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

DECLARATION OF LUWY MUSEY, M.D.
IN RELATION TO *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,058,757

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I, Luwy Musey, M.D., declare as follows:

I. INTRODUCTION

1. I have been asked by counsel for Pfizer Inc. ("Pfizer") to offer my scientific opinions as to whether certain claims of U.S. Patent No. 11,058,757 (the "'757 patent") are anticipated or would have otherwise been obvious to the person of ordinary skill in the art ("POSA") as of the relevant date.

2. Counsel for Pfizer has informed me that claims 1-19 of the '757 patent (the "Challenged Claims") are at issue. (**EX1001**).

3. I understand that my opinions in this Declaration will be submitted as evidence in *inter partes* review ("IPR") proceedings before the Patent Trial & Appeal Board in the U.S. Patent & Trademark Office concerning the '757 patent. I understand Pfizer is the Petitioner in these proceedings and that Pogona, LLC ("Pogona") is the Patent Owner.

4. I am being compensated at my usual rate of $400 per hour plus expenses for my work in connection with this matter. My compensation in no way depends on the outcome of this matter or on the opinions I express. The opinions and conclusions I express herein are based on my review of the materials cited herein, as well as on (1) my general knowledge of pneumococcal conjugate vaccines and vaccine clinical research and (2) my experience and training as a researcher in these fields.

II. QUALIFICATIONS AND EXPERIENCE

5. My current resume is attached as **EX1003**. I have summarized my educational and professional background below.

6. I am a medical doctor trained in General Medicine, Microbiology, Immunology, and Infectious Diseases. Since 2001, I have been involved in vaccine development and led the development of several licensed and investigational live attenuated virus vaccines, inactivated vaccines, and conjugated vaccines. Between 2009 and 2022, my work focused on post-licensure clinical and epidemiological studies of the Merck 23-valent pneumococcal polysaccharide vaccine (PNEUMOVAX® 23), the preclinical and clinical development of the Merck 15-valent pneumococcal conjugate vaccine (VAXNEUVANCE®). I was also involved in the design of the Merck next generation 21-valent pneumococcal conjugate vaccine (CAPVAXIVE®), leading activities related to the selection of pneumococcal serotypes to be included in the vaccine and key ingredients used in the vaccine formulation.

III. THE PERSON OF ORDINARY SKILL IN THE ART

7. I have been informed that the person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to have known all of the relevant art as of the priority date of the '757 patent and is the person to whom the subject matter of the '757 patent is directed.

8. I have been asked to opine as to the qualifications of the POSA to which the claims of the ’757 patent are directed. For the purpose of rendering an opinion on this question, I have further been instructed to assume that the priority date of the ’757 patent is March 31, 2016.

9. I have been informed that factors that may be considered in determining the level of ordinary skill may include: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field. I have further been informed that the POSA may possess the education, skills, and experience of multiple actual people who would work together as a team to solve a problem in the field.

10. In my opinion, the POSA would include a research team with one or more researchers with an M.D. or Ph.D. in immunology, virology, biochemistry, chemistry, epidemiology, clinical safety, or a related discipline, and several years of work experience in vaccinology and in such related fields, and one or more individuals with an advanced degree and experience in drug delivery of vaccines.

11. My opinion as to the qualifications of the POSA would not change if the priority date of the ’757 patent were slightly different from March 31, 2016, for instance, sometime in 2017. Nor would my opinions in this Declaration change were

I to assume the POSA's qualifications to be slightly different from what I have articulated above.

IV. TECHNICAL BACKGROUND

12. The technology at issue in this case relates generally to vaccines targeting the bacterium *Streptococcus pneumoniae*. As I will discuss in later sections of this Declaration, the particular technology claimed in the '757 patent was not new. The concept of conjugate vaccines was first described in the 1920s and '30s, and later in the 1980s, with experiments showing that linking a polysaccharide antigen to a carrier protein increased the immune response of a polysaccharide vaccine.[1] The first conjugate vaccine for use in humans, a *Haemophilus influenzae* type b (Hib) conjugate, was licensed in the U.S. in 1987 and shortly thereafter was introduced into the U.S. infant immunization schedule.[2] The success of the Hib conjugate vaccine in reducing the incidence of invasive Hib disease in childhood has accelerated the development of conjugate vaccines designed to prevent infection by other encapsulated bacteria, such as *S. pneumoniae*.[3]

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[1] EX1026 (Pichichero) at 2505.

[2] EX1004 (Goldblatt) at 1.

[3] EX1004 (Goldblatt) at 1.

13. But before discussing the alleged invention in detail, it is useful to provide background on a few constituent technologies, each of which was also well-known and well-established before the priority date of the '757 patent. These technologies include the selection of multiple serotypes of *S. pneumoniae* to include in vaccine formulations and the conjugation of said serotypes to carrier proteins to enhance an immune response. In this section, I provide background on each approach or terminology. All of the information in this Technical Background section would have been known to the POSA before the priority date of the '757 patent.

A. *Streptococcus pneumoniae* and its serotypes

14. *Streptococcus pneumoniae* is a bacterium that can cause 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 significant healthcare burden, morbidity, and mortality in children and adults.[4] Infections caused by *S. pneumoniae* are referred to as "pneumococcal," and in the past, have collectively caused more than one million deaths per year worldwide.[5]

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[4] EX1027 (WHO) at 94.

[5] EX1027 (WHO) at 94.

15. The outermost surface of many strains of *S. pneumoniae* is a capsular polysaccharide, which consists of a large number of polysaccharide strands covalently bonded to the outer surface of the cell wall, and plays an important role in virulence and immune evasion mechanisms.

16. The capsular polysaccharide of *S. pneumoniae* can take many different forms, called serogroups and serotypes, which are used to classify variations of the bacterium. Serotypes are typically referenced using the "Danish system," which aggregates serotypes into serogroups by structural characteristics. For example, 23A, 23B, and 23F are all serotypes named according to the Danish system that belong to the serogroup 23.

17. To date, researchers have identified more than 100 different pneumococcal serotypes of *S. pneumoniae*. Serotypes vary in their prevalence and virulence across age strata and geographical location. 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. Monitoring pneumococcal serotype prevalence and identifying newly emerging serotypes is essential for designing new pneumococcal vaccines. 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 there is a corresponding increase in the prevalence of non-VT serotypes (i.e., serotypes not included in the vaccine).

18. Epidemiological studies related to the distribution of the circulating pneumococcal serotypes in a given population are based on the isolation of strains of *S. pneumoniae* in individuals with clinical symptoms suggestive of pneumococcal disease as well as natural carriage of S. *pneumoniae* in the nasopharynx from children and adults with or without pneumococcal disease.

B. Pneumococcal conjugate vaccines (PCVs)

19. A vaccine is a pharmaceutical composition administered to stimulate a patient's immune response with the goal to protect the vaccinated individual against a disease. A vaccine works by introducing an antigen, a portion of a disease-causing agent, which stimulates the body's immune system to identify and neutralize the antigen and thereby protect against disease.

20. Vaccines against *S. pneumoniae* stimulate antibodies that "opsonize," or tag, a bacterium. This tagging enables a "macrophage," or white blood cell, to engulf and neutralize the bacterium. This process is referred to as "opsonophagocytosis."

21. For pneumococcal vaccines, the antigen that stimulates the patient's immune system to produce antibodies is a polysaccharide from the capsule of an isolated serotype or group of serotypes of *S. pneumoniae*. These serotype-specific

antibodies are then capable of opsonizing or killing *S. pneumoniae* bacteria expressing the specific capsular polysaccharide.[6]

22. However, polysaccharide antigens induce only a weak immune response when introduced to the body on their own, especially in young children less than two years of age. This led to the development of conjugate vaccines. In a conjugate vaccine, a polysaccharide antigen is conjugated to a carrier protein in order to engage multiple components of the body's immune system and ultimately increase its immunogenic and prophylactic effects.

23. The basic structural design of conjugate vaccines would have been well known to the POSA. The prior art further discloses many potential modifications that can be made to a conjugate vaccine to increase its immunogenic effect.[7]

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[6] EX1028 (Hu) at 287 ("*Streptococcus pneumoniae* (pneumococcus) polysaccharide serotype-specific antibodies that have opsonophagocytic activity are considered a primary mechanism of host defense against pneumococcal disease."); EX1029 (Romero-Steiner) at 165 ("[a pneumococcal] conjugate vaccine elicits antibodies to pneumococcal capsular polysaccharide, and these antibodies protect the host by opsonizing pneumococci and thus facilitating phagocytosis.").

[7] *See generally* EX1030 (Costantino).

24. Often, the carrier proteins used in conjugate vaccines are proteins from a different disease that have been rendered non-toxic. These are referred to as "toxoids."

25. Because of *S. pneumoniae*'s many serotypes, pneumococcal vaccines are generally multivalent, containing purified forms of capsular polysaccharides from multiple serotypes.

26. The first licensed pneumococcal conjugate vaccine that included multiple serotypes was Prevnar® (pneumococcal 7-valent conjugate vaccine; PCV7), manufactured by Wyeth LLC (acquired by Petitioner in 2009).[8] Prevnar® comprised seven serotypes of *S. pneumoniae* (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) conjugated to a toxoid derived from diphtheria (diphtheria CRM_{197} protein).[9] The seven serotypes included in Prevnar® accounted for approximately 80% of IPD cases among U.S. children < 5 years of age before the 7-valent pneumococcal conjugate was licensed in the United States in 2000.[10] Prevnar® became the standard-of-care for infant pneumococcal immunization and remained so for many years. Subsequently, hospitalization rates due to diseases caused by the specific

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[8] EX1045 (Daniels) at 27, tbl.1.

[9] EX1045 (Daniels) at 29.

[10] EX1048 (CDC) at 144-48.

serotypes of Prevnar® significantly decreased in children immunized with Prevnar® and other age groups that did not receive Prevnar®, including the elderly.[11]

27. After the introduction of Prevnar®, an increase in pneumococcal diseases caused by non-Prevnar® serotypes was noted a few years after vaccine implementation.[12] This led to the development of Prevnar 13® (PCV13) a 13-valent pneumococcal conjugate vaccine (CRM_{197} protein), which was licensed in the United States in 2010.[13] Prevnar 13® was introduced to cover all seven serotypes in Prevnar® as well as six of the most prevalent *S. pneumoniae* serotypes that were not included in Prevnar®[14] (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F conjugated to CRM_{197} protein). After Prevnar 13® implementation, pneumococcal disease rates from these new serotypes dropped.[15]

28. The immunological effect of each serotype of a pneumococcal conjugate vaccine can be affected by how the serotype is conjugated to the carrier protein. For instance, some experiments have shown that polysaccharides that are

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[11] EX1045 (Daniels) at 29.

[12] EX1045 (Daniels) at 29.

[13] EX1045 (Daniels) at tbl.1.

[14] EX1045 (Daniels) at tbl.1.

[15] EX1045 (Daniels) at 29.

chemically cross-linked to the protein carrier have exhibited greater immunogenic effect.[16]

29. The selection of serotypes to be included in a pneumococcal conjugate vaccine is based on the epidemiology of pneumococcal disease (serotypes causing most cases of pneumococcal disease). Epidemiological data related to the pneumococcal serotypes causing disease that were included or not included in licensed pneumococcal conjugate vaccines have been widely published since at least 2003, especially from countries with mature pneumococcal disease surveillance systems such as the United States, Canada, the United Kingdom, and many countries in western Europe.[17]

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[16] EX1031 (Wessels) at 2186 ("Immunogenicity testing of a series of vaccines . . . demonstrated higher polysaccharide-specific antibody responses as the extent of cross-linking increased."); EX1032 (Baker) at 144 ("[E]xperiments with [conjugate vaccine compositions] revealed that highly cross-linked preparations were more potent immunogens."); EX1030 (Costantino) at 1052 ("[a]n intermediate crosslinking degree [between a saccharide and a protein] was found optimal.").

[17] EX1033 (Whitney) (reporting epidemiological data from the Centers for Disease Control and Prevention).

30. Following the introduction of Prevnar 13®, extensive surveillance of the epidemiology of pneumococcal diseases and the serotype distribution was conducted to identify serotypes to include in future pneumococcal vaccines. Serotypes are chosen because they all have been previously identified in pneumococcal disease surveillance reports prior to their inclusion in pneumococcal vaccines. This serotype distribution data is published and/or provided by request to enable serotype selection when designing future pneumococcal vaccines.

31. As with other vaccine compositions, pneumococcal conjugate vaccines could be administered by multiple routes well known in the prior art, such as orally, transdermally, or via an injection or aerosol.[18] Typically, the pharmaceutical compositions are administered parenterally, e.g., intravenously, subcutaneously, intradermally, or intramuscularly.[19]

32. But the POSA would have been aware of prior art suggesting that other methods could also be appropriate, such as subcutaneous administration, or intranasal administration, which had been tested and found feasible in mice.[20]

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[18] EX1008 (Alexander), ¶105.

[19] EX1008 (Alexander), ¶117.

[20] EX1024 (Yeh) at e494; EX1034 (Jakobsen) at 1443.

33. In addition to the polysaccharide-carrier protein conjugates described above, pneumococcal conjugate vaccines typically include excipients that were well known in the art, including diluents, adjuvants, surfactants, and others.[21]

V. LEGAL STANDARDS

34. I understand that in an *inter partes* review proceeding such as this one, the Petitioner challenging a patent bears the burden of proof by a preponderance of the evidence to show that a patent claim is either anticipated or would have been obvious to the person of ordinary skill in the art.

A. Anticipation

35. I have been informed that a claim is invalid as anticipated if a single prior art reference discloses every limitation of the claim, either expressly or inherently, as arranged in the claim. I also understand that a reference can anticipate if it discloses a sufficiently small group of possible options for a parameter that the POSA could at once envisage the claimed invention from within that group. I have also been informed that, for a reference to anticipate a claim, the reference must provide disclosure sufficient for the POSA to practice the relevant disclosure without undue experimentation. I understand, however, that a reference does not need to disclose what is already well-known to the POSA. Moreover, I understand that a

[21] EX1008 (Alexander), ¶105; EX1035 (Sogaard) at 276.

prior art reference should be considered for all that it teaches, and not just limited to a particular embodiment or the claimed invention of the prior art.

B. Obviousness

36. I have been informed that a patent claim is invalid if the claimed invention would have been obvious to the POSA at the time the alleged invention was made. Whether a claimed invention would have been obvious depends on (1) the scope and content of the prior art; (2) differences between the prior art and the claims; (3) the level of ordinary skill in the art; and (4) objective indicia of non-obviousness. Objective indicia of non-obviousness (which I understand are also known as secondary considerations) include: copying, long-felt but unsolved need, failure of others, commercial success, unexpected results or properties achieved by the claimed invention, and skepticism of skilled artisans before the invention.

