplan is an article published in 2015 in *Clinical Infectious Diseases*. EX1015 at 1339. It is prior art under 35 U.S.C. § 102(a)(1) and was not before the Examiner. Kaplan addresses the impact of the 13-valent PCV (PCV13) on the prevalence of *S. pneumoniae* serotypes. *Id.* at 1339-40. Kaplan highlights that 23A, 23B, and 35B are among the top-ten most common non-PCV13 serotypes (serotypes not covered by PCV13) isolated from children in the “PCV13 era” from 2011 to 2013 (serotypes in descending order of prevalence, 35B, 21, 23B, 15B, 11, 23A, 15A, 15C, 16, and 31). *Id.* at 1339, 1341-42 & tbl.2; EX1002, ¶¶61-64.

2. Pilishvili

Pilishvili is an article published in 2010 in *The Journal of Infectious Diseases*. EX1016 at 32. It is prior art under 35 U.S.C. § 102(a)(1) and was not before the

Examiner. Pilishvili summarizes the changing prevalence of *S. pneumoniae* serotypes causing IPD in the U.S. following widespread administration of the 7-valent PCV (PCV7). EX1016 at 32. Notably, Pilishvili reports that IPD cases involving serotypes 23A, 23B, and 35B grew significantly across all age groups over the study period (1998-2007). EX1016 at 34-37 & tbls.1-2; EX1002, ¶¶65-66.

3. Waight

Waight is an article published in 2015 in *Lancet Infectious Diseases*, and is prior art under 35 U.S.C. § 102(a)(1). EX1017 at 535. It was not before the Examiner. Summarizing pneumococcal serotype incidence data from England and Wales after the widespread administration of a 13-valent PCV, *id.* at 535-36, Waight reports that serotypes 23A, 23B, and 35B were among the top twenty-four serotypes not covered by the existing standard-of-care vaccine that posed the greatest risk for pneumococcal diseases in young children from 2012 and 2014. *Id.* at 538, 540 & fig. 3 & tbl.2; EX1002, ¶¶67-68.

4. ECDC

The European Centre for Disease Control and Prevention (“ECDC”) published the report “Surveillance of invasive bacterial diseases in Europe, 2012” in 2015. EX1018 at *ii*, 1-2. ECDC is prior art under 35 U.S.C. § 102(a)(1) and was not before the Examiner. ECDC lists serotypes found to cause pneumococcal infectious disease in Europe during 2012. *Id.* at 14, n.8. Among other findings,

ECDC reports that serotypes 23A, 23B, and 35B were among the “most common serotype[s]” that caused “confirmed [invasive pneumococcal disease] cases”; each serotype was among the top ten most prevalent among serotypes not covered by existing PCVs. *Id.* at 14-15, 23-24, & fig. 1.5; EX1002, ¶¶69-70.

5. PHAC

The Public Health Agency of Canada (“PHAC”) published the report “National Laboratory Surveillance of Invasive Streptococcal Disease in Canada: Annual Summary 2013” in December 2014 . EX1019 at 1. PHAC is prior art under 35 U.S.C. § 102(a)(1). It was not before the Examiner, although it was referenced (EX1044 at 2, ¶4) in the earliest provisional application No. 62/316,555 to which the ’757 patent claims priority. *Id.* at 6-7. PHAC reports the status of streptococcal disease in Canada in 2013. Among other findings, PHAC recommends “[c]ontinued vigilance . . . to recognize possible increases” in non-vaccine serotypes not included in the standard-of-care vaccine in Canada, specifically mentioning “23A and 23B.” *Id.* at 57; EX1002, ¶¶71-72.

D. The Vaccine Recommendation References

1. Porro

WO 2014/118201 (“Porro”), entitled “Multivalent Glycoconjugate Vaccines,” published on August 7, 2014. EX1010 at cover page, (43). Porro is prior art under 35 U.S.C. § 102(a)(1). Porro was not before the Examiner. Porro teaches new conjugate antigens and glycoconjugate vaccines against a variety of bacteria,

including *S. pneumoniae*. *Id.* at 1:6-16. Porro describes a group of “[n]ew emerging serotypes of *S. pneumoniae* according to the public available data on epidemiology and antibiotic resistance,” including serotypes 23A and 35B, and recommends that “such antigen Ps [polysaccharides] might be likely included in a further up-dated broad-spectrum vaccine formulation.” *Id.* at 2:9, 66:28-67:9; EX1002, ¶¶74-75.

2. Al-Sherikh

Al-Sherikh is a 2014 article from the *Annals of Laboratory Medicine*. EX1011 at 210. Al-Sherikh is prior art under 35 U.S.C. § 102(a)(1) and was not before the Examiner. Al-Sherikh reports on emerging *S. pneumoniae* serotypes in children with invasive pneumococcal disease (IPD). *Id.* It discloses that non-PCV serotypes 23A and 23B were among the most frequently occurring serotypes, *id.* at 213-14 & fig. 1, and recommends the “[a]ddition of serotype 23A and 15 to . . . improve the PCV performance in IPD prevention.” *Id.* at 210; EX1002, ¶¶76-77.

3. Richter

Richter is an article published in 2014 in *Antimicrobial Agents and Chemotherapy*. EX1013 at 6484. Richter is prior art under 35 U.S.C. § 102(a)(1) and was not before the Examiner. Richter concerns the most common serotypes identified in penicillin-resistant *S. pneumoniae*. *Id.* It reports that 35B was among the three most common serotypes identified among such bacteria, and that serotypes 35B, 23A, and 23B exhibited proportional increases in prevalence. *Id.* at 6485-86.

Richter concludes that this information should inform future vaccine development.

Id. at 6484, 6488; EX1002, ¶¶78-79.

4. Wagenvoort

Wagenvoort is an article published in 2015 in *Vaccine*. EX1014 at 334. Wagenvoort is prior art under 35 U.S.C. § 102(a)(1) and was not before the Examiner. Wagenvoort examines the *S. pneumoniae* serotypes with a high propensity to cause serious disease in vulnerable patients. *Id.* at 334-35. It reports that serotypes 23A and 23B, among others, are likely serotypes to cause disease in these populations and recommends their inclusion in future vaccine formulations. EX1014 at 334, 338-39; EX1002, ¶¶80-81.

E. Lee

Lee is an article published in 2009 in *Clinical and Vaccine Immunology*. EX1020 at 376. Lee is prior art under 35 U.S.C. § 102(a)(1) and was not before the Examiner. Lee explains that the opsonization assay (OPA) is the superior measure of pneumococcal vaccine efficacy because it directly assesses the functional ability of antibodies to opsonize (or tag) and facilitate the phagocytosis of bacterium, which is the actual protective mechanism. *Id.* at 376-77; EX1002, ¶¶20-21. This functional measurement is essential because mere antibody concentration (measured by ELISA) often fails to correlate with real-world vaccine effectiveness, leading Lee to

recommend OPA's use, particularly since it is favored by regulatory agencies.

EX1020 at 380; EX1002, ¶¶82-83.

F. Anttila

Anttila is an article published in 1999 in *Clinical and Experimental Immunology*. EX1021 at 402. Anttila is prior art under 35 U.S.C. § 102(a)(1) and was not before the Examiner. Anttila explains the mechanism whereby antibodies protect the body against *S. pneumoniae* bacteria. *Id.* at 402, 405-406. It explains that “[h]ost protection against [*S. pneumoniae*] is mainly mediated by opsonin-dependent phagocytosis. Therefore, opsonophagocytic activity (OPA) of antibodies to pneumococcal capsular polysaccharides (PS) is believed to measure their functional activity” *Id.* at 402; EX1002, ¶¶84-85.

G. PFL

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) Prevnar® (the Prevnar® FDA Label, or “PFL”) is an FDA label, published on FDA’s website no later than October 2008, for Prevnar®. EX1022 at 1-3, 30. PFL is prior art under 35 U.S.C. § 102(a)(1). It was not before the Examiner.

PFL discloses the routine U.S. schedule in infants and young children and explains that each 0.5 mL dose of Prevnar® contained 2 micrograms of each saccharide for six *S. pneumoniae* serotypes, 4 micrograms of serotype 6B, and 20 micrograms of the carrier protein (CRM₁₉₇). *Id.* at 1, 11; EX1002, ¶¶86-87.

