

UNITED STATES PATENT AND TRADEMARK OFFICE

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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MERCK SHARP & DOHME LLC,  
Petitioner

v.

POGONA, LLC,  
Patent Owner.

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Case No. IPR2026-00221  
U.S. Patent No. 11,058,757

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**DECLARATION OF DENNIS L. KASPER, M.D.  
IN SUPPORT OF PETITION FOR INTER PARTES REVIEW  
OF U.S. PATENT NO. 11,058,757**

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<b>Ex. No.</b>	<b>Description</b>
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Ex-1003	Curriculum Vitae of Dr. Dennis Kasper
Ex-1004	Prosecution History of U.S. Patent No. 11,058,757
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Ex-1006	International Publication No. WO 2017/011338 (“Mekalanos”)
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Ex-1009	International Publication No. WO 2016/207905 (“Matur”)
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Ex-1012	K. Aaron Geno et al., <i>Pneumococcal Capsules and Their Types: Past, Present, and Future</i> , 28 <i>Clin. Microbiol. Rev.</i> 871, 871–899 (2015) (“Nahm”)
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Ex-1017	G.H.J. Wagenvoort et al., <i>Risk and Outcomes of Invasive Pneumococcal Disease in Adults with Underlying Conditions in the Post-PCV7 Era, The Netherlands</i> , 34 <i>Vaccine</i> 334–40 (2016) (“Wagenvoort”)

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Ex-1018	Mark T. Dransfield et al., <i>Superior Immune Response to Protein-Conjugate Versus Free Pneumococcal Polysaccharide Vaccine in Chronic Obstructive Pulmonary Disease</i> , 180 <i>Am. J. Respir. Crit. Care Med.</i> 499–505 (2009) (“Dransfield”)
Ex-1019	Marta Domenech et al., <i>Emerging, Non-PCV13 Serotypes 11A and 35B of Streptococcus pneumoniae Show High Potential for Biofilm Formation In Vitro</i> , 10 <i>PLoS One</i> e0125636 (2015) (“Domenech”)
Ex-1020	Sandra S. Richter et al., <i>Changes in Pneumococcal Serotypes and Antimicrobial Resistance After Introduction of the 13-Valent Conjugate Vaccine in the United States</i> , 58 <i>Antimicrob., Agents Chemother.</i> 6484, 6484–6493 (2014) (“Richter 2014”)
Ex-1021	International Publication No. WO 2007/034280 (“Blay”)
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Ex-1024	Stefan Flasche et al., <i>Effect of Pneumococcal Conjugate Vaccination on Serotype-Specific Carriage and Invasive Disease in England: A Cross-Sectional Study</i> , 8 <i>PLoS Med.</i> e1001017 (2011) (“Flasche”)
Ex-1025	Sarkis K. Mazmanian & Dennis L. Kasper, <i>The Love–Hate Relationship Between Bacterial Polysaccharides and the Host Immune System</i> , 6 <i>Nat. Rev. Immunol.</i> 849 (2006) (“Mazmanian and Kasper 2006”)
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Ex-1034	U.S. Patent No. 9,492,559 (“Emini”)
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Ex-1045	Victor Morais et al., <i>Conjugation Mechanism for Pneumococcal Glycoconjugate Vaccines: Classic and Emerging Methods</i> , 9 <i>Bioengineering</i> 774 (2022) (“Morais”)
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Ex-1048	Scott E. Johnson et al., <i>Correlation of Opsonophagocytosis and Passive Protection Assays Using Human Anticapsular Antibodies in an Infant Mouse Model of Bacteremia for Streptococcus pneumoniae</i> , 180 <i>J. Infect. Dis.</i> 133, 133–40 (1999) (“Johnson”)
Ex-1049	Robert L. Burton et al., <i>Development and Validation of a Fourfold Multiplexed Opsonization Assay (MOPA4) for Pneumococcal Antibodies</i> , 13 <i>Clin. Vaccine Immunol.</i> 1004 (2006) (“Burton”)
Ex-1050	Robert Malley et al., <i>Serotype-Independent Pneumococcal Experimental Vaccines That Induce Cellular as Well as Humoral Immunity</i> , 109 <i>Proc. Nat’l Acad. Sci. U.S.</i> 3623 (2012) (“Malley”)
Ex-1051	INTENTIONALLY LEFT BLANK
Ex-1052	International Publication No. WO 2017/067962 (“Bertaud”)