37. In particular, I have been advised that, for an invention to be regarded as "obvious," the POSA must have had a reason or been motivated to modify the prior art or to combine one or more prior art references in a manner that would yield the claimed invention. I understand, however, that the prior art does not need to contain an explicit reason or motivation to modify the prior art to create the invention, but that a motivation or reason may be found explicitly or implicitly in market forces, design incentives, the interrelated teachings of multiple patents, any

need or problem known in the field of endeavor at the time of the invention, and the background knowledge, creativity, and common sense of the POSA.

38. I have been informed that exemplary rationales that may support obviousness include: (a) combining prior art elements according to known methods to yield predictable results; (b) simple substitution of one known element for another to obtain predictable results; (c) use of known technique to improve similar devices (methods, or products) in the same way; (d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (e) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success or "obvious to try"; (f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and (g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

39. I have also been informed that, for a claim to be obvious, the POSA must have had a reasonable expectation of success with respect to the claimed invention. I understand that a reasonable expectation of success does not, however, require absolute certainty of success, and that obviousness cannot be avoided simply

by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.

40. Importantly, I understand that the use of hindsight in an obviousness analysis is impermissible. In other words, I understand that it is improper to start from the '757 patent as blueprint to work backwards to the claimed invention. As such, I have not used hindsight in my analysis. I further understand that it is *not* hindsight to rely only on knowledge that was within the level of ordinary skill, nor must there be an express motivation to modify or combine the prior art.

41. Finally, I have been informed that, while objective indicia or secondary considerations can support non-obviousness, they are only relevant if there is a nexus between the merits of the claimed invention and the evidence of objective indicia. I understand that, in order to show a nexus, a patentee must show that the evidence of secondary considerations results both from what is claimed and what is novel in the claim. I also understand that a nexus requires a showing that any product asserted to be the source of secondary considerations both embodies and is co-extensive with the claims challenged as obvious.

VI. THE '757 PATENT

42. The '757 patent lists Bruce D. Forrest and Jack D. Love as named inventors, and it is titled "Saccharide-Polypeptide Conjugate Compositions and Methods of Use Thereof."

43. I am aware that the ’757 patent issued on July 13, 2021, from U.S. Application No. 16/089,040, filed on March 31, 2017.

44. I am further aware that the ’757 patent claims priority to U.S. provisional application No. 62/373,807, filed on August 11, 2016; U.S. provisional application No. 62/372,263, filed on August 8, 2016; U.S. provisional application No. 62/330,245, filed on May 2, 2016; and U.S. provisional application No. 62/316,555, filed on March 31, 2016.

45. The only independent claim of the ’757 patent, claim 1, 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.

46. I have been informed that the word “comprising” means that a claim must include the following limitation or limitations, but may include other matter as well. I also understand that the words “at least” mean that the claim requires a composition to include at least two saccharide-protein conjugates from two different serotypes, but encompasses compositions with unlimited numbers of conjugates. Accordingly, the POSA would understand that claim 1 recites an extremely broad open-ended combination of serotypes to be included in possible future candidate pneumococcal conjugate vaccines. I have been informed that claim 1 is considered a “genus” claim.

47. The dependent claims of the '757 patent recite various additional limitations. Some dependent claims, such as claim 3, lists known polypeptides used as a carrier protein, and claim 4 describes known vaccine formulation components. Others, such as claims 15-16, describe known ways of administering a vaccine; claim 18, for example, recites administering a vaccine to a human, and claim 6 describes the known immune response elicited by pneumococcal vaccines. Still others, such as claims 12-14, recite additional serotypes which also appear in the prior art.

VII. CLAIM CONSTRUCTION

48. I am not aware of any disputes as to the meaning of any of the terms of the Challenged Claims. The opinions I express in this declaration would remain the same under any reasonable construction of the Challenged Claims. To the extent Patent Owner offers constructions of the Challenged Claims that contradict the opinions I offer herein, I reserve the right to respond to Patent Owner's constructions.

VIII. SUMMARY OF REFERENCES

49. As I will describe below, in my opinion, Alexander and Gu anticipate or, either alone or in combination with other prior art references, render all of the Challenged Claims obvious. In this section, I briefly summarize the teachings of

Alexander and Gu, and other relevant references, as they would have been understood by the POSA.

A. Alexander (EX1008)

50. Alexander is International Patent Application No. WO2005/120563. The cover of Alexander lists December 22, 2005 as its international publication date, and it is titled "Induction of an Immune Response Against Streptococcus Pneumoniae Polysaccharides."[22]

51. Alexander explains that its invention is directed to "compositions comprising a mixture of at least two *Streptococcus 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."[23]

52. The "pan DR binding peptide sequence" is a sequence of amino acids that match a specific formula, joined together to form a polypeptide.[24]

53. Alexander further explains that its invention encompasses "methods of inducing an immune response in a mammal" by administering a mixture of

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[22] EX1008 (Alexander) at cover page, (43), (54).

[23] EX1008 (Alexander), ¶9.

[24] EX1008 (Alexander), ¶9.

saccharides from at least two *S. pneumoniae* serotypes conjugated to polypeptides.[25] It further encompasses "methods of making a *Streptococcus pneumoniae* vaccine" from conjugating serotype-specific capsular polysaccharides from *S. pneumonia* to polypeptides.[26]

54. In sum, Alexander teaches vaccine compositions including pneumococcal saccharide-polypeptide conjugates, wherein the carrier protein is one or several polypeptide sequences that meet specific, enumerated limitations.[27].

55. Alexander also discloses a set of serotypes to select from when formulating a vaccine composition. It explains: "In some embodiments, the compositions of the invention comprise a mixture of conjugates of a separate pan DR peptide of the invention 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."[28]

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[25] EX1008 (Alexander), ¶10.

[26] EX1008 (Alexander), ¶11.

[27] EX1008 (Alexander), ¶¶10-11.

[28] EX1008 (Alexander), ¶63 (emphases added).

B. Gu (EX1009)

56. Gu is International Patent Application No. WO2015/121783. The cover of Gu lists August 20, 2015 as its international publication date and it is titled "Immunogenic Glycoprotein Conjugates."[29]

57. Gu explains that its invention is directed to a vaccine composed of "glycoconjugates comprising a saccharide covalently conjugated to a carrier protein through a spacer."[30] 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."[31] Gu uses the word "glycoconjugates" to refer to the saccharide-carrier protein conjugates it describes.[32] The terms "conjugate" and "glycoconjugate" are used interchangeably in Gu.[33]

58. Gu also describes a number of carrier proteins that can be used to "increas[e] immunogenicity of poorly immunogenic molecules," including *S.*

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[29] EX1009 (Gu) at cover page, (43), (54).

[30] EX1009 (Gu) at 1:3-4.

[31] EX1009 (Gu) at 1:21-25.

[32] EX1009 (Gu) at 4:11-12.

[33] EX1009 (Gu) at 19:4-5.

pneumoniae capsular polysaccharides.[34] Specifically, Gu lists toxoids of "tetanus, diphtheria, pertussis, *Pseudomonas*, *E. coli*, *Staphylococcus*, and *Streptococcus*" as preferred carriers.[35]

59. Gu further discloses a number of specific pneumococcal (or Pn) serotypes to be included 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,"[36] where Pn refers to pneumococcal.[37]

C. The Serotype Prevalence References

60. As discussed above, for many years leading up to the priority date of March 31, 2016, epidemiological data regarding widely circulating *S. pneumoniae* serotypes had been compiled and published by public health agencies (particularly the Centers for Disease Control and Prevention (CDC) in the U.S., the European Centre for Disease Control and Prevention (ECDC), and the Public Health Agency of Canada (PHAC)), and would have been known to the POSA. Because it is

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[34] EX1009 (Gu) at 1:12-13, 11:17-18.

[35] EX1009 (Gu) at 36:14-19.

[36] EX1009 (Gu) at 11:23-25, 22:31-23:1 (emphases added).

[37] EX1009 (Gu) at 11:17.

naturally of interest to vaccine developers to provide protection against common serotypes of the *S. pneumoniae* bacterium, such information played an important role in vaccine development. As those references describe, the successful immunization of significant portions of the population using earlier generations of pneumococcal conjugate vaccines caused the prevalence of serotypes covered by those vaccines to diminish and the prevalence of other serotypes (not covered by those vaccines) to increase. I rely on several references that address common serotypes of *S. pneumoniae* in different geographical areas in the period leading up to the priority date.

1. Kaplan

61. Kaplan is an article published in 2015 in *Clinical Infectious Diseases*, another peer-reviewed medical journal addressing infectious agents and the diseases they cause.[38]

62. Kaplan addresses the prevalence of different serotypes of *S. pneumoniae* collected from children in the United States with otitis media (*i.e.*, ear infections) and mastoiditis (a complication of such infections involving the spread of the infection to the air cells of the skull).[39] As Kaplan states, "*Streptococcus*

[38] EX1015 (Kaplan) at 1339.

[39] EX1015 (Kaplan) at 1339.

pneumoniae is a common cause of otitis media (OM) in children; mastoiditis remains an important complication of OM."[40] Kaplan specifically addresses the impact of the 13-valent pneumococcal conjugate vaccine (PCV13) on the prevalence of *S. pneumoniae* serotypes.[41]

63. Kaplan highlights the threat of non-PCV13 serotypes, i.e., serotypes not covered by the 13-valent pneumococcal conjugate vaccine. Kaplan reports that the incidence of invasive pneumococcal disease (IPD) in children decreased in the United States following the routine administration of PCV13, and in serotypes newly included in PCV13 in particular.[42] Kaplan also discusses the way in which non-PCV7 serotypes "became important causes of AOM [acute otitis media, an infection of the middle ear] and mastoiditis" after the introduction of the PCV7 vaccine, and highlights the similar decrease in PCV13 serotypes (and total pneumococcal isolates) from in children with those conditions.[43]

64. Kaplan specifically highlights that serotypes 23A, 23B, and 35B are among the top ten most common non-PCV13 serotypes isolated from children in the

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[40] EX1015 (Kaplan) at 1339.

[41] EX1015 (Kaplan) at 1339-40.

[42] EX1015 (Kaplan) at 1343.

[43] EX1015 (Kaplan) at 1343-44.

"PCV13 era" from 2011 to 2013 (serotypes in descending order of prevalence: serotype 35B (n = 37), serotype 21 (n = 20), serotype 23B (n = 20), serotype 15B (n = 18), serotype 11 (n = 17), serotype 23A (n = 14), serotype 15A (n = 14), serotype 15C (n = 14), serotype 16 (n = 11), and serotype 31 (n = 10)).[44] More specifically, serotype 35B is the most common, serotype 23B is the second most common (tied with serotype 21), and serotype 23A is the sixth most common non-PCV13 serotypes isolated.[45]

2. Pilishvili

65. Pilishvili is an article that was published in 2010 in *The Journal of Infectious Diseases*, a peer-reviewed infectious disease journal.[46]

66. Pilishvili summarizes data on the incidence of *S. pneumoniae* serotypes in children and adults in the United States following widespread use of a 7-valent pneumococcal conjugate vaccine (or PCV7). Among other findings, Pilishvili reports significant reductions in invasive pneumococcal disease (or IPD) caused by serotypes included in the licensed 7-valent pneumococcal conjugate vaccine in

[44] EX1015 (Kaplan) at 1341-42, tbl.2.

[45] EX1015 (Kaplan) at 1339, 1341-42 & tbl.2.

[46] EX1016 (Pilishvili) at 32.

children and adults.[47] It also reports significant increases in the prevalence of IPD caused by serotypes other than PCV7-related serotypes, including 23A, 23B, and 35B across all age groups in the period between 1998 and 2007.[48]

3. Waight

67. Waight is an article that was published in 2015 in the journal *Lancet Infectious Diseases*.[49]

68. Waight summarizes data on the incidence of pneumococcal serotypes in England and Wales following the widespread use of a 13-valent pneumococcal conjugate vaccine.[50] Among other findings, Waight lists serotypes 23A, 23B, and 35B as among the top twenty-four 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.[51]

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[47] EX1016 (Pilishvili) at 32.

[48] EX1016 (Pilishvili) at 34-37, tbls.1-2.

[49] EX1017 (Waight) at 535.

[50] EX1017 (Waight) at 535-36.

[51] EX1017 (Waight) at 538, 540 & fig.3 & tbl.2.

4. ECDC

69. "Surveillance of invasive bacterial diseases in Europe, 2012" ("ECDC") is a report published by the European Centre for Disease Control and Prevention in 2015.[52]

70. ECDC lists serotypes found to cause pneumococcal infectious disease in Europe during 2012.[53] 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 multivalent conjugate vaccines.[54]

5. PHAC

71. "National Laboratory Surveillance of Invasive Streptococcal Disease in Canada: Annual Summary 2013" ("PHAC") is a report published by the Public Health Agency of Canada in December 2014.[55]

72. PHAC reports the status of streptococcal disease in Canada in 2013. Among other findings, PHAC notes that "[c]ontinued vigilance . . . is required to

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[52] EX1018 (ECDC) at ii, 1-2.

[53] EX1018 (ECDC) at 14-15, 23-24, & n.8 & fig.1.5.

[54] EX1018 (ECDC) at 15.

[55] EX1019 (PHAC) at 1.

recognize possible increases in other non-PCV13 serotypes circulating in Canada, such as serotype[s] . . . 23A and 23B."[56]

D. The Vaccine Recommendation References

73. Various published prior-art articles apply the epidemiological data that were available regarding different serotypes and use them to make specific recommendations regarding serotypes that would be beneficial to include in pneumococcal conjugate vaccines. I rely on several such articles (as well as one patent application, which I also understand to be prior art that would have been known to the POSA).

1. Porro

74. Porro is International Patent Application No. WO2014/118201 titled "Multivalent Glycoconjugate Vaccines." The cover of Porro lists August 7, 2014 as its international publication date.[57]

75. Porro is directed to conjugate vaccines against numerous diseases.[58] As part of its disclosure, Porro lists a number of "[n]ew emerging serotypes of *S. pneumoniae* according to the public available data on epidemiology and antibiotic

[56] EX1019 (PHAC) at 57.

[57] EX1010 (Porro) at cover page, (43).