H. Vesikari

Vesikari is an article published in 2009 in *The Pediatric Infectious Disease Journal*. EX1023 at S66. Vesikari is prior art under 35 U.S.C. § 102(a)(1), and was not before the Examiner. Vesikari analyzed the immunogenicity of the ten-valent PhiD-CV, a PCV against *S. pneumoniae* that uses saccharides from *S. pneumoniae* conjugated to three different carrier proteins, and found it to be noninferior when compared to Prevnar®. *Id.* Vesikari also compares three dosing regimens, including two homologous series (PHiD-CV primary/PHiD-CV booster dose and Prevnar® primary/Prevnar® booster dose) and one mixed series where the primary vaccine differed from the booster (Prevnar® followed by a PHiD-CV booster dose). *Id.* at S66-68 & fig. 1. The primary series included 3 doses at 2, 3, and 4 months of age and the booster dose was administered at age 12-18 months. *Id.* at S67. The third, mixed-series approach produced a more robust immune response with respect to some serotypes than the other two homologous series. *Id.* at S73-74 & tbl.5; EX1002, ¶¶88-90.

VIII. CLAIM CONSTRUCTION

Petitioner is not aware of any likely claim construction disputes. For purposes of this proceeding, all claim terms should be given their plain and ordinary meaning, as discussed herein.

IX. DETAILED EXPLANATION OF GROUNDS

Every challenged claim is unpatentable. Both Alexander and Gu disclose pharmaceutical compositions wherein each capsular polysaccharide from a *S. pneumoniae* serotype is conjugated to a carrier polypeptide. Both disclose embodiments featuring the specific serotypes recited in claim 1—23A, 23B, and 35B—as well as the limitations of many of the dependent claims. Alexander and Gu also render claim 1 and many dependent claims obvious. EX1002, ¶91.

In addition to these two lead references, a large body of additional prior art encourages the use of the serotypes that supposedly represent a patentable advance, and teaches the remaining limitations of the dependent claims. *Id.*

A. Ground I: Alexander anticipates claims 1-2, 4-8, 11, and 15-19.

Alexander anticipates claim 1 of the '757 patent, as well as claims 2, 4-8, 11, and 15-19, which depend from it. EX1002, ¶92.

1. Claim 1

i. [1.Pre] “A pharmaceutical composition”

Alexander discloses this limitation.¹ Alexander discusses “[t]he compounds of the present invention, and pharmaceutical and vaccine compositions thereof, can

¹ Petitioner assumes for purposes of this Petition that the preamble is limiting, but the claims are unpatentable either way.

be administered to mammals, particularly humans, for prophylactic and/or therapeutic purposes.” EX1008, ¶¶104, 117; EX1002, ¶93.

ii. [1.a] “comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates”

Alexander discloses this limitation. Alexander states that the “present invention provides compositions comprising a mixture of at least two *Streptococcus pneumoniae* capsular polysaccharides from different *Streptococcus pneumoniae* serotypes.” EX1008, ¶9. Alexander also states that these compositions “comprise a mixture of capsular polysaccharides from 2” up to “30 or more . . . serotypes.” *Id.*, ¶63. Alexander further discloses a method for administering a *S. pneumoniae* vaccine, comprising “administering to [a] mammal a mixture of at least two *Streptococcus pneumoniae* capsular polysaccharides from different *Streptococcus pneumoniae* serotypes.” *Id.*, ¶10. As explained further below, Alexander also discloses that these capsular polysaccharides are conjugated to carrier proteins, such as polypeptides. *Id.*, ¶9. The resulting conjugates are “unique” because they comprise conjugates from different *S. pneumoniae* serotypes. EX1002, ¶¶94-97.

Alexander further discloses that these carrier proteins are immunogenic: “[t]he present invention is directed to vaccines which contain as an active ingredient an immunogenically effective amount of a composition comprising at least one conjugate of the present invention.” EX1008, ¶105; *see id.* ¶¶61, 106, 126; EX1002, ¶98.

iii. [1.b] “each comprising individually a capsular polysaccharides [sic] conjugated to a polypeptide”

Alexander discloses this limitation. Alexander describes its invention as a group of serotypes “wherein the capsular polysaccharide from each serotype is conjugated to a separate polypeptide comprising a pan DR binding peptide sequence.” EX1008, ¶9. Alexander further sets out exemplary peptides in which “the pan DR binding oligopeptide and the antigenic determinant are covalently attached to each other.” *Id.*, ¶58; EX1002, ¶¶99-100.

iv. [1.c] “wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B”

Alexander discloses this limitation by describing compositions comprising two or more capsular polysaccharides from serotypes 23A, 23B, and 35B. EX1002, ¶101. Because claim 1 recites a pharmaceutical composition “comprising” saccharide-polypeptide conjugates that include these serotypes, it encompasses compositions containing “at least two” of these listed serotypes—*i.e.*, 23A, 23B, and 35B—along with any combination of other serotypes. *See supra* §IX.A.1.ii; *Vehicular Techs. Corp. v. Titan Wheel Int’l, Inc.*, 212 F.3d 1377, 1383 (Fed. Cir. 2000).

Alexander discloses just such combinations. It expressly states that “the compositions of the invention comprise a mixture of conjugates of a separate [polypeptide] of the invention with capsular polysaccharides from 2” up to “30 or

more of the following serotypes,” followed by a list of 53 serotypes that expressly includes “23A,” “23B,” and “35.” EX1008, ¶63; EX1002, ¶102.

Alexander thus discloses limitation 1.c. A reference that discloses embodiments that “appear[] without special emphasis in a longer list” anticipates those elements. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005); *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App’x 978, 982 (Fed. Cir. 2010); *3form, Inc. v. Lumicor, Inc.*, 678 F. App’x 1002, 1009 (Fed. Cir. 2017). Alexander expressly discloses an embodiment with “2” of the listed serotypes, and thus directs the POSA to select any two serotypes from the list that immediately follows; one such pair, which would have been immediately apparent to the POSA (and, in fact, occur verbatim next to each other) would be “23A, 23B,” satisfying limitation 1.c.² EX1002, ¶¶105-106.

² 23A and 23B suffice to anticipate without 35B, but combinations containing 35B are disclosed as well; “35” refers to serogroup 35, which was known to include three serotypes: 35F, 35A, and 35B. The POSA would thus understand “35” to encompass 35B. Elsewhere, Alexander makes clear that its disclosure encompasses serotype 35B. EX1008, ¶65; EX1002, ¶103.

Far more attenuated combinations of elements have been held sufficient to anticipate. In *William Wrigley Jr. Co. v. Cadbury Adams USA LLC*, for example, the court found a prior art reference anticipatory even though, to reach an anticipating embodiment, the POSA would need to pick specific items from two *separate* lists of elements. 683 F.3d 1356, 1361-62 (Fed. Cir. 2012). And in *In re Gleave*, the court found a reference that listed over one thousand protein sequences to anticipate each sequence on the list. 560 F.3d 1331, 1338 (Fed. Cir. 2009). *See also Warner Chilcott Co., LLC v. Teva Pharms. USA, Inc.*, 89 F. Supp. 3d 641, 657 (D.N.J. 2015), *aff'd*, 642 F. App'x 996 (Fed. Cir. 2016) (reference requiring selection of specific ingredients from three separate lists anticipated). Here, in contrast, the serotypes appear in *one single* list, from which the reader is directed to select any two—an express disclosure of a set of combinations that includes the claim element at issue.

In the alternative, Alexander also anticipates based on its disclosures of much larger combinations; in the embodiment where “30 or more” serotypes are selected from the same list of 53, Alexander discloses using more than half of the options *at once*, meaning that the claimed combination would be selected most of the time even if the reader were to choose at random. Alexander’s disclosure requires no further step on the part of the POSA to make an anticipating embodiment. All the POSA needs to do is select a group of 30 serotypes for a vaccine composition that includes any two of the three in limitation 1.c (all of which are in Alexander’s disclosure). In

Gleave, the Federal Circuit concluded that a very long list of protein sequences anticipated because a POSA is “capable of envisioning how to make any [] sequence” based on the reference’s disclosure. 560 F.3d at 1338. Similarly, Alexander’s disclosure would enable the POSA to envision how to make any combination of 30 or more serotypes—including a great multitude of anticipating combinations. EX1002, ¶¶106-107.

2. Claim 2: “wherein at least one polypeptide comprises a mixture of polypeptides”

Claim 2 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. Alexander discloses the additional limitation of claim 2. EX1002, ¶108.