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Ex-1053	<i>Physicians' Desk Reference</i> 1182–83 (33d ed. 1979) (“PDR 1979 Pneumovax®”)
Ex-1054	<i>Physicians' Desk Reference</i> 880–81, 1431–32 (44th ed. 1990) (“PDR 1990 Pneumovax® 23”)
Ex-1055	Nicholas J. Mantis et al., <i>Role of B Cells and Antibodies in Controlling Bacterial Pathogens</i> , in <i>Encyclopedia of Microbiology</i> 194–200 (Thomas M. Schmidt ed., 4th ed., Elsevier 2019) (“Mantis”)
Ex-1056	S.T. Sigurdardottir et al., <i>Safety and Immunogenicity of CRM197-Conjugated Pneumococcal–Meningococcal C Combination Vaccine (9vPnC-MnCC) Whether Given in Two or Three Primary Doses</i> , 26 <i>Vaccine</i> 4178, 4178–4186 (2008) (“Sigurdardottir”)
Ex-1057	Catherine Satzke et al., <i>Molecular Epidemiology of Streptococcus pneumoniae Serogroup 6 Isolates from Fijian Children, Including Newly Identified Serotypes 6C and 6D</i> , 48 <i>J. Clin. Microbiol.</i> 4298, 4298–4300 (2010) (“Satzke”)
Ex-1058	Sandra S. Richter et al., <i>Changing Epidemiology of Antimicrobial-Resistant Streptococcus pneumoniae in the United States, 2004–2005</i> , 48 <i>Clin. Infect. Dis.</i> e23 (2009) (“Richter 2009”)
Ex-1059	Yao KH et al., <i>Type distribution of serogroup 6 Streptococcus pneumoniae and molecular epidemiology of newly identified serotypes 6C and 6D in China</i> , 70 <i>Diag. Microbiol. Infect. Dis.</i> 291, 291–98 (2011) (“Yao”)
Ex-1060	James J. Calix et al., <i>Elucidation of structural and antigenic properties of pneumococcal serotype 11A, 11B, 11C, and 11F polysaccharide capsules</i> , 193 <i>J. Bacteriol.</i> 5271, 5271–5278 (2011) (“Calix”)
Ex-1061	<i>Emergence of PCV13 Nonvaccine-Specific Streptococcus Pneumoniae Serotypes 6C and 23A, and Serogroups 15, 33, and 35 Isolated from Children in Kansas City, Missouri</i> (2011) (“IDSA Abstract”)

I, Dennis L. Kasper, M.D., declare and state as follows:

## **I. INTRODUCTION**

1. I am a physician-scientist, and I currently hold the positions of William Ellery Channing Professor of Medicine, and Professor of Immunology at Harvard Medical School in Boston, MA.

2. I have been retained on behalf of Merck Sharp & Dohme LLC (“Merck” or “Petitioner”) as an independent expert consultant in the above-referenced *inter partes* review (“IPR”) proceeding to provide information and opinions on the teachings of the prior art and the state of the art, as relevant to the issued claims of U.S. Patent No. 11,058,757 (“the ’757 Patent”). Ex-1001. I understand the ’757 Patent is currently assigned to Pogona, LLC (“Patent Owner” or “PO”).

3. I am being compensated for my time spent in connection with this matter at my usual rate of \$1,500 per hour. My compensation is in no way contingent on the outcome of this or any other proceeding. I have no other direct financial interest in this proceeding.

## **II. BACKGROUND AND QUALIFICATIONS**

4. My full *curriculum vitae* is provided in Ex-1003, but I have summarized below some of the relevant aspects in relation to the issues in this proceeding.

5. Including my medical school training, which began in 1963, I have more than 50 years of academic and professional experience in the fields of medicine and infectious disease. I have run my own research laboratory since 1973, where we have studied the capsular polysaccharides of several extracellular bacteria (both commensal and pathogenic), including their interaction with the immune system.