[58] EX1010 (Porro) at 1:5-10.

resistance."[59] Porro highlights 23A and 35B as two of the eleven emerging serotypes that "might be likely included in a further up-dated broad-spectrum vaccine formulation," and suggests that such a formulation "might well elevate the bar on coverage to 75-80%."[60]

2. Al-Sherikh

76. Al-Sherikh is an article that was published in 2014 in the journal *Annals of Laboratory Medicine*.[61]

77. Al-Sherikh reports on emerging *S. pneumoniae* serotypes.[62] It reports that serotypes 23A and 23B were among the twenty most frequently occurring serotypes in pediatric pneumococcal diseases, and it recommends the addition of serotype 23A and 15 to future pneumococcal conjugate vaccines to improve the performance in invasive pneumococcal disease prevention.[63]

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[59] EX1010 (Porro) at 66:28-30.

[60] EX1010 (Porro) at 67:4-14.

[61] EX1011 (Al-Sherikh) at 210.

[62] EX1011 (Al-Sherikh) at 210.

[63] EX1011 (Al-Sherikh) at 210, 213-14, & fig.1.

3. Richter

78. Richter is an article that was published in 2014 in the journal *Antimicrobial Agents and Chemotherapy*.[64]

79. Richter concerns serotypes identified in penicillin-resistant *S. pneumoniae* strains.[65] It reports that 35B was among the three most common serotypes identified among such bacteria, and that serotypes 35B, 23A, and 23B showed proportional increases in prevalence.[66] Richter also notes that this information should inform future vaccine development.[67]

4. Wagenvoort

80. Wagenvoort is an article published in 2015 in the journal *Vaccine*.[68]

81. Wagenvoort examines the *S. pneumoniae* serotypes that are likely to cause serious disease in high-risk patients.[69] It reports that serotypes 23A and 23B were the two serotypes not included in the then-current multivalent vaccine that were

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[64] EX1013 (Richter) at 6484.

[65] EX1013 (Richter) at 6484.

[66] EX1013 (Richter) at 6484-86.

[67] EX1013 (Richter) at 6484, 6488.

[68] EX1014 (Wagenvoort) at 334.

[69] EX1014 (Wagenvoort) at 334-35.

most likely to cause disease in vulnerable populations, and recommends they be included in future vaccines.[70]

E. Lee

82. Lee is an article that was published in 2009 in *Clinical and Vaccine Immunology*.[71]

83. Lee explains that directly measuring the opsonizing ability of vaccine-induced antibodies provides a better estimate of protective immunity than simply measuring the concentrations of binding or total antibodies (e.g., with ELISA), because functional antibodies mostly contribute to the protection against pneumococcal disease by facilitating the phagocytosis (opsonization) of pneumococci.[72] Vaccines against *S. pneumoniae* stimulate functional antibodies that "opsonize," or tag, a bacterium, causing the bacterium to be engulfed (phagocytosis) and neutralized by a white blood cell.[73] Lee thus describes the use of an opsonization assay (OPA) to test the extent to which a vaccine induces antibodies that opsonize

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[70] EX1014 (Wagenvoort) at 334, 338-39.

[71] EX1020 (Lee) at 376.

[72] EX1020 (Lee) at 376-77.

[73] *See above*, ¶¶20-21.

bacteria.[74] Lee explains that this functional measurement is essential because ELISA results often fail to correlate with actual vaccine effectiveness against IPD and can be misleading in high-risk patients and older adults.[75] Lee highlights that functional assays like OPA are favored by regulatory agencies and recommends their use in evaluating pneumococcal vaccines.[76]

F. Anttila

84. Anttila is an article that was published in 1999 in the journal *Clinical and Experimental Immunology.*[77]

85. The study by Anttila and colleagues was designed to evaluate the contribution of various antibody characteristics (e.g., serotype-specific IgG concentration, subclasses, and avidity) to opsonophagocytic activity against *S. pneumoniae*.[78] Anttila reports that host protection against *S. pneumoniae* is predominantly mediated by opsonin-dependent phagocytosis, establishing opsonophagocytic activity as a key measure of antibodies' functional activity and a

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[74] EX1020 (Lee) at 376-77.

[75] EX1020 (Lee) at 380.

[76] EX1020 (Lee) at 380.

[77] EX1021 (Anttila) at 402.

[78] EX1021 (Anttila) at 402, 405-406.

better potential surrogate of *in vivo* protection than mere antibody concentration.[79] Anttila further 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 . . . ."[80]

G. PFL

86. Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) Prevnar® (the Prevnar® FDA Label, or "PFL") is an FDA label which provides a list of ingredients and other information pertaining to the 7-valent Prevnar® vaccine.[81] PFL was published on the FDA's website at the latest in October 2008.[82]

87. PFL explains that each 0.5 mL dose of the 7-valent Prevnar® vaccine contained 2 micrograms of each saccharide for six *S. pneumoniae* serotypes (4, 9V, 14, 18C, 19F and 23F), and 4 micrograms of serotype 6B (16 micrograms total saccharide); and approximately 20 micrograms of the carrier protein (CRM_{197}) per

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[79] EX1021 (Anttila) at 402.

[80] EX1021 (Anttila) at 402.

[81] EX1022 (PFL) at 1-3.

[82] EX1022 (PFL) at 30.

dose.[83] Prevnar® was administered as a 0.5 mL liquid dose to be given intramuscularly.[84] The routine schedule for administration in the United States was 2, 4, 6, and 12-15 months of age.[85]

H. Vesikari

88. Vesikari is an article that was published in 2009 in *The Pediatric Infectious Disease Journal*.[86]

89. Vesikari analyzes the immunogenicity of PHiD-CV (a 10-valent pneumococcal conjugate vaccine) compared to Prevnar® (a 7-valent pneumococcal conjugate vaccine).[87] Prevnar® and PhiD-CV vaccines were manufactured by different companies and involved *S. pneumoniae* serotypes conjugated to different carrier proteins.[88] PHiD-CV contains saccharides from *S. pneumoniae* conjugated to three different carrier proteins: eight serotypes are conjugated to non-typeable *H. influenzae* (NTHi) Protein D carrier protein, one serotype is conjugated to tetanus

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[83] EX1022 (PFL) at 1.

[84] EX1022 (PFL) at 1.

[85] EX1022 (PFL) at 11.

[86] EX1023 (Vesikari) at S66.

[87] EX1023 (Vesikari) at S66.

[88] EX1023 (Vesikari) at S67.

toxoid carrier protein, and one serotype is conjugated to diphtheria toxoid.[89] The data demonstrated noninferiority of PHiD-CV compared with Prevnar®.[90]

90. Vesikari also compares three dosing regimens: PHiD-CV administered in the primary series followed by a PHiD-CV booster dose; Prevnar® administered in the primary series followed by a Prevnar® booster dose; and Prevnar® administered in the primary series followed by a PHiD-CV booster dose.[91] 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.[92] The third regimen, in which the primary vaccine differed from the booster in its carrier protein, produced a more robust immunogenic response with respect to some serotypes than either of the other two regimens.[93]

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[89] EX1023 (Vesikari) at S67.

[90] EX1023 (Vesikari) at S67.

[91] EX1023 (Vesikari) at S67-68 & fig.1.

[92] EX1023 (Vesikari) at S67.

[93] EX1023 (Vesikari) at S73-75 & tbl.5.

IX. OVERVIEW OF GROUNDS OF UNPATENTABILITY

91. The following table provides an overview of how Alexander or Gu either anticipate or render obvious,[94] alone or in combination with other references, the Challenged Claims of the '757 patent:

Ground	35 U.S.C. §§ 102 or 103	Claim(s)	Prior Art
I	§102	1-2, 4-8, 11, and 15-19	Alexander
II	§103	1-9, 11-12, and 15-19	Alexander
III	§102	1, 3-6, 9, 11-12, 15, and 18-19	Gu
IV	§103	1, 3-6, 9, 11-12, 15, and 18-19	Gu
V	§103	1-9, and 11-19	Alexander or Gu, in view of the Serotype Prevalence References and/or the Vaccine Recommendation References.
VI	§103	6	Alexander or Gu, in view of Lee and/or Anttila
VII	§103	7 and 10	Alexander or Gu, in view of PFL
VIII	§103	2, 16 and 17	Alexander, in view of Vesikari and/or PFL

[94] I denote my anticipation grounds as § 102, referring to 35 U.S.C. § 102, which I have been informed is the statutory basis for invalidity based on anticipation, and my obviousness grounds as § 103, referring to 35 U.S.C. § 103, which I have been informed is the statutory basis for invalidity based on obviousness.

X. CLAIMS 1-19 OF THE '757 PATENT ARE UNPATENTABLE

A. Alexander anticipates claims 1-2, 4-8, 11, and 15-19 of the '757 patent (Ground I).

92. Alexander discloses each and every limitation as arranged in claims 1-2, 4-8, 11, and 15-19 of the '757 patent, as set forth below.

1. Claim 1

i. [1.Pre] "A pharmaceutical composition"[95]

93. Alexander discloses pharmaceutical compositions, namely vaccines.[96]

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

94. Alexander discloses a composition comprising at least two unique immunogenic saccharide-polypeptide conjugates, highlighting the need and ability to combine more than one serotype in order significantly address the burden of pneumococcal disease in children and adults.

95. As discussed above, in the context of pneumococcal conjugate vaccines, the POSA would understand a saccharide-polypeptide conjugate to mean

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[95] I have been told to assume that the preamble to Claim 1 is limiting, but my opinion as to the unpatentability of Claim 1 would remain the same regardless.

[96] EX1008 (Alexander), ¶¶104, 117.

a capsular saccharide from a serotype of *S. pneumoniae* conjugated to a carrier protein.

96. Alexander states that the "present invention provides compositions comprising a mixture of at least two Streptococcus *pneumoniae* capsular polysaccharides from different *Streptococcus pneumoniae* serotypes."[97] It also discloses embodiments in which "the compositions of the invention comprise a mixture of capsular polysaccharides from 2" up to "30 or more . . . serotypes."[98] 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."[99]

97. Alexander discloses, as explained further below, that these capsular polysaccharides are conjugated to carrier proteins.[100] Alexander further discloses that these carrier proteins are immunogenic.[101] The saccharide-polypeptide

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[97] EX1008 (Alexander), ¶9; *see also id.* at Claim 1.

[98] EX1008 (Alexander), ¶63

[99] EX1008 (Alexander), ¶10.

[100] EX1008 (Alexander), ¶9.

[101] EX1008 (Alexander), ¶¶61, 106, 126.

conjugates are unique because they comprise conjugates from different *S. pneumoniae* serotypes.

98. Alexander further discloses that these saccharide-polypeptide conjugates are immunogenic. It explains that "[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 as described herein."[102] Accordingly, Alexander discloses at least two unique immunogenic saccharide-polypeptide conjugates, as required by this claim limitation.

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

99. Alexander discloses a composition wherein each saccharide-polypeptide conjugate comprises individually a capsular polysaccharide conjugated to a polypeptide.

100. Alexander describes its invention as a group of serotypes "wherein the capsular polysaccharide from each serotype is [separately] conjugated to a separate polypeptide comprising a pan DR binding peptide sequence."[103] Alexander further

[102] EX1008 (Alexander), ¶105.

[103] EX1008 (Alexander), ¶9.

sets out exemplary peptides in which "the pan DR binding oligopeptide and the antigenic determinant are covalently attached to each other."[104]

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"

101. Alexander discloses multiple compositions comprising two or more capsular polysaccharides from serotypes 23A, 23B, and 35B, and thus anticipates claim 1.c.

102. Alexander discloses that "[i]n some embodiments, 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 includes "23A," "23B," and "35."[105] Additionally, Alexander discloses in dependent claims 2, 8 and 13 that the invention comprises *S. pneumoniae* "capsular polysaccharides from at least any five of the following serotypes . . . 23A, 23B, . . . 35 . . . ."[106]

103. The POSA would have understood that "35" is a reference to serogroup 35, which, at the time of Alexander's publication, was known to include three

[104] EX1008 (Alexander), ¶58.

[105] EX1008 (Alexander), ¶63.

[106] EX1008 (Alexander), 42:1-6, 43:1-6, 44:1-6.

serotypes: 35F, 35A, and 35B. The POSA would thus understand that the inclusion of serogroup 35 in the list encompasses serotype 35B. Elsewhere, Alexander makes clear that its disclosure encompasses serotype 35B.[107]

104. I have been informed that the word "comprising" means that a claim must include the following limitations, but may include other matter as well. Accordingly, I understand that Claim 1 encompasses all compositions containing at least two of the serotypes 23A, 23B, and 35B, each conjugated to a carrier protein, even if the overall pharmaceutical composition also includes other serotypes.

105. The POSA would therefore interpret Alexander's disclosure as encompassing compositions of 2 or more serotypes, up to 30 or more serotypes, selected from a list of serotypes that includes serotypes 23A, 23B, and 35B. To make a composition that meets the limitations of claim 1.c, the POSA would merely need to select two out of the three claimed serotypes from the serotypes disclosed in Alexander's list, and possibly include 28 or more additional serotypes.

106. Alexander anticipates claim 1.c. I have been informed that if a reference discloses embodiments that meet the limitations of a patent's claim, the reference anticipates the patent even if those embodiments appear without special emphasis as part of a longer list. Therefore, the POSA would understand that

[107] EX1008 (Alexander), ¶65.

Alexander's disclosure of compositions of 2 or more serotypes, up to 30 or more serotypes, selected from a list of serotypes that includes serotypes 23A, 23B, and 35B recited in limitation 1.c, anticipates that limitation.

107. Alexander also requires no further step on the part of the POSA to make an anticipating embodiment. All the POSA needs to do is select 2 or more serotypes, up to 30 or more serotypes, for a vaccine composition that includes any two of the three serotypes recited in limitation 1.c (all of which are in Alexander's disclosure). Thus, Alexander's disclosure would enable the POSA to envision how to make a great multitude of anticipating combinations.

2. Claim 2: "at least one polypeptide comprises a mixture of polypeptides"

108. Claim 2 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[108] Alexander also discloses the additional limitation of claim 2.

109. Claim 2 calls for at least one of the "polypeptide[s]" of claim 1 to "comprise[] a mixture of polypeptides."

110. Put differently, the composition contains conjugates made from more than one different polypeptide. This interpretation is consistent with claim 1: where claim 1 requires two or more polysaccharides conjugated to carrier proteins, but

[108] *See above*, ¶¶93-107.

allows all polysaccharides to be conjugated to identical carrier proteins, claim 2 adds the requirement that the composition include multiple different carrier proteins.

111. The POSA would also have reason to adopt this interpretation based on their background knowledge of vaccine development. The POSA would understand that the inclusion of multiple distinct carrier proteins can increase the immunogenicity of a vaccine composition.[109] Thus, the POSA would understand that the limitation of claim 2, as interpreted here, could improve the immunogenicity of the claimed vaccines.