The specification of the ’757 patent describes embodiments “wherein the polypeptide is the same polypeptide in all the immunogenic saccharide-polypeptide conjugates” or “wherein the polypeptide(s) in the saccharide-polypeptide conjugates are a mixture of different polypeptide(s).” EX1001, 27:45-52. Claim 2 is directed to the latter: compositions including more than one different polypeptide as part of the “[t]he plurality of saccharide-polypeptide conjugates.” *Id.* at 37:48-50. This interpretation is consistent with claim 1: claim 1 requires two or more polysaccharides conjugated to polypeptide carrier proteins, but allows all polysaccharides to be conjugated to identical polypeptide carrier proteins, and claim

2 adds the requirement that the composition include multiple different polypeptide carrier proteins. EX1002, ¶¶109-12.

Alexander anticipates this limitation, as interpreted above. For example, it discusses “mixtures of [] conjugates so that polysaccharides from at least two serotypes are combined in the composition (e.g., a capsular polysaccharide from one serotype conjugated to one [] peptide mixed with a capsular polysaccharide from a second serotype conjugated to a second (*same or different*) [] peptide).” EX1008, ¶34 (emphasis added). Elsewhere, Alexander explains that in some embodiments, “the peptides differ, *e.g.*, a cocktail representing different viral subtypes [or] different epitopes within a subtype” *Id.*, ¶86. Alexander thus discloses embodiments involving mixtures of polypeptides. EX1002, ¶¶112-13.

3. Claim 4: “further comprising an adjuvant; a chelating agent; a surfactant; an emulsifier; a buffering agent; a preservative; a salt; an anti-fungal compound; or a combination thereof”

Claim 4 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. Claim 4 sets forth a series of excipients that are to be included in the pharmaceutical composition. EX1002, ¶¶114, 116. Because the excipients recited in claim 4 are set out “as alternatives,” a disclosure of compositions involving any one of them is sufficient to anticipate. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001).

Alexander anticipates claim 4 in several ways. For example, it states that the disclosed vaccines “further typically include an adjuvant.” EX1008, ¶105. Alexander states that “the compositions of the present invention” include a “surfactant and propellant” for aerosol administration. *Id.*, ¶123. Alexander further discloses administering its compositions with “buffering agents.” *Id.*, ¶117. Moreover, Alexander discloses that the vaccines can be emulsified in incomplete Freund’s adjuvant (CFA/IFA), which was known to include an emulsifier. *Id.*, ¶¶101, 105, 130-33. Further, Alexander discloses that “[t]he vaccines” disclosed “typically include an adjuvant” such as incomplete Freund’s adjuvant, aluminum phosphate, aluminum hydroxide, or alum. *Id.*, ¶105. Because each of these disclosures reads on the limitation of claim 4, the claim is anticipated. EX1002, ¶¶115-16.

4. Claim 5: “wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition”

Claim 5 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. EX1002, ¶117.

Alexander also discloses the additional limitation of claim 5. EX1002, ¶¶117-18. Alexander notes, “[t]ypically, the pharmaceutical compositions are administered parenterally, *e.g.*, intravenously, subcutaneously, intradermally, or intramuscularly.”

EX1008, ¶117. Alexander also discloses an intranasal administration, describing “aerosol administration” of its compositions. *Id.*, ¶123.

Because claim 5 sets out these forms in the alternative, Alexander’s disclosure of any one form within the claim is sufficient to anticipate this claim. *Brown*, 265 F.3d at 1351. In fact, Alexander expressly discloses all these well-known delivery routes. And a POSA would have understood that PCVs had been administered intramuscularly, and that other methods of administration were also possible. EX1002, ¶119.

5. Claim 6: “wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response”

Claim 6 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. EX1002, ¶120.

Alexander also discloses the additional limitation of claim 6. *Id.* It was well-known that opsonophagocytosis is the mechanism by which PCVs trigger an immune system response by their hosts. *Id.*, ¶21 & n.6. Thus, when Alexander discloses conjugates that elicit an immunogenic response against *S. pneumoniae*, EX1008, ¶¶26, 34, the POSA would understand that to be a disclosure of compositions wherein at least one saccharide-polypeptide conjugate elicits an opsonophagocytic response. EX1002, ¶121. In fact, any PCV that is immunogenic

inherently includes conjugates that elicit an opsonophagocytic response. Alexander therefore anticipates claim 6. *Id.*

6. Claim 7: “wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition”

Claim 7 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. EX1002, ¶122.

Alexander also discloses the additional limitation of claim 7. EX1002, ¶¶123-24. It observes that “[t]he concentration of compositions of the present invention . . . can vary widely, *i.e.*, from less than about 0.1%, usually at or at least about 2% to as much as 20% to 50% or more by weight” EX1008, ¶118. Alexander further observes that for compositions prepared for aerosol administration, “[t]ypical percentages of the composition are 0.01-20% by weight, preferably 1-10%.” *Id.*, ¶123. By disclosing a range of concentrations narrower than claim 7’s range (which recites a minimum concentration of .001% and no maximum concentration), Alexander anticipates this claim. *See, e.g., ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012).

7. Claim 8: “wherein the immunogenic saccharide-polypeptide conjugates comprise: (i) the capsular polysaccharide at least partially embedded in the polypeptide, (ii) the capsular polysaccharide chemically cross-linked to the polypeptide,

**and/or (iii) the capsular polysaccharide at least partially
chemically cross-linked to the polypeptide”**

Claim 8 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. EX1002, ¶125.

Alexander also discloses the additional limitation of claim 8. It explains that the “[d]esired polysaccharides may be conjugated to the polypeptides . . . by enzymatic or chemical reactions” . . . “using a variety of linkers . . . [including] [c]rosslinking agents.” EX1008, ¶¶87, 92; *see also id.* ¶¶93-95 (explains crosslinking can be performed using commercially available agents). Since “crosslinking agent,” is considered here as meaning “chemically cross-linked,” Alexander thus anticipates the limitations of claim 8. EX1002, ¶126.

Because claim 8 sets out these limitations in the alternative, Alexander’s disclosure of any one limitation within the claim is sufficient for anticipation. *Brown*, 265 F.3d at 1351. Accordingly, Alexander’s disclosure of “[c]rosslinking agents” anticipates regardless of whether the resulting linkage leads to a polysaccharide that is “chemically cross-linked” (*i.e.*, “(ii)”) or “partially chemically cross-linked” (*i.e.*, “(iii)”). EX1002, ¶126.

Claim 8 raises the possibility that the cross-linking might be partial. This does not affect the anticipation analysis because the claim language encompasses both polysaccharides that are “chemically cross-linked” and “partially chemically cross-linked.” So long as a polysaccharide is conjugated using a “crosslinking agent” as

Alexander discloses, it must be one or the other—*i.e.*, at least some of the polysaccharide molecules must be cross-linked to the polypeptide molecules—and so the resulting composition falls within the scope of the claim either way. Thus, Alexander’s disclosure of “conjugating [the serotype] to the polypeptides” using “[c]rosslinking agents” anticipates regardless of whether the resulting linkage leads to a polysaccharide that is “chemically cross-linked” (*i.e.*, “(ii)”) or “partially chemically cross-linked” (*i.e.*, “(iii)”). EX1002, ¶127.

8. Claim 11: “A method comprising administering to a subject a first composition, wherein the first composition is the pharmaceutical composition of claim 1”

Claim 11 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. EX1002, ¶128.

Alexander also discloses the additional limitation of claim 11, which sets forth a method of administering the composition of claim 1 to a subject. It states: “In some embodiments, the methods comprise administering to the mammal a mixture of at least two *Streptococcus pneumoniae* capsular polysaccharides” EX1008, ¶10; *see also id.*, ¶104 (disclosing that the “compounds of the present invention can be administered to mammals, particularly humans, for prophylactic and/or therapeutic purposes”). Thus, Alexander anticipates claim 11. EX1002, ¶129.

9. Claim 15: “wherein the pharmaceutical composition is administered intramuscularly”

Claim 15 depends from claim 11, and Alexander anticipates claim 11 for the reasons described above. EX1002, ¶130.

Alexander also discloses the additional limitation of claim 15—intramuscular administration of its vaccine—and thus anticipates claim 15. EX1008, ¶117; EX1002, ¶131.

10. Claim 16: “wherein the administering to the subject the first composition occurs at least about four weeks before or at least about four weeks after an administration of a second composition comprising an immunogenic saccharide-polypeptide conjugate”

Claim 16 depends from claim 11, and Alexander anticipates claim 11 for the reasons described above. EX1002, ¶132.