6. One major focus of our work particularly relevant to this proceeding is the development of human vaccines, including polysaccharide-protein conjugate vaccines. For example, we elucidated the structure of nine capsular polysaccharides and important surface proteins of group B *Streptococcus* (the foremost cause of serious neonatal bacterial infections) as well as their role in pathogenesis, deriving a highly immunogenic polysaccharide-protein conjugate vaccine.

7. I am a named inventor on dozens of patents and patent applications worldwide, including approximately 40 issued U.S. patents, many of which relate to polysaccharide-protein conjugate vaccines.

8. I received an M.D. degree in 1967 from University of Illinois School of Medicine in Chicago, IL. I was also awarded an honorary A.M. degree in 1986 from Harvard University in Cambridge, MA.

9. After receiving my medical degree, I did my resident training (in Medicine) at New York Hospital - Cornell University Medical Center in New York, NY, and at Peter Bent Brigham Hospital (a predecessor of BWH) in Boston, MA. I

also completed an Infectious Disease fellowship at Harvard Medical Unit, Boston City Hospital in Boston, MA.

10. I received my first faculty academic appointment in 1973 at Harvard Medical School, and in 1985 I was promoted to tenured Professor. Since 1973, I have also held various clinical appointments in the fields of Medicine and Infectious Disease, including leadership positions, at hospitals affiliated with Harvard Medical School. I served as the Executive Dean for Academic Programs at Harvard Medical School from 1997 until 2004.

11. From 1969 to 1972, I served as Major in the U.S. Army Medical Corps., and as Senior Investigator in the Department of Bacterial Diseases at the Walter Reed Army Institute of Research in Washington, DC. My work was centered on developing polysaccharide and protein vaccines for meningococcus. I have also held several major administrative leadership positions (as well as committee memberships) in regional, national and international institutions, agencies and committees involved in the study of infectious disease.

12. Since 1970, I have been a member of several prominent professional societies, and have been elected to leadership positions in the International Society for Anaerobic Bacteria, and the International Society for Infectious Diseases. Specifically, I was elected to membership in the American Academy of Microbiology in 1985, National Academy of Medicine in 2001, and the National

Academy of Sciences in 2018. Prior to that, I was elected to the American Society of Clinical Investigation in 1978 and to the Association of American Physicians in 1984. I received a Research Career Development Award and a Merit Award from the National Institutes of Health. I was awarded the Squibb Award (now called Oswald Avery Award) from the Infectious Diseases Society of America in 1985 and the Professor John McArthur Award from the Biomedical Research Institute at Brigham and Women's Hospital in 2006. I was awarded the Albany Prize in Medicine and Biomedical Science in 2023 and the Paul Ehrlich and Ludwig Darmstaedter Prize in 2024. I am currently a Fellow in the American Association for the Advancement of Science, the American Academy of Microbiology, American Association of Immunology, the Infectious Disease Society of America, American Society for Clinical Investigation, and Association of American Physicians, and a member of both the National Academy of Medicine and the National Academy of Science.

13. To date, I have authored or co-authored approximately 280 original research investigations in peer-reviewed publications, and approximately 220 additional publications (reviews, books/textbooks, chapters, monographs, editorials and case reports). I have also served as the Infectious Disease Editor for Harrison's Principles of Internal Medicine since 1990 (13th through 22nd edition) and as Editor-in-Chief of the 16th and 19th editions. As a research mentor, I have trained

approximately 90 postdoctoral fellows and graduate students, most of whom are now faculty at various institutions throughout the world.

14. Apart from my academic experience, I have consulted over the years for various pharmaceutical and biotechnology companies, including Merck Vaccines, Baxter Therapeutics, Genome Therapeutics, Novartis Vaccines and Cangene Corporation. I have also been a Member of the Scientific Advisory Boards of Microbia (Ironwood Pharmaceuticals), Therasim, Inc., and Selecta Biosciences. Finally, I have been involved in an advisory capacity for the Crohn's and Colitis Foundation of America.