112. Alexander anticipates claim 2 under this interpretation. It discusses "compositions comprising 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 pan DR binding peptide mixed with a capsular polysaccharide from a second serotype conjugated to a second (*same or different*) pan DR binding peptide)."[110] Alexander further discusses an embodiment involving "*Streptococcus* polysaccharide/pan DR binding peptide mixtures," thus suggesting to the POSA that there would even be reason to use a mixture of two different polypeptides conjugated to the same serotype to potentially increase

[109] EX1008 (Alexander), ¶84.

[110] EX1008 (Alexander), ¶34 (emphasis added).

immunogenicity.[111] Elsewhere, Alexander further explains that in some embodiments, "the peptides differ, e.g., a cocktail representing different viral subtypes [or] different epitopes within a subtype . . . ."[112] By disclosing embodiments where saccharides are conjugated to multiple different polypeptides, Alexander discloses embodiments involving a "mixture of polypeptides," thus anticipating claim 2.

113. Further, Alexander explains that the peptides involved in its invention can be modified in various ways to improve their functionality. It explains, "additional amino acids can be added to the termini of the peptides" to facilitate linking to the antigen, to couple to a carrier, or "for modifying the physical or chemical properties of the peptide."[113] Thus, a POSA would have understood from the disclosures of Alexander that different polypeptides may have different, pharmaceutically useful effects.

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[111] EX1008 (Alexander), ¶104.

[112] EX1008 (Alexander), ¶86.

[113] EX1008 (Alexander), ¶84.

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"

114. Claim 4 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[114] Alexander also discloses the additional limitation of claim 4.

115. Alexander discloses that the vaccine compositions of its invention "further typically include an adjuvant."[115] For aerosol administration, Alexander discloses that "the compositions of the present invention" are "supplied . . . along with a surfactant and propellant."[116] Alexander further discloses administering its "compositions [with] pharmaceutically acceptable auxiliary substances . . . such as buffering agents."[117] Additionally, Alexander discloses that the vaccines can be emulsified in incomplete Freund's adjuvant (CFA/IFA), which was known to contain an emulsifier.[118] Further, Alexander discloses that aluminum salts are used as

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[114] *See above*, ¶¶93-107.

[115] EX1008 (Alexander), ¶105.

[116] EX1008 (Alexander), ¶123.

[117] EX1008 (Alexander), ¶117.

[118] EX1008 (Alexander), ¶¶101, 130, 140.

adjuvants in vaccines, such as aluminum hydroxide, aluminum phosphate, or alum.[119]

116. I have been informed that because claim 4 sets out multiple excipients in the alternative, the disclosure of compositions containing any one of the excipients is sufficient to anticipate this claim. Accordingly, any one of these disclosures in Alexander anticipates claim 4.

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"

117. Claim 5 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[120] Alexander also discloses the additional limitation of claim 5.

118. Claim 5 sets out routes of administering a vaccine that were well known in the art. Alexander discloses each of these routes. It notes, "[t]ypically, the pharmaceutical compositions are administered parenterally, e.g., intravenously, subcutaneously, intradermally, or intramuscularly."[121] Alexander also discloses an

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[119] EX1008 (Alexander), ¶105.

[120] *See above*, ¶¶93-107.

[121] EX1008 (Alexander), ¶117.

intranasally administrable form, describing "aerosol administration" of its compositions and observing that "[a] carrier can [] be included, if desired, as with lecithin for intranasal delivery."[122]

119. Because claim 5 sets out these forms in the alternative, I understand that Alexander's disclosure of any one form within the claim is sufficient to anticipate this claim. As all of these well-known delivery routes were disclosed in Alexander, Alexander thus anticipates claim 5. The POSA would also have understood, from their background knowledge of the field, that pneumococcal conjugate vaccines had been successfully administered intramuscularly, but that other methods of delivery were also possible.[123]

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

120. Claim 6 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[124] Among other limitations, Alexander

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[122] EX1008 (Alexander), ¶123.

[123] *See above*, ¶32; EX1024 (Yeh) (discussing subcutaneous delivery); EX1034 (Jakobsen) (discussing intranasal delivery).

[124] *See above*, ¶¶93-107.

discloses conjugates that elicit an immunogenic response.[125] Alexander also discloses the additional limitation of claim 6.

121. Alexander states that the "present invention is useful for eliciting an immune response, typically, a humoral response, to antigenic determinants of a carbohydrate immunogen, and in particular *Streptococcus pneumonia* capsular polysaccharides."[126] Humoral response is defined in Alexander as "an antibody-mediated immune response directed towards various regions of an antigenic determinant."[127] The POSA would have understood from their background knowledge that an immunogenic pneumococcal vaccine (conjugated or unconjugated to a carrier protein) generates antibodies, which in turn cause the opsonophagocytosis of *S. pneumoniae* bacteria.[128] Accordingly, the POSA would

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[125] *See above*, ¶97.

[126] EX1008 (Alexander), ¶34.

[127] EX1008 (Alexander), ¶26.

[128] EX.1028 (Hu) at 287 ("*Streptococcus pneumoniae* (pneumococcus) polysaccharide serotype-specific antibodies that have opsonophagocytic activity are considered a primary mechanism of host defense against pneumococcal disease."); EX1029 (Romero-Steiner) at 165 (a pneumococcal "conjugate vaccine elicits antibodies to pneumococcal capsular polysaccharide, and these antibodies

have understood that by disclosing immunogenic conjugates, Alexander necessarily discloses conjugates that elicit an opsonophagocytic response, thus anticipating claim 6.

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"

122. Claim 7 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[129] Alexander also discloses the additional limitation of claim 7.

123. Alexander discloses embodiments that fall within the weight limitation of claim 7. It observes that "[t]he concentration of compositions of the present invention . . . can vary . . . from less than about 0.1%, usually at or at least about 2% to as much as 20% to 50% or more by weight . . . ."[130] 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%."[131]

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protect the host by opsonizing pneumococci and thus facilitating phagocytosis.").

[129] *See above*, ¶¶93-107.

[130] EX1008 (Alexander), ¶118.

[131] EX1008 (Alexander), ¶123.

124. By disclosing a range of concentrations that fall within claim 7's range—again, claim 7 recites a minimum concentration of .001% and no maximum concentration—Alexander anticipates this claim.

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"

125. Claim 8 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[132] Alexander also discloses the additional limitation of claim 8.

126. As I have explained above, the POSA would have understood that a capsular polysaccharide corresponding to a *S. pneumoniae* serotype could have been linked to a carrier protein in multiple ways, and that certain methods of linking could enhance the immunogenic effect of the resulting vaccine composition.[133] In any event, Alexander expressly discloses this concept. It explains that the polysaccharide comprising a *S. pneumoniae* serotype can be connected to the polypeptide "using a variety of linkers . . . [including] [c]rosslinking agents."[134] The

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[132] *See above*, ¶¶93-107.

[133] *See above*, ¶28; EX1030 (Costantino) at 1052.

[134] EX1008 (Alexander), ¶92.

use of a "crosslinking agent," in this context, means "chemically cross-linked," and thus satisfies the limitations of claim 8. (Because claim 8 sets out its limitations in the alternative ("and/or"), I understand that Alexander's disclosure of any one limitation is sufficient for anticipation.)

127. 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." The degree of cross-linking typically refers to the number of covalent bonds formed between a carrier protein and a polysaccharide antigen. It is well known that both insufficient and excessive cross-linking can compromise the vaccine-induced immune response and therefore the vaccine effectiveness.[135] So long as a polysaccharide is "connected" 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 necessarily falls within the scope of the claim. Alexander's disclosure of "connect[ing] [the serotype] to the polypeptide" using "[c]rosslinking agents" anticipates regardless of whether the resulting linkage leads to a polysaccharide that

[135] EX1037 (Lees); EX1030 (Costantino).

is "chemically cross-linked" (i.e., "(ii)") or "partially chemically cross-linked" (i.e., "(iii)").

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

128. Claim 11 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[136] Alexander also discloses the method of claim 11.

129. Alexander discloses using the composition it describes by "administering to the mammal a mixture of at least two *Streptococcus pneumoniae* capsular polysaccharides . . . ."[137] As discussed above, such a mixture disclosed by Alexander satisfies the limitations of claim 1, anticipating the limitation of claim 11.[138]

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

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[136] *See above*, ¶¶93-107.

[137] EX1008 (Alexander), ¶10.

[138] *See above*, ¶¶93-107.

130. Claim 15 depends from claim 11. As I have explained above, Alexander anticipates the method of claim 11.[139] Alexander also discloses the additional limitation of claim 15.

131. Alexander discloses "pharmaceutical compositions [that] are administered parenterally, e.g., intravenously, subcutaneously, intradermally, or intramuscularly."[140] Accordingly, Alexander anticipates claim 15.

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"

132. Claim 16 depends from claim 11. Alexander anticipates the method of claim 11, as discussed above.[141] Alexander also discloses the additional limitation of claim 16.

133. Alexander discloses the possibility of a second (or booster) dose, 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

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[139] *See above*, ¶¶128-29.

[140] EX1008 (Alexander), ¶117.

[141] *See above*, ¶¶128-29.

individual."[142] The POSA would have understood that such "boosting doses" would also comprise the immunogenic saccharide-polypeptide conjugates disclosed in Alexander, as discussed above. Alexander therefore discloses administering the first composition of claim 16 "at least about four weeks before . . . an administration of a second composition comprising an immunogenic saccharide-polypeptide conjugate." Claim 16 is thus anticipated by Alexander.

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."

134. Claim 17 depends from claim 16, and it further specifies that the second composition comprises a capsular polysaccharide from a serotype of *Streptococcus pneumoniae* conjugated to a second polypeptide. The specification of the '757 patent expressly states that the second polypeptide (of the second composition's conjugate) can be the same polypeptide as the first polypeptide.[143] The specification also makes clear that the second composition's conjugate is, like the first composition's, a conjugate of that polypeptide with a *Streptococcus pneumoniae*

[142] EX1008 (Alexander), ¶116.

[143] EX1001 ('757 patent) at col.48, ll.7-18.

polysaccharide (though the serotypes may differ).[144] Accordingly, claim 17 is anticipated for the same reasons, and by the same disclosures in Alexander, as claim 16.

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

135. Claim 18 depends from claim 11. As I have explained above, Alexander anticipates the method of claim 11.[145] Alexander also discloses the additional limitation of claim 18.

136. Specifically, Alexander discloses administering pharmaceutical compositions to a human subject. For example, it says, "[t]he compounds of the present invention, and pharmaceutical and vaccine compositions thereof, can be administered to . . . humans, for prophylactic and/or therapeutic purposes."[146] Alexander further states, "[t]hese data clearly demonstrate that the increase in immunogenicity associated with conjugation of the polysaccharide to the pan DR binding peptide and its compatibility with formulation formats that can be used for human vaccine products."[147]

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[144] EX1001 ('757 patent) at col.50, ll.25-37; EX1001 at cols.47-52.

[145] *See above*, ¶¶128-29.

[146] EX1008 (Alexander), ¶104.

[147] EX1008 (Alexander), ¶138.

137. The POSA would have understood from the disclosure of Alexander as a whole that it is directed to developing vaccines to prevent human disease. For example, Alexander explains that "[i]n some embodiments, *Streptococcus* polysaccharide/pan DR binding peptide conjugates of the invention are used to treat . . . [symptoms] associated with infection of *humans* . . . with *Streptococcus pneumoniae*."[148] The POSA would further have understood from their background knowledge in the field that *S. pneumoniae* is a human pathogen which spreads via human vectors. Accordingly, the disclosures of Alexander would have given the POSA reason to develop the disclosed compositions as human treatments, thus anticipating claim 18.

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"

138. Claim 19 depends from claim 1. As I have explained above, Alexander anticipates the composition of claim 1.[149] Alexander also discloses the method of claim 19.

139. Alexander discloses the possibility of combining the claimed conjugates with an excipient and an adjuvant. For example, Alexander explains:

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[148] EX1008 (Alexander), ¶104.

[149] *See above*, ¶¶93-107.

"For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating . . . [an] excipient[] . . . ."[150] Alexander further discloses that vaccine formulations of its disclosed compositions "typically include an adjuvant."[151]

140. Moreover, the POSA would have known, from their background knowledge of the field, that multiple adjuvants, surfactants, and buffering agents would have been appropriate for inclusion in a pneumococcal vaccine composition.[152] The POSA would have understood from the disclosure of Alexander that a vaccine composition typically includes multiple inactive ingredients to stabilize or enable the administration of the composition. Accordingly, the disclosures of Alexander anticipate claim 19.

B. Alexander renders obvious claims 1-9, 11-12 and 15-19 of the '757 patent (Ground II).

141. Alexander renders obvious claims 1-9, 11-12, and 15-19 to the POSA, in light of the teachings of Alexander, to formulate each of the above claims.

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[150] EX1008 (Alexander), ¶122.

[151] EX1008 (Alexander), ¶105.

[152] *See above*, ¶33; EX1036 (Giudice); EX1035 (Sogaard).

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

142. I understand that because Alexander anticipates claims 1-2, 4-8, 11, and 15-19 as discussed above in Section X.A., Alexander likewise renders obvious these claims.

143. In the alternative, claim 1 would have been obvious to the POSA in light of Alexander. As I have discussed above, Alexander discloses the limitation of claim 1.[153] And as to limitation 1.c, as explained above in §X.A.1.iv., Alexander discloses that should the POSA follow Alexander's teaching and make a vaccine composition including 2 or more serotypes, up to 30 or more serotypes, even if the POSA were to choose serotypes at random, a substantial percentage of those compositions would meet limitation 1.c. However, the POSA would not have selected serotypes at random. Instead, the POSA would have understood from the teachings of Alexander 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.[154] In addition, as I will explain in greater detail below, each of

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[153] *See above*, ¶¶93-107.

[154] EX1008 (Alexander), ¶7 ("Current pneumococcal vaccine formulations are combination vaccines containing a mixture of the capsular polysaccharides from

serotypes 23A, 23B, and 35B was identified in the prior art as being among the most prevalent serotypes causing pneumococcal diseases after widespread use of Prevnar 13® and thus strong candidates for inclusion in future pneumococcal conjugate vaccines.[155]

144. The POSA would therefore have been motivated to include, in the vaccine composition disclosed in Alexander, at least two, if not all three, serotypes recited in limitation 1.c—23A, 23B, and 35B. The POSA would also have reasonably expected, based on Alexander, to succeed in making such a composition. Thus, Alexander alone renders claim 1 obvious.