Alexander also discloses the additional limitation of Claim 16. Alexander discloses the possibility of a second (or booster) vaccine, administered four weeks after the initial dose. It observes, “[i]mmunizing doses followed by boosting doses at established intervals, e.g., from one to four weeks, may be required, possibly for a prolonged period of time to effectively immunize an individual.” EX1008, ¶116. The POSA would have understood that such “boosting dose” would comprise the immunogenic saccharide-polypeptide conjugates disclosed in Alexander (and claimed in the ’757 patent). The POSA therefore would have understood Alexander to anticipate claim 16. EX1002, ¶133.

11. Claim 17: “The method of claim 16, wherein the second composition comprises an immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide from a serotype of *Streptococcus pneumoniae* conjugated to a second polypeptide”

Claim 17 depends from claim 16, and Alexander anticipates claim 16 for the reasons described above. EX1002, ¶134.

Alexander also discloses the additional limitation of claim 17. The ’757 patent’s specification expressly indicates that the second polypeptide (of the second composition’s conjugate) can be identical to the first polypeptide. EX1001, 48:7-18. It also makes clear that the second composition’s conjugate is a conjugate of that polypeptide with a *S. pneumoniae* polysaccharide, just like the first composition’s conjugate (though permitting serotype differences). *Id.*, 50:25-37; *see generally id.* at cols.47-52. Therefore, claim 17 is anticipated for the same reasons, and by the same disclosures of Alexander, as in claim 16. EX1002, ¶134.

12. Claim 18: “The method of claim 11 wherein the subject is a human”

Claim 18 depends from claim 11, and Alexander anticipates claim 11 for the reasons described above. EX1002, ¶135.

Alexander also discloses the additional limitation of claim 18. For example, Alexander states that the compositions it discloses “can be administered to . . . humans, for prophylactic and/or therapeutic purposes.” EX1008, ¶104; *see also id.*, ¶138 (discussing use in “human vaccine products”). And, of course, the entire

purpose of developing vaccines in this field is to prevent human disease, as Alexander explains, giving the POSA reason to develop the disclosed compositions as human treatments. *Id.* Thus, claim 18 is anticipated. EX1002, ¶¶136-37.

13. Claim 19: “A method of making a composition comprising: contacting the plurality of immunogenic saccharide-polypeptide conjugates of claim 1 with an excipient, an adjuvant, or any combination thereof”

Claim 19 depends from claim 1, and Alexander anticipates claim 1 for the reasons described above. EX1002, ¶138.

Alexander also discloses the limitation of claim 19. As discussed above in §IX.A.1, *supra*, Alexander discloses the “conjugates of claim 1.” It further discloses combining those conjugates with an excipient and adjuvant. *See supra* §IX.A.3. For example, Alexander explains: “For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating . . . [an] excipient[]” EX1008, ¶122. Alexander further states that the disclosed vaccines “typically include an adjuvant,” and lists example adjuvants. EX1008, ¶105. The POSA also would have understood from Alexander’s disclosure that a vaccine composition typically includes multiple inactive ingredients. Accordingly, the disclosures of Alexander anticipate the limitation of claim 19. EX1002, ¶¶139-40.

B. Ground II: Alexander renders obvious claims 1-9, 11-12, and 15-19.

1. Claims 1-2, 4-8, 11, and 15-19

Alexander discloses claims 1-2, 4-8, 11 and 15-19 for the reasons discussed in §IX.A. EX1002, ¶142. Alexander also renders these claims obvious because it anticipates them. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (“[A]nticipation is the epitome of obviousness.”) (citation omitted); *see also* EX1002, ¶141.

If the Board finds that Alexander does not disclose a composition with saccharide-polypeptide conjugates comprising at least two capsular polysaccharides from serotypes 23A, 23B, and 35B—limitation 1.c of claim 1, *supra* §IX.A.1.iv—Alexander still renders claim 1 obvious. The POSA would have understood that including additional serotypes in a vaccine composition could broaden the disease coverage of the vaccine and would thus have been motivated to include additional serotypes that were prevalent or associated with high disease burden. Each of serotypes 23A, 23B, and 35B was identified in Alexander as a strong candidate for inclusion in a future vaccine. The POSA would therefore have been motivated to include them, and would have reasonably expected to succeed in making such a pharmaceutical composition. EX1002, ¶¶143-44.

- 2. Claim 3: “wherein at least one polypeptide of the plurality comprises CRM₁₉₇, tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein**

A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from *N. meningitidis*, a purified protein derivative of tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof”

Claim 3 depends from claim 1. EX1002, ¶145. Alexander renders obvious the additional limitation of claim 3, which recites a Markush group of polypeptides for use in saccharide-polypeptide conjugates that includes “CRM₁₉₇.” While Alexander’s examples use pan DR binding peptides, EX1008, ¶9, Alexander further states that as of 2005, the sole PCV available was a “seven-valent formulation to a nontoxic diphtheria variant (CRM197) PREVNAR® from Wyeth.” EX1008, ¶8. The POSA would have understood CRM₁₉₇ to be a known, proven alternative polypeptide for use in a PCV, whose successful use in an approved vaccine would have motivated the POSA to select it, and would have had a reasonable expectation of success in using CRM₁₉₇ because of its history of clinical and licensed use in a PCV, thus rendering claim 3 obvious over Alexander. EX1002, ¶¶146-47.

3. Claim 9: “wherein a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated”

Claim 9 depends from claim 1. EX1002, ¶148. Alexander renders obvious the additional limitation of claim 9. As stated above, Alexander renders claim 3 obvious because it teaches that CRM₁₉₇ is a “nontoxic diphtheria variant” that is

conjugated to the saccharides in Prevnar®. EX1008, ¶8. Such knowledge would have motivated a POSA to use this polypeptide as a commercially available and licensed alternative to the pan DR binding peptide in developing a PCV. EX1002, ¶¶24, 148. Accordingly, Alexander also renders obvious claim 9 for the same reasons. Given the motivation to use a “nontoxic diphtheria variant” CRM₁₉₇ in the composition as taught in Alexander, the claim limitation “wherein a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated” is necessarily satisfied. *Id.*, ¶148.

4. **Claim 12: “further comprising at least one additional immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide from a unique *Streptococcus pneumoniae* serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34”**

Claim 12 depends from claim 1, and Alexander renders obvious the additional limitation of claim 12. EX1002, ¶149. Alexander describes embodiments comprising “a mixture of conjugates . . . with capsular polysaccharides from 2, . . . 30 or more of the following serotypes,” and then lists a group of serotypes including 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20, 22F, and 34. EX1008, ¶63. The POSA would understand that increasing the number of serotypes in a PCV could broaden the vaccine’s disease coverage. Alexander teaches embodiments comprising up to 30 serotypes, including many of the serotypes listed in claim 12. *Id.* Alexander thus would have motivated the POSA to develop a pharmaceutical

composition with this array of serotypes, and would have reasonably expected, based on this reference and the longstanding trend in the art toward including more serotypes, to succeed in making such a composition. EX1002, ¶150.

C. Ground III: Gu anticipates claims 1, 3-6, 9, 11-12, 15, and 18-19.

Gu anticipates claim 1 of the '757 patent, as well as claims 3-6, 9, 11, 15, and 18-19, which depend from it. EX1002, ¶151.

1. Claim 1

i. [1.Pre] “A pharmaceutical composition”

Gu discloses this limitation. Gu states that it relates to “immunogenic compositions,” EX1009 at 1:7, which it defines as “any pharmaceutical composition containing an antigen” that “can be used to elicit an immune response in a subject.” *Id.* at 51:19-21. Gu also states that “the glycoconjugates of the invention [are] used in the production of immunogenic compositions.” *Id.* at 12:15-17; EX1002, ¶152.

ii. [1.a] “comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates”

Gu discloses this limitation. EX1002, ¶¶153-54. For example, Gu explains that “[t]he immunogenic compositions of the invention may [] comprise . . . a plurality of capsular polysaccharide-protein conjugates.” EX1009 at 57:11-12.

Gu also contemplates vaccine compositions involving multiple conjugates, explaining that “[t]he immunogenic amount of the different polysaccharide components in an immunogenic composition may diverge.” *Id.* at 63:9-10. Further,

claim 25 of Gu recites “[a]n immunogenic composition comprising *at least one* glycoconjugate.” *Id.* at 123:9-11 (emphasis added). By saying “at least” Gu conveys to the POSA compositions that have multiple glycoconjugates. The POSA would also understand that if a composition has more than one glycoconjugate, each is “unique”; the POSA would understand that a composition where all the glycoconjugates are the same serotype would not be described as having multiple glycoconjugates. EX1002, ¶153.