### **III. MATERIALS CONSIDERED**

15. In forming my opinions, I have considered the materials listed in the Exhibit List attached to this Declaration. I have also considered the materials I discuss in my Declaration, including, for example, the '757 Patent, the prosecution history of the '757 Patent, and the background and prior art references cited in my Declaration. In addition, my opinions are further based on my education, training, experience, and knowledge in the relevant field.

### **IV. LEGAL STANDARDS**

16. I am not an attorney and offer no legal opinions. For the purposes of my Declaration, I have been informed about certain aspects of the law that are relevant to my analysis, as summarized below.

**A. Level of Ordinary Skill in the Art**

17. I have been informed by counsel and I understand that a patent is to be understood from the perspective of a person of ordinary skill in the art (“POSITA”), a hypothetical person who is presumed to be familiar with the relevant scientific field and its literature at the time of the invention. I have been instructed by counsel to apply March 31, 2016, as the invention date or priority date for my analysis.

18. I additionally understand that a POSITA is a person of ordinary creativity in his or her field and is aware of all relevant prior art as of the invention date. I also understand that a POSITA is capable of understanding the scientific principles applicable to the pertinent field and able to fit the teachings of multiple prior art references together.

19. I understand that the level of ordinary skill in the art may be determined by reference to certain factors, including: (1) the educational level of the inventors, (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.

20. It is my opinion that the claims of the ’757 Patent are generally directed to multivalent immunogenic pneumococcal conjugate vaccines that include specific serotypes (23A, 23B, and/or 35B). In my opinion, a POSITA would have been an individual or team with Ph.D. degrees in the biological and chemical sciences and at

least 2 years of work experience, or an M.D. degree and at least 6 years of work experience, developing conjugate vaccines, including specifically growing sufficient quantities of bacteria, extracting, purifying and analyzing bacterial polysaccharides, conjugating polysaccharides to a carrier protein (and analyzing the conjugates), and performing immunologic testing.

**B. Claim Construction**

21. I understand from counsel that the meaning of claim terms is interpreted based on their plain and ordinary meaning from the viewpoint of a POSITA at the time of the alleged invention based on the claims, specification, and prosecution history. In my opinion, none of the claim terms require construction in order to evaluate the validity of the claims. I note, however, that the claims are written in Markush format.

22. Specifically, I have been informed by counsel that independent Claim 1, which recites “wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B,” is written in the Markush format. I also understand that dependent Claim 12, which recites “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,” is also written in Markush format. I understand that this type of claim format indicates that the

members of the Markush group are considered to be equivalents and that if one member of the Markush group is anticipated or obvious (*e.g.*, 23A), Patent Owner is precluded from arguing that any other member recited in the claim (*e.g.*, 23B) is not anticipated or obvious.

23. Additionally, I note that independent Claim 1 does not recite any particular carrier protein or conjugation technique. *See* Ex-1001, Cl. 1. Accordingly, independent Claim 1 broadly encompasses conventional pneumococcal conjugate vaccines, using *any* carrier protein and *any* conjugation method.

### **C. Invalidity**

24. I understand that I am to determine whether the claimed invention is anticipated or obvious by a preponderance of the evidence standard. I understand that the preponderance of the evidence standard is satisfied as long as the proposition is more likely to be true than not true.

#### **1. Anticipation**

25. I understand that a patent claim is invalid as anticipated if a single prior art reference describes each and every limitation of the claimed invention arranged in the same way as it is claimed. I further understand that an express disclosure of each claim limitation is not required; a reference anticipates a limitation if that limitation is either expressly or inherently disclosed in the reference. I also understand that when the prior art discloses a genus or range, it can anticipate the

claims to a species or subset if the prior art disclosure is sufficiently small that one of ordinary skill in the art could at once envisage the claimed species.

## **2. Obviousness**

26. I understand that a patent claim is invalid as obvious if the claimed subject matter, as a whole, would have been obvious to a POSITA as of the priority date of the patent based on one or more prior art references. I understand that an obviousness analysis must consider (1) the scope and content of the prior art, (2) the differences between the claims and the prior art, (3) the level of ordinary skill in the pertinent art, and (4) secondary considerations, if any, of non-obviousness (such as unexpected results, commercial success, long-felt but unmet need, failure of others, copying by others, and skepticism of experts).