2. Claim 3: "wherein at least one polypeptide of the plurality comprises CRM_{197}, 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

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the more common serotypes and are effective against invasive disease in older children and adults.").

[155] *See below*, ¶¶199-216.

tuberculin(PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

145. Claim 3 depends from claim 1. As I have explained above, Alexander anticipates, or in the alternative renders obvious, the composition of claim 1.[156] Alexander also renders obvious the additional limitation of claim 3.

146. Alexander discloses capsular polysaccharides that are conjugated to carrier proteins—the pan DR binding peptide sequence.[157] However, Alexander also teaches that a pneumococcal conjugate vaccine was available having "a seven-valent formulation [consisting of capsular polysaccharides from 7 serotypes, each conjugated] to a nontoxic diphtheria variant (CRM_{197}) PREVNAR® from Wyeth."[158] The POSA would therefore have understood CRM_{197} to be a known, alternative polypeptide to the pan DR binding peptide sequence that could be conjugated to the capsular polysaccharides of claim 1. And because that polypeptide had been successfully used in a commercially available vaccine, and it was therefore part of an established approach to making pneumococcal conjugate vaccines, the POSA would have had a reason to use CRM_{197} as an alternative to the pan DR binding peptide in Alexander's examples.

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[156] *See above*, ¶¶93-107, 142-44.

[157] EX1008 (Alexander), ¶9.

[158] EX1008 (Alexander), ¶8.

147. For similar reasons, the POSA would have had a reasonable expectation of success in using CRM_{197}; it had been used before in a similar context to make a pneumococcal conjugate vaccine composition, and indeed one that was shown to be clinically effective against pneumococcal disease. Thus, claim 3 would have been obvious over Alexander.

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

148. Claim 9 depends from claim 1. As I have explained above, Alexander anticipates, or in the alternative renders obvious, the composition of claim 1.[159] As I also explained above, Alexander renders obvious claim 3, because it would have been obvious to use CRM_{197} as an alternative to the pan DR binding peptide sequence. Claim 9 would have been obvious for the same reasons. As I have explained above, a toxoid is a modified toxin from a pathogenic microorganism whose toxin activity has been mitigated.[160] CRM_{197} is such a toxoid; it is a non-toxic, variant form of diphtheria toxin. Therefore, in a formulation containing CRM_{197}, "a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated" as claim 9 requires, and so claim 9 would have been obvious over Alexander as well.

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[159] *See above*, ¶¶93-107, 142-44.

[160] *See above*, ¶24.

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"

149. Claim 12 depends from claim 1. As I have explained above, Alexander anticipates, or in the alternative renders obvious, the composition of claim 1.[161] Alexander also renders obvious the additional limitation of claim 12.

150. Alexander discloses embodiments comprising "a mixture of conjugates . . . with capsular polysaccharides from 2, 3 . . . or more of the following serotypes," and then lists a group of serotypes including serotypes 23A, 23B and 35B recited in claim 1, along with serotypes 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20, 22F, and 34 recited in claim 12.[162] Thus, claim 12 would have been obvious to the POSA in light of Alexander. Alexander expressly suggests including the serotypes listed in claim 12 in a vaccine composition. The POSA would have understood that including additional, specific serotypes can broaden the disease coverage of a vaccine, and would thus have been motivated to include the serotypes recited in claim 12 and disclosed in Alexander. The POSA would have reasonably expected, based on this

[161] *See above*, ¶¶93-107, 142-44.

[162] EX1008 (Alexander), ¶63.

reference and the longstanding trend in the art toward including more serotypes, to succeed in making such a composition.

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

151. Gu discloses each and every limitation as arranged in claims 1, 3-6, 9, 11-12, 15, and 18-19 of the '757 patent.

1. Claim 1

i. [1.Pre] "A pharmaceutical composition"

152. Gu states that the field of its invention relates to "immunogenic compositions,"[163] and defines "immunogenic composition" as "any pharmaceutical composition containing an antigen . . . which can be used to elicit an immune response in a subject."[164] Gu further discloses a number of embodiments in which "the glycoconjugates of the invention [are] used in the production of immunogenic compositions."[165]

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

153. Gu discloses this limitation. For example, Gu explains that "[t]he immunogenic compositions of the invention may [] comprise . . . a plurality of

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[163] EX1009 (Gu) at 1:7.

[164] EX1009 (Gu) at 51:19-21.

[165] EX1009 (Gu) at 12:15-17.

capsular polysaccharide-protein conjugates."[166] Gu also contemplates vaccine compositions containing multiple conjugates, explaining that "[t]he immunogenic amount of the different polysaccharide components in an immunogenic composition may diverge . . . ."[167] Further, claim 25 of Gu recites "[a]n immunogenic composition comprising *at least one* glycoconjugate."[168] This is a teaching of compositions that comprise at least two saccharide-polypeptide conjugates. 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.

154. Gu further discloses that these glycoconjugates are immunogenic. Gu is titled "Immunogenic Glycoprotein Conjugates," and it explains that it is directed to "immunogenic compositions" comprising glycoconjugates of saccharides and carrier proteins.[169] Gu further states that "[g]lycoconjugates of the invention

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[166] EX1009 (Gu) at 57:11-12.

[167] EX1009 (Gu) at 63:9-10.

[168] EX1009 (Gu) at 123:9-11 (emphasis added).

[169] EX1009 (Gu) at cover page, (54).

comprising a bacterial capsular polysaccharide can be used in the production of antibodies against such a bacterial capsular polysaccharide."[170] 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 conjugate vaccine development.

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

155. Gu explains that its immunogenic composition includes glycoconjugates comprising "a saccharide covalently conjugated to a carrier protein."[171] It discloses embodiments in which the saccharide in this formulation is a capsular polysaccharide, *i.e.*, a saccharide obtained from a *S. pneumoniae* serotype.[172]

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"

156. Gu describes specific 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," where the POSA would

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[170] EX1009 (Gu) at 30:32-31:2.

[171] EX1009 (Gu) at 29:15-17.

[172] EX1009 (Gu) at 11:17-25, 22:31-23:1, 58:20-25.

understand that "Pn" refers to pneumococcal.[173] Gu also discloses additional embodiments where "the Pn capsular polysaccharide is selected from the group consisting of Pn-serotype 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 9N, 10A, I IA, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20, 22F**, 23A, 23B**, 23F, 33F and **35B** capsular polysaccharides."[174]

157. I have been informed that the word "comprising" means that a claim must include the following limitations, but may include other matter as well. Accordingly, I understand that claim 1 encompasses all compositions of at least two of the serotypes 23A, 23B, and 35B, even if those compositions also include other serotypes.

158. The POSA would understand that Gu discloses, for example, a composition comprising serotypes 23A and 23B, each conjugated to a carrier protein, which would meet limitation 1.c. Gu therefore anticipates limitation 1.c.

159. Further, the POSA would understand that Gu discloses compositions including glycoconjugates with capsular polysaccharides from multiple serotypes, including the ones recited in limitation 1.c. For example, Gu recites a list of 28 serotypes from which its pharmaceutical composition can be drawn, including all

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[173] EX1009 (Gu) at 11:23-25; 13:5-7; 22:31-23:1 (emphases added).

[174] EX1009 (Gu) at 12:27-13:2; 22:25-31 (emphases added).

the serotypes listed in claim 1.[175] Accordingly, the POSA would understand that Gu discloses a host of compositions which comprise glycoconjugates with at least two of the three serotypes listed in limitation 1.c. In light of Gu's express contemplation of compositions comprising multiple serotypes,[176] and its disclosure of specific embodiments drawn from only 8 serotypes—including all three of serotypes 23A, 23B, and 35B—the POSA would at once envisage a vaccine composition containing at least two of the required serotypes.

2. Claim 3: "at least one polypeptide of the plurality comprises CRM_{197}, 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"

160. Claim 3 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[177] Gu also discloses the additional limitation of claim 3.

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[175] EX1009 (Gu) at 11:18-21, 22:30-31.

[176] *See above*, ¶153.

[177] *See above*, ¶¶152-59.

161. Gu lists numerous embodiments in which the protein carrier conjugated to the *S. pneumoniae* saccharide consists of "toxins, toxoids or any mutant cross-reactive material (CRM) of the toxin from tetanus, diphtheria, pertussis . . . and *Streptococcus*."[178] It further discloses an embodiment in which the "carrier is of diphtheria toxoid CRM_{197}."[179] Gu further discloses an embodiment in which the carrier is selected from a group which includes, amongst other carriers, CRM_{197}, TT (tetanus toxoid) or fragment of TT, DT (diphtheria toxoid), cholera toxoid, pertussis proteins, pneumococcal pneumolysn, pneumococcal surface protein PspA, pneumococcal adhesion protein (PsaA), keyhole limpet hemocyanin (KLH), OMPC (meningococcal outer membrane protein—usually extracted from N. meningitidis serogroup B), purified protein derivative of tuberculin (PPD), and PD (Haemophilus influenzae protein D).[180]

162. I have been informed that because claim 3 sets out these carrier protein candidates in the alternative, Gu's disclosure of any one of the carriers within the claim is sufficient for anticipation.

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[178] EX1009 (Gu) at 36:15-18.

[179] EX1009 (Gu) at 36:18-19.

[180] EX1009 (Gu) at 37:4-38:2.

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"

163. Claim 4 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[181] Gu also discloses the additional limitation of claim 4.

164. Gu explains that "[i]n some embodiments, the immunogenic compositions comprise an adjuvant."[182] 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.[183] Gu further states that in other embodiments, "a formulation of the invention . . . comprises one or more non-ionic surfactants."[184] Gu describes a specific embodiment formulated in a buffering agent, specifically

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[181] *See above*, ¶¶152-59.

[182] EX1009 (Gu) at 13:28.

[183] EX1009 (Gu) at 55:13-17.

[184] EX1009 (Gu) at 57:22.

sodium succinate buffer.[185] And Gu states that the invention "may further comprise one or more preservatives."[186]

165. Moreover, the POSA would have known, from his or her background knowledge of the field, that multiple adjuvants, surfactants, emulsifiers, buffering agents, preservatives, and/or salts would have been appropriate for inclusion in a pneumococcal vaccine composition.[187]

166. As I have explained above with respect to Alexander,[188] any of these disclosures in Gu are sufficient to anticipate claim 4.

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"

167. Claim 5 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[189] Gu also discloses the additional limitation of claim 5.

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[185] EX1009 (Gu) at 58:20-25.

[186] EX1009 (Gu) at 57:11-12.

[187] *See above*, ¶33; EX1036 (Giudice); EX1035 (Sogaard).

[188] *See above*, ¶¶114-16.

[189] *See above*, ¶¶152-59.

168. Gu 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."[190] Gu therefore expressly discloses the additional limitation of claim 5, and in fact expressly discloses each of the options for a route of administration that claim 5 recites.

169. As I have explained with respect to Alexander,[191] any of these disclosures in Gu is sufficient to anticipate claim 5.

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

170. Claim 6 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[192] Among other limitations, Gu discloses glycoconjugates that elicit an immunogenic response.[193] Gu also discloses the additional limitation of claim 6.

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[190] EX1009 (Gu) at 57:31-58:3.

[191] *See above*, ¶¶117-19.

[192] *See above*, ¶¶152-59.

[193] *See above*, ¶154.

171. Gu expressly discloses embodiments wherein the conjugates elicit an opsonophagocytic response. 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."[194] Gu further states that in some embodiments, "the antibodies produced against bacterial polysaccharides are functional . . . in an opsonophagocytic killing assay."[195]

172. The POSA would have understood from their background knowledge that an immunogenic pneumococcal vaccine (conjugated or unconjugated to a carrier protein) generates antibodies, which in turn cause the opsonophagocytosis of *S. pneumoniae* bacteria.[196] Accordingly, the POSA would have understood that by

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[194] EX1009 (Gu) at 30:30-32.

[195] EX1009 (Gu) at 31:4-6.

[196] EX1028 (Hu) at 287 ("*Streptococcus pneumoniae* (pneumococcus) polysaccharide serotype-specific antibodies that have opsonophagocytic activity are considered a primary mechanism of host defense against pneumococcal disease."); EX1029 (Romero-Steiner) at 165 (a pneumococcal "conjugate vaccine elicits antibodies to pneumococcal capsular polysaccharide, and these antibodies

disclosing immunogenic conjugates, Gu necessarily discloses conjugates that elicit an opsonophagocytic response, thus anticipating claim 6.

173. Additionally, the POSA would have understood from Gu that opsonophagocytosis is the mechanism by which a pneumococcal capsular polysaccharide-based vaccine kills *S. pneumoniae* and thus protects the host. For example, Gu states that "opsonizing 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."[197] The POSA would therefore have understood that by disclosing immunogenic saccharide-polypeptide conjugates, Gu thus discloses conjugates that elicit an opsonophagocytic response and anticipates claim 6.

6. Claim 9: "wherein a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated"

174. Claim 9 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[198] Gu also discloses the additional limitation of claim 9.

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protect the host by opsonizing pneumococci and thus facilitating phagocytosis.").

[197] EX1009 (Gu) at 54:15-18.

[198] *See above*, ¶¶152-59.

175. Gu discloses the use of toxoids or any mutant-cross reactive material (CRM) of the toxin from various bacteria, including tetanus and diphtheria, as carrier proteins for the capsular polysaccharide.[199] As I have explained above, a toxoid is a modified toxin from a pathogenic microorganism whose toxin activity has been mitigated.[200] Gu explains as much, noting that "suitable carrier proteins include *inactivated bacterial toxins* such as cholera toxoid."[201] Further, Gu discloses CRM_{197}, which is a non-toxic, mutant form of diphtheria toxin.[202] Gu thus discloses polypeptides wherein the toxin activity is mitigated.

176. The POSA would have understood from the disclosure of Gu that the carrier proteins of pneumococcal vaccine compositions are typically inactivated—indeed, the POSA would have known that this is necessary to prevent them from harming the subject. Accordingly, as the POSA would have understood to use polypeptides with at least partly mitigated toxin activity based on the disclosures of Gu, claim 9 is anticipated.

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[199] EX1009 (Gu) at 36:15-18.

[200] *See above*, ¶24.

[201] EX1009 (Gu) at 37:35 (emphasis added).

[202] EX1009 (Gu) at 36:17-19.

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

177. Claim 11 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[203] Gu also discloses the additional limitation of claim 11.

178. Gu explains, "one aspect of 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 . . . ."[204] As discussed above, such immunogenic compositions satisfy the limitations of claim 1.[205]

179. As I have explained above with respect to Alexander,[206] any of these disclosures in Gu is sufficient to anticipate claim 11.