Gu further discloses that its glycoconjugates are immunogenic as early as its title. EX1009 at cover page, (54). It explains that its disclosures are directed to “immunogenic compositions” comprising glycoconjugates of saccharides and carrier proteins. *Id.* at cover page, (57). Gu further states that “[g]lycoconjugates of the invention comprising a bacterial capsular polysaccharide can be used in the production of antibodies against such a bacterial capsular polysaccharide.” *Id.* at 30:32-31:2. The POSA would understand that a composition that induces the production of antibodies is “immunogenic,” and indeed, that producing an immunogenic composition is the very purpose of PCV development. EX1002, ¶154.

iii. [1.b] “each comprising individually a capsular polysaccharides [sic] conjugated to a polypeptide”

Gu discloses this limitation. EX1002, ¶155. Gu explains that its composition includes glycoconjugate comprising “a saccharide covalently conjugated to a carrier protein.” EX1009 at 29:14-17. It discloses embodiments in which the saccharide is

a capsular polysaccharide, *i.e.*, a saccharide derived from an *S. pneumoniae* serotype.

Id. at 11:17-25.

- iv. [1.c] “wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B”

Gu discloses this limitation, EX1002, ¶¶156-58, which as discussed above encompasses compositions containing at least two capsular polysaccharides from the listed serotypes. *See supra* §IX.A.1.iv; *Vehicular Techs.*, 212 F.3d at 1383.

Gu discloses embodiments in which “the Pn capsular polysaccharide is selected from the group consisting of serotype 2, 9N, 15A, 17F, 20, **23A**, **23B**, and **35B** capsular polysaccharides.” EX1009 at 22:31-23:1 (emphasis added), where the POSA would understand “Pn” as a shorthand for pneumococcal. EX1002, ¶158. It also expressly states, as discussed in §IX.C.1.iii, *supra*, that immunogenic compositions may include conjugates of multiple serotypes. The POSA would therefore understand Gu’s disclosure to encompass compositions comprising, for example, conjugates of serotypes 23A and 23B. EX1002, ¶¶157-58.

Further, the POSA would understand that Gu discloses the use of compositions including glycoconjugates with capsular polysaccharides from multiple serotypes, including the ones recited in the claim. Gu also recites an embodiment listing a mere 8 serotypes, including all three of claim 1’s serotypes. EX1009 at 22:31-23:1. Accordingly, the POSA would understand that Gu discloses

compositions which comprise glycoconjugates with at least two of the three serotypes listed in limitation 1.c, and the POSA would at once envisage a vaccine composition involving glycoconjugates with at least two of the required serotypes. *See e.g., Perricone*, 432 F.3d at 1376; *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962). Accordingly, Gu anticipates claim 1. EX1002, ¶159.

2. Claim 3

Claim 3 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation. EX1002, ¶¶160-62. Gu lists numerous embodiments in which the protein carrier conjugated to the saccharide consists of “toxins, toxoids or any mutant cross-reactive material (CRM) of the toxin from tetanus, diphtheria, pertussis . . . and *Streptococcus*” or can be selected from a group which includes several of the polypeptides as recited claim 3. EX1009 at 36:15-18, 37:4-38:2. It further discloses an embodiment in which the “carrier is of diphtheria toxoid CRM₁₉₇.” *Id.* at 36:18-19. Gu’s disclosure of any one of the additional carriers within the claim is sufficient to anticipate claim 3. *Brown*, 265 F.3d at 1351.

3. Claim 4

Claim 4 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation. EX1002, ¶163. Gu explains that “[i]n some embodiments, the immunogenic compositions comprise an adjuvant.”

EX1009 at 13:28. Additionally, Gu discloses that “[s]uitable adjuvants to enhance effectiveness of the composition include . . . aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate” and “oil-in-water emulsion formulations” including 0.5% Tween 80, which a POSA would understand is an emulsifier. *Id.* at 55:13-17. Gu further states that in other embodiments, “a formulation of the invention . . . comprises one or more non-ionic surfactants.” *Id.* at 57:22. Gu describes a specific embodiment formulated in a buffering agent, specifically sodium succinate buffer. *Id.* at 58:20-25. Gu also states that the invention “may further comprise one or more preservatives.” *Id.* at 57:11-12. The POSA would have also known, from his or her background knowledge, that a multitude of adjuvants, surfactants, emulsifiers, buffering agents, preservatives and/or salts could be included in PCVs. As in Ground I, *supra* §IX.A.1.3, any of these disclosures in Gu is sufficient to anticipate claim 4. EX1002, ¶¶164-66.

4. Claim 5

Claim 5 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation. EX1002, ¶167. It states that “[d]irect delivery of immunogenic compositions of the present invention . . . may be accomplished by parenteral administration (intramuscularly, intraperitoneally, intradermally, subcutaneously, intravenously, or to the interstitial space of a tissue); . . . or by . . . intranasal . . . administration.” EX1009 at 57:31-58:3. As in Ground

I, *supra* §IX.A.1.4, Gu discloses not just individual methods of administration within claim 5 (which would be sufficient to anticipate) but in fact expressly discloses the entire list, thus anticipating claim 5. EX1002, ¶¶168-69.

5. Claim 6

Claim 6 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation, specifying embodiments wherein the conjugates elicit an opsonophagocytic response. EX1002, ¶170. For example, after disclosing embodiments involving the three serotypes listed in claim 1, Gu explains: “In another aspect, the glycoconjugates or immunogenic compositions of the invention can be used to generate antibodies that are functional as measured . . . via an opsonophagocytic killing assay.” EX1009 at 30:30-32. Gu further states that in some embodiments, “the antibodies produced against bacterial polysaccharides are functional . . . in an opsonophagocytic killing assay.” Gu at 31:4-6. Gu thus anticipates claim 6. EX1002, ¶¶171-72.

Further, the POSA would understand from Gu that opsonophagocytosis corresponds to the immunogenic efficacy of a vaccine. For example, Gu states that “opsonising antibodies correlate with a protective immune response,” so a pneumococcal vaccine can be “assayed by measuring the percent decrease in the bacterial count in an opsonophagocytosis assay.” EX1009 at 54:15-18. The POSA would have known that opsonophagocytosis is the mechanism by which a PCV

stimulates its host's immune system. *See also* EX1009 at 63:22-26 (“An immune response may be detected . . . by measuring the ability of the antibodies so induced to enhance the opsonophagocytic ability of particular white blood cells, as described herein.”). Accordingly, the POSA would have understood that by disclosing immunogenic conjugates, Gu necessarily discloses conjugates that elicit an opsonophagocytic response, thus anticipating claim 6. EX1002, ¶173.

6. Claim 9

Claim 9 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation. EX1002, ¶174. As explained above, *supra* IX.C.2, Gu discloses the use of toxoids of various diseases, including tetanus and diphtheria, as carrier proteins for the capsular polysaccharide. EX1009 at 36:15-18. And as discussed above, *supra* §V.A.2, a toxoid is a disease protein for which its toxic activity has been mitigated. Gu explains as much, noting that “suitable carrier proteins include *inactivated bacterial toxins* such as cholera toxoid.” EX1009 at 37:35 (emphasis added). Gu thus anticipates claim 9 by disclosing compounds wherein the toxin activity of a polypeptide is mitigated. EX1002, ¶¶175-76.

7. Claim 11

Claim 11 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation. EX1002, ¶177. It explains, “the

invention provides a method of inducing an immune response . . . comprising administering to a subject an immunologically effective amount of any of the immunogenic compositions described herein” EX1009 at 60:8-12; *see also id.*, 15:3-5, 32:18-21. Such immunogenic compositions satisfy the limitations of claim 1. And any of these disclosures is sufficient to anticipate claim 11. EX1002, ¶¶178-79.

8. Claim 12

Claim 12 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation. EX1002, ¶180. Gu discloses an immunogenic composition comprising a “glycoconjugate which comprises a Pn capsular polysaccharide derived from *S. pneumoniae*” and in specific embodiments “the Pn capsular polysaccharide is selected from the group consisting of Pn-serotype[s]” and then lists a group of serotypes including 23A, 23B and 35B recited in claim 1 of the ’757 patent, along with serotypes 8, 9N, 10A, 11A, 12F, 15A, 15B, 20, and 22F recited in this claim. EX1009 at 12:27-13:7. The POSA would at once envisage a composition with at least one additional serotype drawn from among 8, 9N, 10A, 11A, 12F, 15A, 15B, 20, and 22F. *E.g.*, *Perricone*, 432 F.3d at 1376; *Petering*, 301 F.2d at 681. Thus, Gu anticipates claim 12. EX1002, ¶¶181-83.