27. I understand that obviousness may be shown by a combination of prior art references. I understand that a reference may also be combined with the knowledge of a POSITA, and that this knowledge may be used to combine multiple references. I further understand that a POSITA is presumed to know the relevant prior art. I understand that the obviousness analysis may take into account the inferences and creative steps that a POSITA would employ.

28. I understand that in determining whether a combination of prior art references renders a claim obvious, it is helpful to consider whether there is some teaching, suggestion, or motivation to combine the references and a reasonable

expectation of success in doing so. I understand, however, that an explicit teaching, suggestion, or motivation to combine is not required. Rather, the following factors may be considered in evaluating the existence of a motivation to combine: (1) the interrelated teachings of multiple references; (2) the effects of demands known to those of ordinary skill or present in the marketplace; and (3) the background knowledge possessed by a POSITA.

29. I understand that in order to evaluate the obviousness of the '757 Patent claims over a given prior art combination, I should analyze whether the prior art references disclose every limitation of the challenged claims either explicitly or inherently, as those references are read by the POSITA at the time of the invention. Then, I am to determine whether that combination makes the claimed invention as a whole obvious to the POSITA by a preponderance of the evidence, at the time of the invention.

30. I understand that a patent claiming a combination of elements from the prior art is obvious if the improvement is no more than the predictable use of prior art elements according to their established functions. When there is a design need or market pressure to solve a problem and the prior art suggests a finite number of identified, predictable solutions, a skilled artisan has good reason to pursue the known options within their technical grasp. If this leads to the anticipated success, it

is likely that the product is not one of innovation but rather one of ordinary skill and common sense.

31. I understand that under an obviousness analysis, all that is required is a reasonable expectation of success in combining the prior art references. A guarantee or absolute certainty of success based on the prior art is not required.

## V. SUMMARY OF MY OPINIONS

32. In my opinion, Claims 1–19 of the '757 Patent are anticipated and/or obvious based on the following grounds:

<b>Ground</b>	<b>Summary</b>
1	Claims 1, 3, and 12 are anticipated by Porro (Ex-1005)
2	Claims 1–5, 8–9, 11–12, 15, and 18–19 are anticipated by Mekalanos (Ex-1006)
3	Claims 1–12, 15, and 18–19 are obvious over Mekalanos (Ex-1006)
4	Claims 1–19 are obvious over Mekalanos in view of Porro and Siber (Ex-1007)

## VI. TECHNOLOGY BACKGROUND

### A. Bacterial Vaccines

33. Vaccines prevent infectious diseases by priming the immune system prior to exposure to pathogens, such as bacteria, viruses, or parasites. They mimic

disease-causing agents to stimulate the immune system and build up defense against those agents. *See* Ex-1027 (CDC).

34. The purpose of a vaccine is to induce immunologic memory to pathogens using the vaccine's prior to exposure to the pathogen. *See id.* A successful vaccine should generate potent and long-lasting memory immune cells which will protect the host against disease for long periods of time. Immunologic memory will result in the immune system responding to an encounter with a microbe very quickly, thereby protecting the vaccinee from infection.

35. An important class of potent disease-producing microbes is extracellular bacteria that typically cause disease in young children. *See, e.g.,* Ex-1041 (Finn), 1<sup>1</sup>; Ex-1029 (Mäkelä); Ex-1011 (Plotkin), 8–9, 29, 48. Examples of such pathogens are *Haemophilus influenzae*, *Streptococcus pneumoniae* (pneumococcus), *Neisseria meningitidis* (meningococcus), and *Streptococcus agalactiae* (group B Streptococcus). *See id.* Infection with these pathogens can cause severe outcomes, such as sepsis, pneumonia, acute otitis media, meningitis, and death, as well as other clinical syndromes. *See id.*

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<sup>1</sup> Citations are to stamped pages, except for the '757 patent (Ex-1001), Porro (Ex-1005), Mekalanos (Ex-1006), and Siber (Ex-1007), which reference original pages, column, and/or line numbers.