8. 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

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[203] *See above*, ¶¶152-59.

[204] EX1009 (Gu) at 60:8-12.

[205] *See above*, ¶¶152-59.

[206] *See above*, ¶¶128-29.

6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34"

180. Claim 12 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[207] Gu also discloses the additional limitation of claim 12.

181. 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-serotypes" 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 claim 12.[208]

182. I have been informed that the word "comprising" means that a claim must include the following limitations, but may include other matter as well. Accordingly, I understand that claim 12 encompasses compositions that include two or more of the serotypes 23A, 23B, and 35B, and at least one additional serotype selected from 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34, even if those compositions also include other serotypes. I also have been informed that the phrase "at once envisaging" is used in court cases to

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[207] *See above*, ¶¶152-59.

[208] EX1009 (Gu) at 12:27-13:4.

describe a situation in which a class of possible options is sufficiently defined and limited that the POSA would immediately bring it to mind and consider it. By this definition, based on the disclosure of Gu, a POSA would "at once envisage" a pharmaceutical composition that includes at least two of serotypes 23A, 23B, and 35B with at least one additional serotype picked from among 8, 9N, 10A, 11A, 12F, 15A, 15B, 20, and 22F.

183. Gu therefore anticipates claim 12.

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

184. Claim 15 depends from claim 11. As I have explained above, Gu anticipates the composition of claim 11.[209] Gu also discloses the additional limitation of claim 15.

185. Gu states, "[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) . . . ."[210]

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[209] *See above*, ¶¶152-59.

[210] EX1009 (Gu) at 57:31-58:3.

186. As I have explained with respect to Alexander,[211] any of these disclosures is sufficient to anticipate claim 15.

10. Claim 18: "The method of claim 11 wherein the subject is a human"

187. Claim 18 depends from claim 11. As I have explained above, Gu anticipates the composition of claim 11.[212] Gu also discloses the additional limitation of claim 18.

188. Gu also discloses a method for administering the compounds to humans. For example, it observes, "[i]n certain embodiments, the dose is formulated for administration to a human subject."[213]

189. As I have explained above with respect to Alexander,[214] any of these disclosures is sufficient to anticipate claim 18.

11. 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"

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[211] *See above*, ¶¶130-31.

[212] *See above*, ¶¶177-79.

[213] EX1009 (Gu) at 59:12-13.

[214] *See above*, ¶¶135-37.

190. Claim 19 depends from claim 1. As I have explained above, Gu anticipates the composition of claim 1.[215] Gu also discloses the method of claim 19.

191. Gu discloses the combination of conjugates recited in claim 1 with an adjuvant, noting, "[i]n some embodiments, the immunogenic compositions comprise an adjuvant."[216]

192. Moreover, the POSA would have known, from their background knowledge of the field, that multiple excipients and/or adjuvants would have been appropriate for inclusion in a pneumococcal vaccine composition.[217]

193. As I have explained above with respect to Alexander,[218] any of these disclosures is sufficient to anticipate claim 19.

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

194. I understand that because Gu anticipates Claims 1, 3-6, 9, 11-12, 15, and 18-19 as discussed above in Section X.C., Gu likewise renders obvious these claims.

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[215] *See above*, ¶¶152-59.

[216] EX1009 (Gu) at 13:29; 14:19-31.

[217] *See above*, ¶33; EX1036 (Giudice); EX1035 (Sogaard).

[218] *See above*, ¶140.

195. Alternatively, claim 1 and claim 12 would have been obvious to the POSA in light of Gu. As I have discussed above, Gu discloses the limitation of claim 1 and claim 12.[219] Regarding limitations 1.c of claim 1 and claim 12 of the '757 patent, it would have been obvious to the POSA, in light of the teachings of Gu, to formulate a composition with saccharide-polypeptide conjugates comprising capsular polysaccharides from the serotypes listed in limitation 1.c of claim 1 or in claim 12. In a list of only eight preferred serotypes (2, 9N, 15A, 17F, 20, 23A, 23B, and 35B), Gu expressly teaches all three of the serotypes recited in claim 1.c—23A, 23B, and 35B—as well as three of the serotypes recited in claim 12—9N, 15A, and 20.[220] The POSA would have understood that increasing the number of serotypes in a pneumococcal vaccine would broaden its disease coverage. The POSA would therefore have been motivated to include these additional serotypes from the preferred list disclosed in Gu in such a vaccine composition, including the ones recited in limitation 1.c and claim 12. Indeed, it would have been obvious to include all eight of the serotypes disclosed in one list in Gu, as the skilled artisan would have recognized as of the priority date that adding eight serotypes to prior art

[219] *See above*, ¶¶152-59, 180-82.

[220] EX1009 (Gu) at 11:23-25, 22:31-23:1.

pneumococcal conjugate vaccines would have been manageable to do.[221] The POSA 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. In addition, as I explained earlier in Ground II, each of serotypes 23A, 23B, and 35B was identified in the prior art as being among the most prevalent serotypes causing pneumococcal diseases after widespread use of PCV13, and thus strong candidates for inclusion in future vaccines.[222] Gu thus renders claim 1 and 12 obvious, as well as the remaining claims which depend on claim 1.

E. 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 (Ground V).

196. Each of claims 1, 12, 13, and 14 includes limitations directed to the selection of particular serotypes to use in the claimed vaccine compositions. The remaining claims 2-9, 11, and 15-19 include various generic limitations that, as discussed above, were disclosed in Alexander or Gu, or else were well known in the art of making pneumococcal conjugate vaccines.[223]

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[221] *Compare* EX1008 (Alexander), ¶63 (teaching "30 or more" serotypes in a single vaccine).

[222] *See above*, ¶143.

[223] *See above*, ¶¶108-40, 145-48, 160-79, 183-92.

197. As I have explained, the leading serotypes causing invasive pneumococcal diseases are provided regularly in disease surveillance reports from many countries.[224] An analysis of pneumococcal serotype distribution causing invasive and non-invasive pneumococcal diseases over a period of multiple years would have given the POSA a good insight about trends, persistence, antibiotic resistance, 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 conjugate vaccines. Each of the Serotype Prevalence References—Kaplan, Pilishvili, Waight, ECDC, and PHAC—provides such information, and individually and collectively would have given the POSA reasons to select the particular additional serotypes that are recited in claims 1, 12, 13, and 14, as I discuss in this section.

198. As several publications further expressly state, and as the POSA would have recognized, serotypes that were particularly common—and especially serotypes that had become more common in the wake of earlier pneumococcal vaccination campaigns—would have been good candidates for inclusion in future pneumococcal vaccines. For convenience, I have called these additional references the Vaccine Recommendation References—Porro, Al-Sherikh, Richter, and

[224] *See above*, ¶29.

Wagenvoort. They, too, individually, collectively, and together with the Serotype Prevalence References, would have given the POSA reason to select the serotypes recited in claims 1, 12, 13, and 14.

199. Accordingly, the combination of Alexander or Gu with the Serotype Prevalence References and/or the Vaccine Recommendation References renders obvious claims 1, 12, 13, and 14, as well as the other dependent claims related to formulating pneumococcal conjugate vaccines.

1. Claim 1

200. For the reasons I have discussed above in Grounds I-IV, both Alexander and Gu disclose the *Streptococcus pneumoniae* saccharide-polypeptide conjugate vaccine composition of claim 1 in the '757 patent.[225] Indeed, the notion of conjugating pneumococcal capsular polysaccharides to carrier proteins had been known for decades. For example, the pneumococcal 7-valent conjugate vaccine (diphtheria CRM_{197} protein), Prevnar® (PCV7) vaccine was approved in the United States in 2000 and the pneumococcal 13-valent conjugate vaccine (diphtheria CRM_{197} protein), Prevnar 13® (PCV13) was approved in the United States in

[225] *See above*, ¶¶93-107, 142-44, 152-59, 193-94.

2010.[226] Alexander and Gu also both disclose the specific serotypes listed in claim 1, i.e., 23A, 23B, and 35B.[227]

201. Additionally, it would have been obvious to the POSA to include at least two of the three serotypes recited in claim 1 in a composition in view of epidemiological data disclosed in each of the Serotype Prevalence References. For example, as discussed above, Kaplan reports on the prevalence of serotypes that were not present in the 13-valent pneumococcal conjugate vaccine (PCV13) (in the context of otitis media, one of the common infections arising from *S. pneumoniae*), and the POSA would have been motivated to develop vaccines containing the serotypes that Kaplan found to be most common following the widespread use of PCV13.[228] Kaplan found that serotype 35B was the most common and serotype 23B was the second most common (tied with serotype 21) non-PCV13 serotypes isolated, both recited in claim 1, and serotype 23A, also recited in claim 1, was the sixth most common.[229] Thus, Kaplan provided the POSA a motivation to develop a

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[226] EX1004 (Goldblatt) at 1; EX1045 (Daniels) at tbl.1.

[227] EX1008 (Alexander), ¶63; EX1009 (Gu) at 22:27-23:7.

[228] *See above*, ¶¶61-64; EX1015 (Kaplan) at 1341-42.

[229] EX1015 (Kaplan) at 1341-42, tbl.2.

pneumococcal saccharide-polypeptide conjugate vaccine that includes at least two, if not all three, serotypes recited in claim 1, and especially serotypes 35B and 23B.

202. In addition, Pilishvili reports significant increases in the prevalence of serotypes 23A, 23B, and 35B across all age groups in the period between 1998 and 2007.[230] Pilishvili highlights that the "rate of IPD caused by serotype 23A increased from 0.2 to 0.5 cases per 100,000 population (+147%; 95% CI, +13% to +450%) and from 0.4 to 2.2 cases per 100,000 population (+514%; 95% CI, +227% to +980%) among 50–64-year-old and >65-year-old adults, respectively."[231] 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.[232] ECDC includes serotypes 23A, 23B, and 35B among the "most common serotype[s]" that caused "confirmed [invasive pneumococcal disease] cases" in European countries in 2011.[233] PHAC reports similar results for Canada, and notes that "[c]ontinued vigilance . . . is

[230] EX1016 (Pilishvili) at 37, tbl.2.

[231] EX1016 (Pilishvili) at 34.

[232] EX1017 (Waight) at 540.

[233] EX1018 (ECDC) at 15.

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."[234]

203. These conclusions are further supported by each of the Vaccine Recommendation References, which also would have provided the POSA a motivation to include serotypes 23A, 23B, and 35B, recited in claim 1, in a pneumococcal saccharide-polypeptide conjugate vaccine. 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%."[235] 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.[236] Richter explains that serotype 35B was among the three most common serotypes in penicillin-resistant *S. pneumoniae*, and that serotypes 23A and 23B showed proportional increases in prevalence.[237] Wagenvoort states that serotypes 23A and 23B were the

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[234] EX1019 (PHAC) at 57.

[235] EX1010 (Porro) at 66:28-67:14.

[236] EX1011 (Al-Sherikh) at 210.

[237] EX1013 (Richter) at 6484.

two most likely serotypes to cause disease in vulnerable populations that were not included in the then-current multivalent vaccine.[238]

204. In view of the teachings of the Vaccine Recommendation References and/or Serotype Prevalence References, the POSA would have been motivated to include at least two of the highly prevalent serotypes 23A, 23B, and 35B into the pneumococcal saccharide-polypeptide conjugate vaccine of Alexander or Gu. Indeed, several of these references directly state that the serotypes they identify should be included in a future vaccine due to their prevalence and virulence.[239] Further, given the maturity of pneumococcal saccharide-polypeptide conjugate vaccine technology, the widespread recommendations to include additional serotypes, and the clear trend in the industry towards inclusion of additional serotypes, the POSA would have had a reasonable expectation of success in being able to do so.

2. Claim 12: "further comprising at least one additional immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide from a unique *Streptococcus*

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[238] EX1014 (Wagenvoort) at 334.

[239] EX1011 (Al-Sherikh) at 210 (recommending 23A); EX1013 (Richter) at 6484 (growth of 35B should inform future vaccine development); EX1014 (Wagenvoort) at 334 (recommending selection of 23A and 23B into future vaccines).

> ***pneumoniae* serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34"**

205. Claim 12 depends from claim 1. As I have explained above, Alexander and Gu each anticipates, or in the alternative renders obvious, the composition of claim 1, alone or in combination with the Serotype Prevalence References and/or Vaccine Recommendation References.[240]

206. Claim 12 adds a requirement for "one additional immunogenic saccharide-polypeptide conjugate" selected from a list of serotypes: 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34.

207. As discussed above, Alexander discloses embodiments comprising the serotypes 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20, 22F, and 34.[241] Gu discloses embodiments comprising the serotypes 8, 9N, 10A, 11A, 12F, 15A, 15B, 20, and 22F.[242]

208. Further, each of the Serotype Prevalence References—Kaplan, Pilishvili, Waight, ECDC, and PHAC—and certainly, all of them together, would have given the POSA reason to select at least one additional serotype from within

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[240] *See above*, ¶¶93-107, 142-44, 152-59, 193-203.

[241] EX1008 (Alexander), ¶63.

[242] EX1009 (Gu) at 11:18-21.

this list and would have provided a motivation to the POSA to add at least one additional serotype from the list in claim 12. Kaplan reports 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.[243] The POSA would have seen one or all three as serotypes that there would be reason to include. 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.[244] Waight reports that "[n]on-PCV13 serotypes 8, 10A, 12F, 15A, and 24F increased significantly in 2013/14."[245] ECDC lists serotypes 6C, 8, 12F, 15A, and 22F as among "[t]he 10 most common [invasive pneumococcal disease] serotypes reported in 2012" in European countries, and includes 9N, 11A, and 16F as among the top 25 most common serotypes.[246] PHAC reports an increase in pneumococcal diseases caused by serotypes 8, 9N, 10A, 11A, 12F, 15B, 20, and

[243] EX1015 (Kaplan) at 1341-42, tbl.2.

[244] EX1016 (Pilishvili) at 37, tbl.2.

[245] EX1017 (Waight) at 538-40 & tbl.2.

[246] EX1018 (ECDC) at 14, tbl.1.3, & n.8.