9. Claim 15

Claim 15 depends from claim 11, and Gu anticipates claim 11 for the reasons described above. Gu also discloses this limitation. EX1002, ¶184. It states, “[d]irect delivery of immunogenic compositions of the present invention to a subject may be accomplished by parenteral administration (intramuscularly, intraperitoneally, intradermally, subcutaneously, intravenously, or to the interstitial space of a tissue).” EX1009 at 57:31-58:3. Accordingly, Gu anticipates claim 15. EX1002, ¶¶185-86.

10. Claim 18

Claim 18 depends from claim 11, and Gu anticipates claim 11 for the reasons described above. Gu also discloses this limitation. EX1002, ¶187. For example, it observes, “[i]n certain embodiments, the dose is formulated for administration to a human subject.” EX1009 at 59:12-13. Thus, Gu anticipates claim 18. EX1002, ¶¶188-89.

11. Claim 19

Claim 19 depends from claim 1, and Gu anticipates claim 1 for the reasons described above. Gu also discloses this limitation. EX1002, ¶190. As discussed above, Gu discloses the conjugates recited in claim 1. It further discloses the combination of those conjugates with an adjuvant, noting, “[i]n some embodiments, the immunogenic compositions comprise an adjuvant.” EX1009 at 13:29; *see also*

id., 14:19-26, 14:27-31, 29:10-20 (disclosing use of excipients in immunogenic compositions). Accordingly, Gu anticipates claim 19. EX1002, ¶¶191-93.

D. Ground IV: Gu renders obvious claims 1, 3-6, 9, 11-12, 15, and 18-19.

Gu discloses claims 1, 3-6, 9, 11-12, 15, and 18-19 for the reasons discussed above, *supra* §IX.C. Thus, Gu renders these claims obvious because it anticipates them. *Connell*, 722 F.2d at 1548. EX1002, ¶194.

In addition, if the Board concludes that Gu fails to anticipate a composition having saccharide-polypeptide conjugates comprising capsular polysaccharides from the specific serotypes required by limitation 1.c of claim 1 or in claim 12, Gu renders those claims (and the remaining claims in this Ground, which depend on claim 1) obvious for an additional reason: Gu expressly teaches, in one list of a mere eight preferred serotypes, all three of the serotypes recited in claim 1 (23A, 23B, and 35B), as well as three of the serotypes recited in claim 12 (9N, 15A, and 20). EX1009 at 11:23-25. The POSA would understand that increasing the number of serotypes in a PCV would broaden its disease coverage. The POSA would therefore have been motivated to add the serotypes recited in Gu's specific list, to a composition. The POSA also would have reasonably expected, based on this reference and the longstanding trend in the art toward including more serotypes, to succeed in making such a composition. EX1002, ¶195.

E. Ground V: Claims 1-9 and 11-19 would have been obvious over Alexander or Gu, in view of the Serotype Prevalence References and/or the Vaccine Recommendation References.

As discussed above, *supra* §§IX.A-D, Alexander or Gu anticipate and render obvious claims 1 and 12, and thus the other dependent claims 2-9, 11, and 15-19 included in Grounds I-IV. EX1002, ¶196. But if there were any doubt about those Grounds' teachings of the particular serotypes recited in claims 1 and 12, the wealth of prior art disclosing Patent Owner's supposedly inventive serotype selection should dispel it. That same art points to the additional serotypes of claims 13 and 14.

The POSA seeking to design an improved PCV would have looked to the literature, and epidemiological data, for emerging serotypes of concern and been motivated to combine this information with Alexander or Gu. That information motivates the development of a PCV with the claimed serotypes and would have rendered the claims obvious. EX1002, ¶197.

For convenience, Petitioner groups references that address the prevalence of pneumococcal serotypes in a world with widely-used PCVs as the Serotype Prevalence References—Kaplan, Pilishvili, Waight, ECDC, and/or PHAC—and references that specifically recommend vaccine serotypes as the Vaccine Recommendation References—Porro, Al-Sherikh, Richter, and Wagenvoort. Dr. Musey explains that the leading serotypes causing invasive pneumococcal diseases

are provided regularly in disease surveillance reports from many countries. An analysis of the serotypes over a period of multiple years would have given the POSA a good insight about trends, persistence, and the importance of some serotypes compared to others in their contribution to the burden of pneumococcal disease, and thus support their inclusion in future pneumococcal vaccines. Petitioner includes this mountain of art not because multiple secondary references are needed to show obviousness—they are not—but to demonstrate that the serotype-selection question before the POSA was consistently and repeatedly answered by the field with the serotypes Patent Owner claims. EX1002, ¶¶197-98.

Accordingly, the combination of Alexander or Gu with the Serotype Prevalence References and/or Vaccine Recommendation References renders obvious claims 1, 12, 13, and 14, and the other claims addressed in Grounds I-IV. EX1002, ¶¶199, 218-20.

1. Claim 1

As discussed above, *supra* §§IX.A.1, B.1, C.1, D.1, Alexander or Gu disclose every element of claim 1 including conjugates comprising capsular polysaccharides from serotypes 23A, 23B, and 35B. EX1002, ¶200. Thus, Alexander or Gu renders these claims obvious because it anticipates them. *Connell*, 722 F.2d at 1548.

It also would have been obvious to a POSA to include at least two of these serotypes in a vaccine composition in view of the epidemiological data disclosed in

any one of the Serotype Prevalence References (EXs1015-19), and certainly all together, *see* EX1002, ¶¶201-202:

- Kaplan identified serotype 35B as the most common, and serotypes 23B and 23A as the second and sixth most common non-PCV13 serotypes isolated, respectively, following the widespread use of PCV13. EX1015 at 1341-42 & tbl.2.
- Pilishvili reports significant increases in the prevalence of serotypes 23A, 23B, and 35B across all age groups in the period between 1998 and 2007. EX1016 at 32, 34-35 & tbls.1-2.
- Waight lists serotypes 23A, 23B, and 35B as among the top serotypes not covered by the existing standard-of-care vaccine that were most likely to cause pneumococcal diseases in young children between 2012 and 2014. EX1017 at 538, 540 & Fig. 3 & tbl.2.
- ECDC includes all three of serotypes 23A, 23B, and 35B among the “most common serotype[s]” that caused “confirmed [invasive pneumococcal disease] cases” in European countries in 2011. EX1018 at 14-15, 23-24, & Fig. 1.5.
- PHAC reports similar results for Canada, and notes that “[c]ontinued vigilance . . . is required to recognize possible increases in other []

serotypes [not included in the standard-of-care vaccine] in Canada, such as serotype[s] . . . 23A and 23B.” EX1019 at 57.

Each of the Vaccine Recommendation References also teaches at least two of these serotypes and directs a POSA to their use, *see* EX1002, ¶203.

- Porro reports that serotypes 23A and 35B are “[n]ew emerging serotypes of *S. pneumoniae*,” and suggests that they “might be likely included in a further up-dated broad-spectrum vaccine formulation” that could “elevate the bar on coverage to 75-80%.” EX1010 at 66:28-67:14.
- Al-Sherikh teaches that serotypes 23A and 23B are among the twenty most frequently occurring serotypes in pediatric pneumococcal diseases, and expressly recommends the inclusion of serotype 23A in a future vaccine formulation. EX1011 at 210, 213-14.
- Richter explains that serotype 35B was among the three most common serotypes in penicillin-resistant *S. pneumoniae* and growth of 35B should inform future vaccine development, and that serotypes 23A and 23B showed proportional increases in prevalence. EX1013 at 6484-86, 6488.
- Wagenvoort states that serotypes 23A and 23B were the two most likely serotypes to cause disease in vulnerable populations that were not

included in the then-current multivalent vaccine and recommends 23A and 23B for selection into future vaccines. EX1014 at 334, 338-39.