22F in all age groups between 2010 and 2013 and notes serotype 22F as the most prevalent serotype in Canada in 2013.[247]

209. The Vaccine Recommendation References similarly would have provided reason to select an additional serotype from the list recited in claim 12. Any one of Porro, Al-Sherikh, Richter, or Wagenvoort would have provided motivation to the POSA to add an additional serotype so as to meet the requirements of claim 12 as well. 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.[248] Al-Sherikh describes how serotypes 8 and 12F are prevalent in young pneumococcal patients and how "[a]ddition of . . . 15 to the vaccine would improve the PCV performance in IPD prevention."[249] Richter discusses the prevalence of serotypes 6C, 9N, 11A, 15A, 15B, 15C, 16F, and 22F.[250] Specifically, Richter found that among multidrug resistant strains (MDR), defined as "nonsusceptibility to penicillin (PNSP[)] . . . combined with resistance to ≥2 non-β-lactam antimicrobials," 15A, 6C, and 35B were three out of the four major serotypes

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[247] EX1019 (PHAC) at 5.

[248] EX1010 (Porro) at 27:30-28:6, 66:28-67:14.

[249] EX1011 (Al-Sherikh) at 210, 213-14 & fig. 4.

[250] EX1013 (Richter) at 6487, tbl.4.

in 2012-13.[251] And in penicillin-resistant *S. pneumoniae* (PRSP), 35B was the second most predominant serotype in 2012-13.[252] Moreover, Richter also reports that "[a]mong the PNSP subset, serotypes showing a proportional increase were 35B, 15B, and 23B," and "[a]mong MDR strains, the largest proportional increases were observed in serotypes 35B, 15B, and 23A."[253] Richter also recognizes that serotypes 6C, 11A, and 22F were "[p]redominant serotypes" in all *S. pneumoniae* isolates in 2012-13.[254] 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.[255]

210. The POSA would have found it obvious to combine the known design of a pneumococcal conjugate vaccine with the specific serotypes identified as important in the art. Indeed, several of the references directly explain the relevance of their findings to future vaccine development.[256] Furthermore, Merck had already

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[251] EX1013 (Richter) at 6484, 6486, & tbl.4.

[252] EX1013 (Richter) at 6484, 6487, & tbl.4.

[253] EX1013 (Richter) at 6484.

[254] EX1013 (Richter) at 6487 & tbl.4.

[255] EX1014 (Wagenvoort) at 338-39 & fig.1.

[256] EX1011 (Al-Sherikh) at 210 (also highlighting addition of serotype 15 to the

added serotype 22F to its candidate vaccine (V114), which was in clinical trials, with the plan to administer it as a primary/booster series to the infant cohort and as a single dose to the adult cohort.[257]

211. Given these teachings, the POSA would have had a motivation to select at least one of the additional serotypes recited in claim 12 (above and beyond those recited in claim 1) and therefore to make a composition meeting the requirements of claim 12. As discussed above in connection with claim 1, the POSA also would have had a reasonable expectation of success in doing so.

3. Claims 13 and 14

212. Claims 13 and 14 depend from claim 1. As I have explained above, Alexander and Gu each anticipates, or in the alternative renders obvious, the

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vaccine would improve the PCV performance in IPD prevention); EX1013 (Richter) at 6484 (serotype distribution is critical as a guide to future vaccine development); EX1014 (Wagenvoort) at 334, 339 (noting that serotypes like 10A, 23A, and 23B with high propensities to affect risks groups can be important for selecting (future) vaccine serotypes).

[257] EX1050 at 7-9.

composition of claim 1, alone or in combination with the Serotype Prevalence References and/or Vaccine Recommendation References.[258]

213. I have been informed that the use of the word "comprising" means that the claim encompasses all of the enumerated limitations, and possibly more, while the word "consisting of" means that the claim encompasses only the enumerated limitations.

214. Claim 13 requires a longer list of serotypes than claim 12; the plurality of unique immunogenic saccharide-polypeptide conjugates must contain "conjugate [sic]" comprising polysaccharides from serotype comprising "6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B." The only difference between claim 13 and claim 14 is that claim 13 uses the word "comprising," while claim 14 uses the words "consisting of," before the list of serotypes. The claims are otherwise identical, including in their list of serotypes. However, the POSA would have understood that both claim 13 and 14 are ultimately "comprising" claims because each uses the word "comprising" earlier in the claim. For example, claim 14 refers to a composition that "comprises" saccharide-polypeptide conjugates from a serotype "consisting of" the recited list. Accordingly, the POSA would have understood that the two claims have the same scope.

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[258] *See above*, ¶¶93-107, 142-44, 152-59, 193-203.

215. Alexander alone discusses a composition containing majority of these serotypes; it describes embodiments comprising "a mixture of conjugates . . . with capsular polysaccharides from" as many as "30 or more" of a list of serotypes including 9N, 15A, 15C, 16F, 23A, 23B, and 35.[259] Gu's eight-serotype list discussed above includes 9N, 15A, 23A, 23B, and 35B.[260] The POSA would have understood that "35" is a reference to serogroup 35, which, at the time of Alexander's publication, was known to include three serotypes: 35F, 35A, and 35B. The POSA would thus understand that the inclusion of serogroup 35 in the list encompasses serotype 35B. Elsewhere, Alexander makes clear that its disclosure encompasses serotype 35B.[261]

216. Further, as discussed above,[262] several references also recommended the inclusion of serotypes 23A, 23B, and 35B, the serotypes from claim 1, and numerous references also recommended including serotypes 6C, 9N, 15A, 15C, and 16F in future vaccines. By the priority date, the POSA would have been motivated to include the remaining serotype listed in claim 13—6C—in a pneumococcal

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[259] EX1008 (Alexander), ¶63.

[260] EX1009 (Gu) at 13:5-7.

[261] EX1008 (Alexander), ¶65.

[262] *See above*, ¶¶199-216.

conjugate vaccine. Porro reports that serotype 6C is a "[n]ew emerging serotype[] of *S. pneumoniae*," and suggests that it "might be likely included in a further updated broad-spectrum vaccine formulation."[263] Richter highlighted serotype 6C as a "major" and "predominant" multidrug resistance serotype identified in 2012-2013 after the introduction of PCV13 in 2010.[264] Richter also identified serotype 6C as "major" in multi-drug resistant isolates.[265] And Wagenvoort further described serotype 6C as being more common among high-risk patients.[266] ECDC lists serotype 6C as one of the top ten most common pneumococcal serotypes not covered by any of the PCV vaccines observed in European countries in 2012.[267]

217. These disclosures, alone or in combination, would have motivated the POSA to include all of the recited serotypes in a PCV and thus to practice claims 13 and 14. And in light of these disclosures, as discussed above, the POSA would have had a reasonable expectation of success in doing so.

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[263] EX1010 (Porro) at 66:28-67:14

[264] EX1013 (Richter) at 6484.

[265] EX1013 (Richter) at 6485-87 & tbl.4.

[266] EX1014 (Wagenvoort) at 337.

[267] EX1018 (ECDC) at 1, 2.

4. Claims 2-9, 11, and 15-19

218. Each of claims 2-9, 11, and 15-19 discuss other aspects of a pharmaceutical composition, or the making of a pharmaceutical composition, that meets the limitations set out in the other claims.

219. For the reasons I have discussed above, Alexander or Gu explicitly teach these limitations.[268] Further, the POSA would have understood that these limitations are typical for the administration and manufacture of pneumococcal conjugate vaccines.

220. Accordingly, the POSA would have been motivated to practice each of these claims when following the teachings of Alexander or Gu, as well as the additional disclosures of the Serotype Prevalence References and/or the Vaccine Recommendation References, and would have had a reasonable expectation of success in doing so.

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

221. Claim 6 recites the pharmaceutical composition of claim 1, "wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response."

[268] *See above*, ¶¶118-40, 160-92.

222. For the reasons discussed above in Grounds I-IV, Alexander and Gu each anticipates, or in the alternative renders obvious, the pharmaceutical composition of claim 1 and the limitation of claim 6.[269]

223. Lee further explains that "the protective immunity" conferred by pneumococcal conjugate vaccines can be "estimated better by directly measuring opsonic capacity of vaccine-induced antibodies."[270] The reason for this, Lee explains, is that "the antibodies provide protection *by opsonizing pneumococci* for phagocytes."[271]

224. 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 . . . ."[272]

225. Thus, the POSA would have understood that ensuring that vaccines induce an opsonophagocytic response is important because (1) it enables measurement of the vaccine's ability to kill *S. pneumoniae*, and thus infer the

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[269] *See above*, ¶¶93-107, 120-21, 142-44, 152-59, 170-73, 193-94.

[270] EX1020 (Lee) at 376.

[271] EX1020 (Lee) at 376 (emphasis added).

[272] EX1021 (Anttila) at 402.

vaccine's efficacy, and (2) the opsonophagocytic response is the mechanism by which the vaccine protects the subject through the induction of serotype-specific antibodies.

226. Indeed, the POSA would have understood that opsonophagocytosis by vaccine-induced antibodies is the very means by which a vaccine protects a subject from *S. pneumoniae* bacteria; thus, the limitation of claim 6 essentially requires that the vaccine exhibit minimal efficacy with respect to a single serotype.

227. Accordingly, the POSA would have been motivated to include a pneumococcal conjugate vaccine that elicits an opsonophagocytic response, and, based on Alexander or Gu in view of Lee and/or Anttila, would have had a reasonable expectation of success in doing so, thus rendering claim 6 obvious.

G. Claims 7 and 10 would have been obvious over either Alexander or Gu, in view of PFL (Ground VII).

228. Claims 7 and 10 both recite certain weight-based limitations on the vaccine conjugate of claim 1.

229. As I have explained above in Grounds I-V, Alexander and Gu each anticipates, or in the alternative renders obvious, the vaccine conjugate of claim 1.[273]

[273] *See above*, ¶¶93-107, 142-44, 152-59, 193-94.

230. PFL, which sets out the formulation of Prevnar®, a pneumococcal 7-valent conjugate vaccine, discloses a vaccine conjugate which meets or renders obvious the weight-based limitations in claims 7 and 10.

231. Prevnar® was the global standard-of-care for pneumococcal vaccinations for many years. The vaccine contained the seven leading serotypes associated with invasive pneumococcal disease prior to its licensure in 2000, formulated with an aluminum adjuvant.[274] It was also the first vaccine composition that demonstrated the clinical efficacy of conjugate vaccines against diseases caused by *S. pneumoniae*. Later, the vaccine was demonstrated to be safe and effective in reducing the burden of pneumococcal disease in vaccinated young children (direct protection) and unvaccinated older children and adults (indirect protection).

232. Accordingly, the POSA would have been motivated to begin with the formulation components of Prevnar® in designing a pneumococcal conjugate vaccine in view of the disclosures of Alexander or Gu, and would have had a reasonable expectation of success in doing so in light of Prevnar® being the global standard-of care, thus rendering claims 7 and 10 obvious.

1. 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."

[274] EX1022 (PFL).

233. Claim 7 depends from claim 1. As I have explained above in Grounds I-V, each of Alexander and Gu discloses pharmaceutical compositions comprising mixtures of saccharide-polypeptide conjugates, including the capsular polysaccharides corresponding to the serotypes referenced in claim 1.[275] Alexander anticipates the limitation of claim 7 for the reasons discussed above, and also independently supplies a motivation for the POSA to develop vaccine composition with conjugates in the amount recited in claim 7.

234. PFL further discloses a pharmaceutical composition comprising a mixture of saccharide-polypeptide conjugates wherein the conjugates are present by at least 0.001% by weight.

235. PFL explains that the 7-valent Prevnar® vaccine included 2 micrograms of each saccharide for six *S. pneumoniae* serotypes (4, 9V, 14, 18C, 19F, and 23F), and 4 micrograms of serotype 6B (16 micrograms total saccharide); and approximately 20 micrograms of the carrier protein (CRM_{197}), for a total of 36 micrograms of saccharide-polypeptide conjugate per dose.[276] Prevnar® is administered as a 0.5 mL liquid dose.[277]

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[275] *See above*, ¶¶93-107, 142-44, 152-59, 193-94.

[276] EX1022 (PFL) at 1.

[277] EX1022 (PFL) at 1.

236. The POSA would have understood based on this information that the saccharide-polypeptide conjugates of Prevnar® were collectively present in an amount of at least 0.001% by weight, based on the weight of the pharmaceutical composition. It is well known 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. For example, each 0.5 mL dose of a vaccine composition weighs approximately 0.5 grams since the primary component is water (density of water is 1 gram per mL). Thus, Prevnar® contains 36 micrograms, or 0.000036 grams, of the saccharide-polypeptide conjugates, per 0.5 grams of vaccine composition. This is about 0.0072% of the weight of the vaccine composition (0.000036 divided by 0.5 yields a concentration of 0.0072%).

237. Accordingly, the POSA would have been motivated, in making a pneumococcal vaccine containing saccharide-polypeptide conjugates as disclosed in Alexander or Gu, to include those conjugates at a concentration equivalent to the existing standard-of-care dosage as taught by PFL, and would have done so with a reasonable expectation of success, thus rendering claim 7 obvious.

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."

238. Claim 10 depends from claim 1. As I have explained above, each of Alexander and Gu discloses, or in the alternative renders obvious, pharmaceutical

compositions comprising mixtures of saccharide-polypeptide conjugates, including the capsular polysaccharides corresponding to the serotypes referenced in claim 1.[278]

239. PFL further discloses a pharmaceutical composition comprising a mixture of saccharide-polypeptide conjugates wherein at least some of the conjugates are individually present by at least 0.001% by weight. As I have explained above,[279] it is well known 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.

240. PFL explains that in the 7-valent Prevnar® vaccine, there are 2 micrograms of each saccharide for six *S. pneumoniae* serotypes (4, 9V, 14, 18C, 19F, and 23F), 4 micrograms of serotype 6B, and approximately 20 micrograms of the carrier protein (CRM_{197}), for a total of 36 micrograms of saccharide-polypeptide conjugate per dose.[280] Even if there is some variability among the weights of the different saccharide-polypeptide conjugates in PFL, the POSA would recognize that since there are 36 micrograms total of saccharide-polypeptide conjugate per dose, and seven different serotypes (each corresponding to one conjugate), there would be

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[278] *See above*, ¶¶93-107, 142-44, 152-59, 193-94.

[279] *See above*, ¶235.

[280] EX1022 (PFL) at 1.

on average more than 5 micrograms each of the saccharide-polypeptide conjugates, and that at least one is present in that amount: 36 ÷ 7 > 5.

241. That fact would have rendered the limitation of claim 10 obvious. Prevnar® is administered as a 0.5 mL dose that primarily contains water.[281] Because a 0.5 mL dose weighs about (in fact, slightly more than) 500 mg, and .001% of that weight thus corresponds to 5 micrograms, the reasoning above means that the concentration of one or more saccharide-polypeptide conjugates in PFL exceeds 0.001%.

242. The POSA would have also understood that optimizing the concentration of a saccharide-polypeptide conjugate in a pharmaceutical composition, as disclosed in Alexander or Gu, is routine during development. In the course of that optimization, it would be logical and a POSA would have been motivated to use as a starting point—and very possibly the endpoint—the same concentration at which saccharide-polypeptide conjugates are present in the existing, commercially available standard-of-care vaccine doses, and would have done so with a reasonable expectation of success. As discussed, the POSA would have recognized that this concentration averages approximately 0.001%, as taught by PFL. Claim 10 therefore would have been obvious.

[281] EX1022 (PFL) at 1.

H. Claims 2 and 16-17 would have been obvious over Alexander in view of Vesikari and/or PFL (Ground VIII).

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

244. Claim 16 depends from claim 11, which recites a method for administering the vaccine composition of claim 1. Claim 16 and claim 17, which further limits claim 16, add limitations related to the administration and composition of a second (or booster) dose.

245. For the reasons discussed above in Grounds I-IV, Alexander and Gu each anticipates, or in the alternative renders obvious, the pharmaceutical composition of claim 1.[282] Furthermore, as discussed above in Grounds I-IV, Alexander and Gu both anticipate, or in the alternative render obvious, claim 11;[283] and Alexander anticipates, or in the alternative render obvious, claims 2, 16, and 17.[284] In view of Vesikari and/or PFL, Alexander renders obvious claims 2, 16, and 17.

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[282] *See above*, ¶¶93-107, 142-44, 152-59, 193-94.

[283] *See above*, ¶¶128-29, 143, 177-79, 193.

[284] *See above*, ¶¶108-13, 132-34, 142.

1. Claim 2: "at least one polypeptide comprises a mixture of polypeptides"

246. As I have explained above, the POSA would interpret claim 2 to refer to a pharmaceutical composition containing conjugates made from more than one different polypeptide.[285]

247. Alexander anticipates this limitation for the reasons discussed above, and also independently supplies a motivation for the POSA to consider including multiple different carrier proteins, for the same or different serotypes, in a vaccine composition.[286]

248. Additionally, Alexander renders this limitation obvious in light of the prior art, including Vesikari. Vesikari, for example, describes the administration of a vaccine consisting of saccharides from *S. pneumoniae* conjugated to three different carrier proteins.[287] As it discusses, the 10-valent pneumococcal conjugate vaccine (PHiD-CV) contains eight serotypes conjugated to non-typeable *H. influenzae* (NTHi) Protein D carrier protein, one serotype conjugated to tetanus toxoid carrier protein, and one serotype conjugated to diphtheria toxoid.[288] The data demonstrated

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[285] *See above*, ¶¶108-13.

[286] *See above*, ¶¶108-13.

[287] EX1023 (Vesikari) at S67.

[288] EX1023 (Vesikari) at S67.

noninferiority of PHiD-CV when compared to the 7-valent pneumococcal conjugate vaccine (Prevnar®) for the serotypes in common between the two vaccines.[289]

249. In light of these data and the teachings of Alexander, the POSA would have been motivated to consider the inclusion of multiple different polypeptides in a pneumococcal conjugate vaccine composition as taught by Vesikari and would have had a reasonable expectation of success in doing so, rendering claim 2 obvious.

2. Claim 16: "wherein the administering to the subject of 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"

250. Claim 16 depends from claim 11. As discussed above in Grounds I-II, Alexander anticipates, or in the alternative, renders obvious, the method of claim 11, as discussed above.[290] Also discussed above, Alexander anticipates, or in the alternative render obvious, claim 1.[291]

251. Alexander teaches administering a second (or booster) dose of the vaccine several weeks after the initial dose. Alexander explains that initial doses "are followed by boosting doses . . . pursuant to a boosting regimen over weeks to

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[289] EX1023 (Vesikari) at S73.

[290] *See above*, ¶¶128-29, 142.

[291] *See above*, ¶¶93-107, 142-44.

months,"[292] and that "[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."[293]

252. 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.[294] Further, PFL disclosed that Prevnar® (pneumococcal 7-valent conjugate vaccine) had a routine schedule for administration at 2, 4, 6, and 12-15 months of age.[295] In addition, several dosing schedules of pneumococcal conjugate vaccination were clinically evaluated and implemented in various countries, including dosing intervals for the first 2 infant doses varying between 4 weeks and 8 weeks apart.[296]

253. Accordingly, the POSA would have been motivated to combine the known concept of administering a second (or booster) dose as disclosed by Alexander with an interval of about or more than four weeks between the two doses

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[292] EX1008 (Alexander), ¶112.

[293] EX1008 (Alexander), ¶116 (emphases added).

[294] EX1023 (Vesikari) at S66.

[295] EX1022 (PFL) at 11.

[296] EX1038 (Whitney) at S179.

in view of the successful vaccine schedules disclosed in Vesikari and/or PFL, and would have had a reasonable expectation of success in doing so, thus rendering claim 16 obvious.

3. Claim 17: "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."

254. As I have explained above, Alexander anticipates, or in the alternative renders obvious, the method of claim 16.[297] Further, Alexander renders claim 17 obvious over Vesikari.[298]

255. Claim 17 depends from claim 16, and it further specifies that the second composition comprises a capsular polysaccharide from a serotype of *Streptococcus pneumoniae* conjugated to a second polypeptide. The specification of the '757 patent expressly states that the second polypeptide (of the second composition's conjugate) can be an identical or different polypeptide as the first polypeptide.[299] The specification also makes clear that the second composition's conjugate is—like

[297] *See above*, ¶¶132-33, 142.

[298] *See below*, ¶¶254-57.

[299] EX1001 ('757 patent), col.48, ll.7-23.

the first composition's conjugate—a conjugate of that polypeptide with a *Streptococcus pneumoniae* polysaccharide (though the serotypes may differ).[300]

256. Alexander teaches that "[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" and that the first carrier peptide can be identical to or different from the second carrier peptide.[301]

257. Vesikari also supplies data suggesting that administering a vaccine in a primary series comprising one carrier protein and a booster dose vaccine comprising a different carrier protein can increase the immune system response with respect to certain serotypes, relative to primary/booster series which involve the same carrier protein in both doses.[302] Vesikari compares three dosing regimens: PHiD-CV administered in the primary series followed by a PHiD-CV booster dose; Prevnar® administered in the primary series followed by a Prevnar® booster dose; and Prevnar® administered in the primary series followed by a PHiD-CV booster

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[300] EX1001 ('757 patent), col.50, ll.25-37; *see generally id.* at cols.47-52.

[301] EX1008 (Alexander) at ¶¶34, 86, 116.

[302] EX1023 (Vesikari) at S73.

dose.[303] 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.[304] The third regimen, in which the primary vaccine differed from the booster in its carrier protein, produced a more robust immunogenic response with respect to some serotypes than either of the other two regimens.[305]

258. Accordingly, the POSA would have been motivated to combine the knowledge that administering vaccines with multiple protein carriers as taught by Alexander can form effective vaccines and can increase the immunogenic effect, as suggested by the data in Vesikari, and would have had a reasonable expectation of success in doing so, thus rendering claim 17 obvious.

XI. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

259. I understand that Patent Owner bears the burden of coming forward with evidence of any secondary considerations supporting the non-obviousness of the ’757 patent. I understand that Patent Owner has not yet provided such evidence in this proceeding, and I am not aware of such evidence. I reserve the right to

[303] EX1023 (Vesikari) at S67-68 & fig.1.

[304] EX1023 (Vesikari) at S67.

[305] EX1023 (Vesikari) at S69, S72-74 & tbl.5.

respond to Patent Owner's evidence of secondary considerations if and when such evidence is provided to me.

* * *

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 23 December 2025

Luwy Musey, M.D.

APPENDIX A

APPENDIX A - LIST OF MATERIALS CONSIDERED

Exhibit	Short Name	Document
EX1001	’757 patent	U.S. Patent No. 11,058,757
EX1002	Musey Dec.	Declaration of Luwy Musey
EX1003		Curriculum Vitae of Luwy Musey
EX1004	Goldblatt	Goldblatt, *Conjugate Vaccines*, CLIN. EXP. IMMUNOL. Vol. 119, pp. 1-3 (2000)
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., *Distribution of Serotypes and Antibiotic Susceptibility Patterns Among Invasive Pneumococcal Diseases in Saudi Arabia*, ANNALS OF LABORATORY MEDICINE, Vol. 34, 210-15 (2014)
EX1013	Richter	Richter et al., *Changes in Pneumococcal Serotypes and Antimicrobial Resistance after Introduction of the 13-Valent Conjugate Vaccine in the United States*, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Vol. 58, No. 7, 6486-89 (2014)
EX1014	Wagenvoort	Wagenvoort et al., *Risk and Outcomes of Invasive Pneumococcal Disease in Adults with Underlying Conditions in the Post-PCV7 Era, The Netherlands*, VACCINE, Vol. 34, 334-40 (2016)
EX1015	Kaplan	Kaplan et al., *Multicenter Surveillance of Streptococcus pneumoniae Isolates from Middle Ear and Mastoid Cultures in the 13-Valent Pneumococcal Conjugate Vaccine Era*, CLINICAL INFECTIOUS DISEASES 60:1339-1345 (2015)

EX1016	Pilishvili	Pilishvili et al., *Sustained Reductions in Invasive Pneumococcal Disease in the Era of Conjugate Vaccine*, JOURNAL OF INFECTIOUS DISEASE, No. 201, 32-41 (2010)
EX1017	Waight	Waight et al., *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*, LANCET INFECTIOUS DISEASES, Vol. 15, 535-43 (2015)
EX1018	ECDC	European Centre for Disease Control and Prevention, *Surveillance of Invasive Bacterial Diseases in Europe*, 2012 (Stockholm: ECDC, 2015)
EX1019	PHAC	Public Health Agency of Canada, Streptococcus and STI Unit, *National Laboratory Surveillance of Invasive Streptococcal Disease in Canada*: Annual Summary 2013 (Winnipeg, Manitoba: PHAC, 2014)
EX1020	Lee	Lee et al., *Immune Response in Infants to the Heptavalent Pneumococcal Conjugate Vaccine Against Vaccine-Related Serotypes 6A and 19A*, CLINICAL AND VACCINE IMMUNOLOGY, Vol. 16, No. 3, 376-81 (2009)
EX1021	Anttila	Anttila et al., *Contribution of Serotype-Specific IgG Concentration, IgG Subclasses, and Relative Antibody Avidity to Opsonophagocytic Activity Against Streptococcus Pneumoniae*, CLINICAL AND EXPERIMENTAL IMMUNOLOGY, Vol. 118, 402-07 (1999)
EX1022	PFL	Prevnar® FDA Label

EX1023	Vesikari	Vesikari et al., *Immunogenicity of the 10-Valent Pneumococcal Non-Typeable Haemophilus Influenzae Protein D Conjugate Vaccine (PHiD-CV) Compared to the Licensed 7vCRM Vaccine*, THE PEDIATRIC INFECTIOUS DISEASE JOURNAL, Vol. 28, No. 4, S66-S76 (2009)
EX1024	Yeh	Yeh et al., *Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine in Infants and Toddlers*, PEDIATRICS, Vol. 126, No. 3, e493-e505 (2010)
EX1026	Pichichero	Pichichero, *Protein Carriers of Conjugate Vaccines*, HUMAN VACCINES & IMMUNOTHERAPEUTICS, 2505-23 (2013)
EX1027	WHO	World Health Organization, *Pneumococcal Conjugate Vaccine for Childhood Immunization*, WEEKLY EPIDEMOL. REC. 82(12) 93, 94 (2007)
EX1028	Hu	Hu et al., *Approach to Validating an Opsonophagocytic Assay for Streptococcus Pneumoniae*, CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Vol. 12, No. 2, 287-95 (2005)
EX1029	Romero-Steiner	Romero-Steiner et al., *Use of Opsonophagocytosis for Serological Evaluation of Pneumococcal Vaccines*, CLINICAL AND VACCINE IMMUNOLOGY, Vol. 13, No. 2, 165-69 (2006)
EX1030	Costantino	Costantino et al., *The Design of Semi-Synthetic and Synthetic Glycoconjugate Vaccines*, EXPERT OPINIONS IN DRUG DISCOVERY, Vol. 6, No. 10, 1045-66 (2011)
EX1031	Wessels	Wessels et al., *Structural Properties of Group B Streptococcal Type III Polysaccharide Conjugate Vaccines that Influence Immunogenicity and Efficacy*, INFECTION

		AND IMMUNITY, Vol. 66, No. 5, 2186-92 (1998)
EX1032	Baker	Baker et al., *Safety and Immunogenicity of Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccines for Group B Streptococcal Types Ia and Ib*, JOURNAL OF INFECTIOUS DISEASES, Vol. 179, 142-50 (1999)
EX1033	Whitney 2003	Whitney et al., *Decline in Invasive Pneumococcal Disease after the Introduction of Protein-Polysaccharide Conjugate Vaccine*, N. ENGL. J. MED. 1737-1746 (2003)
EX1034	Jakobsen	Jakobsen et al., *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*, INFECTION AND IMMUNITY, Vol. 70, No. 3, 1443-52 (2002)
EX1035	Sogaard	Søgaard, *The Clinical Use of Adjuvants in Pneumococcal Vaccination*, HUMAN VACCINES, Vol. 7, No. 2, 276-80 (2011)
EX1036	Giudice	Giudice and Rappuoli, Genetically Derived Toxoids for use as Vaccines and Adjuvants, VACCINE, Vol. 17, S44-S52 (1999)
EX1037	Lees	Lees et al., *Versatile and Efficient Synthesis of Protein-Polysaccharide Coinjugate Vaccines Using Aminooxy Reagents and Oxime Chemistry*, VACCINE 716-729 (2006)
EX1038	Whitney 2014	Whitney et al., *Dosing Schedules for Pneumococcal Conjugate Vaccine Considerations*, THE PEDIATRIC INFECTIOUS DISEASE JOURNAL, S172-S181 (2014)

EX1045	Daniels	Daniels et al., *A Review of Pneumococcal Vaccines: Current Polysaccharide Vaccine Recommendations and Future Protein Antigens*, J. PEDIATRIC PHARMACOLOGY AND THERAPEUTICS, Vol. 21, No. 1, 27-35 (2016)
EX1048	CDC	Centers for Disease Control and Prevention, *Invasive Pneumococcal Disease in Children 5 Years After Conjugate Vaccine Introduction – Eight States, 1998-2005*, MORBIDITY AND MORTALITY WEEKLY REPORT, Vol. 57, No.6, 144-48 (2008)
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)