These references, on their own or collectively, demonstrate that each of these serotypes was well known in the prior art as being especially prevalent or virulent, and the POSA would therefore have been motivated to include them in the PCV of Alexander or Gu. Indeed, several of the references expressly state that the serotypes they identify should be included in a future vaccine. Accordingly, and as Dr. Musey explains, it would have been obvious to include in a PCV of Alexander or Gu the serotypes required by claim 1 as taught by the Serotype Prevalence References and Vaccine Recommendation References, and the POSA would have had a reasonable expectation of success, as illustrated by the multiple teachings of PCVs that included these serotypes. EX1002, ¶204.

2. Claim 12

Claim 12 depends from claim 1. Any one of Alexander, Gu, the Serotype Prevalence References or the Vaccine Recommendation References also provides a motivation to add an additional conjugate comprising a capsular polysaccharide from a serotype meeting the requirements of claim 12. Alexander discloses embodiments comprising the serotypes 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20, 22F, and 34. EX1008, ¶63. Gu discloses embodiments comprising the serotypes

8, 9N, 10A, 11A, 12F, 15A, 15B, 20, and 22F. EX1009 at 11:18–21. EX1002, ¶¶205-207.

Each of the Serotype Prevalence References likewise would have provided a motivation to a POSA to add at least one additional serotype required by claim 12, *see* EX1002, ¶208:

- Kaplan disclosed that serotype 15B was the fourth, 15A was the seventh, and 15C was the eighth most common non-PCV13 serotypes isolated from cultures from children in the “PCV13 era” from 2011 to 2013. EX1015 at 1341-42 & tbl.2.
- Pilishvili reports increases in the prevalence of serotypes 8, 9N, 10A, 11A, 15A, 15B/C, 16F, and 22F in the time period spanning 1998 to 2007, across all age groups. EX1016 at 37, tbl. 2.
- Waight reports that “[n]on-PCV13 serotypes 8, 10A, 12F, 15A, and 24F increased significantly in 2013/14.” EX1017 at 538-40 & tbl.2.
- ECDC lists serotypes 6C, 8, 12F, 15A, and 22F as among “[t]he 10 most common IPD serotypes reported in 2012” in European countries not covered by any of the licensed PCV vaccines, and includes 9N, 11A, and 16F as among the top 25 most common serotypes. EX1018 at 14, tbl.1.3 & n.8.

- PHAC reports an increase in serotypes 8, 9N, 10A, 11A, 12F, 15B, 20 and 22F in all age groups between 2010 and 2013 and notes serotype 22F as the most prevalent in Canada in 2013. EX1019 at 5.

The same is true of the Vaccine Recommendation References, *see* EX1002,

¶209:

- Porro teaches that “any combination” of a group of serotypes including 6C, 8, 9N, 10A, 11A, 12F, 15B, 20, and 22F “may be contemplated” for a multivalent vaccine. EX1010 at 27:30-28:6, 66:28-67:14.
- Al-Sherikh describes how serotypes 8 and 12F are prevalent in young pneumococcal patients and recommends inclusion of serotype 15 to the PCV to enhance its efficacy for preventing IPD. EX1011 at 210, 213-214 & fig. 4.
- Richter identifies 6C, 11A, and 22F as “[p]redominant” in all isolates and 15A and 15B in some especially concerning antibiotic-resistant ones and stressing the use of serotype distribution to inform creation of new vaccines. EX1013 at 6484, 6487, tbl.4.
- Wagenvoort reports that serotypes 8, 10A, 12F, and 15B are significantly more likely to be associated with pneumococcal infections in high-risk patients and recommends 10A for selection into future vaccines. EX1014 at 338-39 & fig.1.

Several of the Vaccine Recommendation References directly explain the relevance of their findings to future vaccine development. Accordingly, and as Dr. Musey explains, it would have been obvious to include in a PCV the serotypes required by claim 1, along with one of the additional serotypes recited in claim 12, and the POSA would have had a reasonable expectation of success, as illustrated by the multiple disclosures of PCVs including these serotypes. EX1002, ¶¶210-11.

3. Claims 13 and 14

Both claims 13 and 14 depend from claim 1. Claim 13 recites “wherein the plurality of unique immunogenic saccharide-polypeptide conjugate[s] comprise[] individually capsular polysaccharides from a *Streptococcus pneumoniae* serotype comprising 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.” Claim 14 states the same, replacing the final “comprising” with “consisting of.” While claim 13’s “comprising” language permits the “plurality” of “saccharide-polypeptide conjugate” to include additional serotypes and claim 14 does not, both claims recite “comprising” one level out: that is, even claim 14 refers to a conjugate that “comprises” polysaccharides from a serotype “consisting of” the recited list. Thus, properly interpreted, the two claims have the same scope. EX1002, ¶¶212-14.

Both claims would have been obvious over Alexander or Gu combined with the Serotype Prevalence and/or Vaccine Recommendation References. Most of the serotypes on the list are disclosed in Alexander and Gu already. As discussed,

Alexander discloses embodiments with “30 or more” of a list including serotypes 9N, 15A, 15C, 16F, 23A, 23B, and 35. EX1008, ¶63. Gu’s eight-serotype list discussed above includes serotypes 9N, 15A, 23A, 23B, and 35B. EX1009 at 11:23-25, 13:5-7. In addition, as discussed above in claim 12, numerous references recommended the inclusion of serotypes 23A, 23B, and 35B (the list from claim 1), *supra* §IX.E.1, and multiple references counseled inclusion of serotypes 6C, 9N, 15A, 15C, and 16F, *supra* §IX.E.2. Richter also highlighted how “major” serotype 6C was, and flagged serotypes 15A and 15C as “predominant” in antibiotic-resistant isolates. EX1013 at 6485-87 & tbl.4. Wagenvoort further described serotype 6C as being especially common among high-risk patients. EX1014 at 337; EX1002, ¶¶215-17.

These disclosures would have motivated the POSA, as Dr. Musey explains, to include all of the recited serotypes in a PCV and thus to practice claims 13 and 14, and would have supplied a reasonable expectation of success. EX1002, ¶217.

F. Ground VI: Claim 6 would have been obvious over either Alexander or Gu, in view of Lee and/or Anttila.

Claim 6 depends from claim 1 and is anticipated and obvious over Alexander or Gu alone, as discussed above, *supra* §§IX.A.5, IX.B.1, IX.C.5, IX.D. Lee and Anttila each provide further support for the obviousness of including at least one saccharide-polypeptide conjugate that elicits an opsonophagocytic response. EX1002, ¶¶221-22.

Lee explains that “the protective immunity” conferred by PCVs can be “estimated better by directly measuring opsonic capacity of vaccine-induced antibodies.” EX1020 at 376. That is because “the antibodies provide protection *by opsonizing pneumococci*.” *Id.* (emphasis added); EX1002, ¶223.

Similarly, Anttila explains that “[h]ost protection against [*S. pneumoniae*] is mainly mediated by opsonin-dependent phagocytosis. Therefore, opsonophagocytic activity (OPA) of antibodies to pneumococcal capsular polysaccharides (PS) is believed to measure their functional activity” EX1021 at 302; EX1002, ¶224.

Thus, it would have been obvious to a POSA in view of Lee and/or Anttila, to ensure that the PCV as disclosed by either Alexander or Gu induced an opsonophagocytic response since (1) it enables measurement of the vaccine’s efficacy and (2) the opsonophagocytic response is a mechanism by which the vaccine protects the subject and would have done so with a reasonable expectation of success. In other words, opsonophagocytosis by vaccine-induced antibodies is the very means by which a vaccine protects a patient from bacteria. Claim 6 essentially recites that the vaccine exhibits minimal efficacy with respect to a single serotype. That would have been obvious. EX1002, ¶¶225-27.

G. Ground VII: Claims 7 and 10 are obvious over either Alexander or Gu, in view of PFL.

Both claims 7 and 10 depend from claim 1. The limitations of claims 7 and 10 would have been obvious over either Alexander or Gu combined with PFL, the

Pprevnar® label. Pprevnar® was the “global standard in pneumococcal disease prevention,” at least until Pprevnar 13® was released. EX1025 at 1. In making a PCV, the POSA would have had reason to look to the compositional limitations expressed in the most widely distributed PCV. EX1002, ¶¶228-32.

1. Claim 7

PFL discloses this limitation. EX1022 at 1. It is well known to the POSA that the percentage of active ingredients by weight in a vaccine composition is very low and the majority of a vaccine composition’s weight is composed of water. PFL explains that Pprevnar® included 2 micrograms of each saccharide for six *S. pneumoniae* serotypes, 4 micrograms of serotype 6B, and approximately 20 micrograms of the carrier protein, for a total of 36 micrograms of saccharide-polypeptide conjugate. *Id.* Pprevnar® was administered in 0.5 mL liquid doses. *Id.* The density of water is 1 gram/mL, meaning each dose should weigh approximately 0.5 grams. Thus, the saccharide-polypeptide conjugates occur at 36 micrograms, or 0.000036 grams, per 0.5 grams of vaccine. 0.000036 divided by 0.5 yields a concentration of 0.0072%. Therefore, the saccharide-polypeptide conjugates of Pprevnar® are collectively present in an amount of at least 0.001% by weight, based on the weight of the pharmaceutical composition.

The POSA would have found it obvious to optimize the concentration of the saccharide-polypeptide conjugates in making a *S. pneumoniae* PCV as this work is

considered routine during development. Given that the concentration in the standard-of-care vaccines would be at least 0.001% as taught by PFL, this established dosage would reasonably serve as a starting point for study in view of the disclosures of Alexander or Gu. EX1002, ¶243. Thus, a POSA would have found claim 7 obvious. EX1002, ¶¶233-37.

2. Claim 10: “wherein each of the immunogenic saccharide-polypeptide conjugates is present in an amount of at least 0.001%, by weight, based on the weight of the pharmaceutical composition.”

PFL also teaches this limitation. EX1022 at 1. Again, PFL explains that Prevnar® contained 36 micrograms of saccharide-polypeptide conjugate per dose. EX1022 at 1. Given a total of 36 micrograms of saccharide-polypeptide conjugates per dose and seven corresponding serotypes in a Prevnar® dose, a POSA would nonetheless conclude each of the seven conjugates is, on average, present in an amount exceeding 5 micrograms ($36 \div 7 > 5$); thus, at least one conjugate reaches or surpasses this 5 microgram threshold. EX1002, ¶¶238-40.

The limitation of claim 10 is therefore obvious. 0.5 mL of Prevnar® weighs about 500 mg. As 5 micrograms corresponds to 0.001% of the dose’s weight, the previous conclusion—that at least one saccharide-polypeptide conjugate is present in an amount of 5 micrograms or more—directly implies that the concentration of that conjugate in Prevnar® is greater than 0.001%. EX1002, ¶241.

The POSA would have found it obvious to optimize the concentration of the saccharide-polypeptide conjugates in making a *S. pneumoniae* vaccine as this work is considered routine during development. Given that the concentration in the standard-of-care vaccines would be at least 0.001% as taught by PFL, this established dosage would reasonably serve as a starting point for study in view of the disclosures of Alexander or Gu. Thus, a POSA would have found claim 10 obvious. EX1002, ¶242.

H. Ground VIII: Claims 2 and 16-17 are obvious over Alexander in view of Vesikari and/or PFL.

Claim 2 depends from claim 1, and adds a limitation requiring that the pharmaceutical composition incorporate multiple different polypeptides as carrier proteins.

Claim 16 depends from claim 11, which recites a method for administering the composition of claim 1. Claim 16 requires that a second (or booster) dose occurs at least four weeks before or after the initial dose. Claim 17 further limits claim 16, specifying that the second composition comprises a capsular polysaccharide from a serotype of *Streptococcus pneumoniae* conjugated to a second polypeptide.

As discussed above—*supra* §IX.A.1, 8; §IX.C.1, 7—Alexander and Gu both anticipate claims 1 and 11, and Alexander anticipates claims 2, 16, and 17, *supra* §IX.A.2, 10, 11. In view of Vesikari and/or PFL, Alexander also renders obvious claims 2, 16, and 17. EX1002, ¶¶243-45.

1. Claim 2

As discussed above, *supra* §IX.A.2, the POSA would interpret claim 2 to refer to a pharmaceutical composition involving two or more saccharide-polypeptide conjugates, wherein for at least one of the conjugates, the polypeptide portion of the combination is a mixture of different polypeptides. Thus, claim 2 adds the requirement that the composition include multiple different polypeptide carrier proteins. EX1002, ¶246.

Alexander anticipates this limitation for the reasons discussed above, *supra* §IX.A.2, and also independently supplies a motivation for the POSA to consider including multiple different carrier proteins in a vaccine composition. EX1002, ¶247.

Additionally, Alexander renders this limitation obvious when combined with the prior art. Vesikari describes the administration of the 10-valent vaccine PHiD-CV, consisting of polysaccharides from ten *S. pneumoniae* serotypes conjugated with three different carrier proteins. EX1023 at S67. Vesikari demonstrated noninferiority of PHiD-CV when compared to 7vCRM (Prevnar®) for the shared serotypes. *Id.* Thus, the POSA would be motivated to look to and follow Vesikari's teachings of a mixture of polypeptide carrier proteins to improve immunogenicity of a PCV composition, and would have had a reasonable expectation of success in doing so. *Id.* at S73; EX1002, ¶¶248-49.

2. Claim 16

Alexander anticipates this limitation for the reasons discussed above, *supra* §IX.A.10, and also independently supplies a motivation for the POSA to administer two doses of a composition at least about four weeks or more than four weeks apart. EX1002, ¶250.

Additionally, Alexander also renders this claim obvious as it teaches that initial immunization doses “are followed by boosting dosages . . . pursuant to a boosting regimen over weeks to months,” and “**established intervals**, *e.g.*, from one to **four weeks**, may be required, possibly for a prolonged period of time to effectively immunize an individual.” EX1008, ¶¶112, 116 (emphases added); EX1002, ¶251.

The prior art also teaches that the two doses can be administered at least about four weeks or more than four weeks apart. Vesikari, for example, discussed administration of a vaccine at 2-3-4 months of age and a booster dose at 12-18 months. EX1023 at S66-67. The standard vaccination schedule in PFL for Prevnar® included doses administered at 2, 4, 6, and between 12 and 15 months of age. EX1022 at 11. Given the need to maximize immunogenicity while maintaining a clinically convenient schedule, the POSA would have found it obvious to combine the known concept of administering a second (or boosting) dose as disclosed by Alexander with an interval of about or more than four weeks between the doses, with

a reasonable expectation of success, since such schedule was already widely used and demonstrated in established schedules like Vesikari and PFL. EX1002, ¶¶252-53.

3. Claim 17

Claim 17 depends from claim 16. Alexander anticipates this limitation for the reasons discussed above, *supra* §IX.A.11, and also independently supplies a motivation for the POSA to administer a second composition comprising a capsular polysaccharide conjugated to a second polypeptide. EX1002, ¶254.

The specification of the '757 patent expressly states that the second polypeptide (of the second composition's conjugate) can be identical or different to the first polypeptide. EX1001, 48:7-23. As discussed above in claim 16, *supra* §IX.A.10., Alexander teaches administering a second (or booster) vaccine dose "at established intervals . . . to effectively immunize an individual." EX1008, ¶116. Alexander also teaches that the second carrier polypeptide can be the same or different as the first carrier polypeptide. EX1008, ¶¶34, 86. Vesikari also evaluated three dosing schedules (a 3-dose primary series and booster) including two homologous series and one heterologous series (Prevnar® primary/PhiD-CV booster). *Id.* Crucially, the heterologous series induced a superior immunogenic response for certain serotypes relative to the homologous series, so Vesikari's data suggests that varying the carrier protein between the initial (primary) doses and the

booster dose vaccine can enhance the immune system's response to specific serotypes. EX1023 at S69, S72-74 & tbl.5. This enhanced response is observed when compared to vaccination series where the same carrier protein is used for both the primary and booster administrations. *Id.*; EX1002, ¶¶255-57.

Motivated by the goal of optimizing the immunogenic response without compromising the efficacy of the vaccine series, a POSA would have found it obvious to combine the knowledge that multiple protein carriers can form effective vaccines as taught by Alexander informed by the data in Vesikari to enhance the immunogenic effect, with a reasonable expectation of success. EX1002, ¶258.

X. CONCLUSION

For the reasons above, trial should be instituted, and each of claims 1-19 of the '757 patent should be cancelled.

Dated: December 23, 2025

Respectfully submitted,

/David M. Krinsky/

David M. Krinsky (Reg. No. 72,339)

Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,058,757 contains, as measured by the word-processing system used to prepare this paper, 13,973 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: December 23, 2025

Respectfully submitted,
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Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on December 23, 2025, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,058,757 and supporting exhibits to be served by Federal Express Priority Overnight on the Patent Owner at the following correspondence address of record as listed on Patent Center:

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Dated: December 23, 2025

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