36. Many bacterial pathogens, including pneumococcus, are encapsulated by polysaccharides (“capsular polysaccharides”), long polymers composed of many repeating units of simple sugars that serve as a protective external layer for the pathogen. *See* Ex-1011 (Plotkin), 47. These capsular polysaccharides constitute a major virulence factor, and antibodies directed against them facilitate the opsonization of the bacteria for phagocytosis (i.e., the main immune defense mechanism against gram positive bacterial pathogens). *See* Ex-1028 (Obaro), 2; Ex 1011 (Plotkin), 46–47. These antibodies are critical in protection against infections making capsular polysaccharides attractive molecules for use as antigens in vaccines. *See, e.g.,* Ex-1028 (Obaro), 2; Ex-1011 (Plotkin), 46–47.

37. By March 2016, capsular polysaccharides had been successfully used in vaccines in adults and older children for decades. Ex-1011 (Plotkin), 46, 50–51. For example, vaccines consisting of individually extracted purified capsular polysaccharides had been proven effective to immunize against *meningococcus* groups A and C and *S. pneumoniae*. *See* Ex-1029 (Mäkelä), 2–3. These vaccines are referred to as polysaccharide vaccines or unconjugated polysaccharide vaccines.

### **1. Polysaccharide-Polypeptide Conjugates in Bacterial Vaccines**

38. While polysaccharide vaccines were immunogenic in adults and older children, they induce poor antibody response in infants and younger children, a

population particularly susceptible to infection with encapsulated bacteria. *See* Ex-1029 (Mäkelä), 2; Ex-1030 (Rappuoli), 1. The poor immunologic response to polysaccharide vaccines in younger children is due to the lack of “helper T-cell” involvement, which is a prerequisite for high-level antibody response and induction of immunologic memory. *See* Ex-1028 (Obaro), 3–4. Instead, capsular polysaccharides are mainly recognized by B-cells, which results in production of IgM antibodies, which are not long-lived. *Id.* And, the B cells do not persist as “memory B cells,” which are needed for protective immunity against exposure to the pathogen.

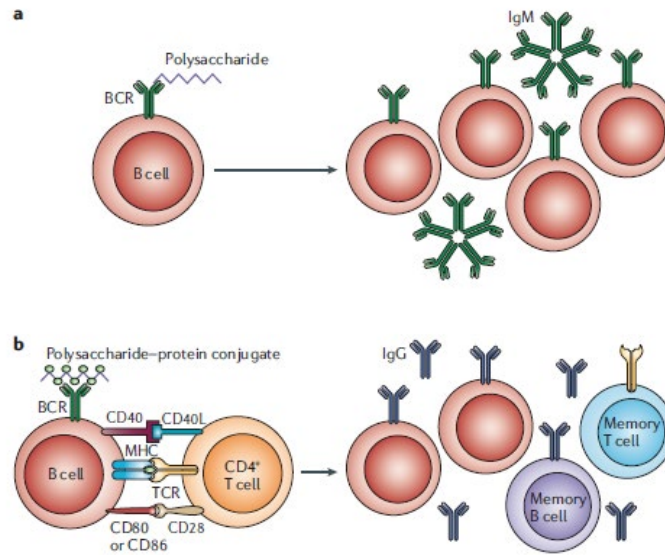
39. Researchers found they could enhance the immune response to capsular polysaccharides by coupling the polysaccharide antigens to protein (or polypeptide<sup>2</sup>) carriers, a process called conjugation. *See* Ex-1031 (Avery); Ex-1028 (Obaro), 4. Through conjugation of bacterial polysaccharides to carrier proteins, a robust, long-term T-cell dependent immune response can be achieved even in younger children. *See, e.g.*, Ex-1028 (Obaro), 3–4; Ex-1033 (Kniskern), 4; Ex-1039 (Lesinski), 3. This is because polysaccharide-protein conjugates not only activate B cells (through the cross-linking of B cell receptors by the polysaccharide), but also recruit helper T

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<sup>2</sup> In the context of conjugate vaccines, the terms carrier polypeptide and carrier protein are used interchangeably. *See* Ex-1001, 5:9–11 (“A polypeptide can be a protein...”).

cells, which recognize a peptide from the protein antigen or a fragment of the polysaccharide coupled to a peptide and attached to the major histocompatibility type 2 molecule to provide additional stimulatory signaling to the B cells. *See, e.g.*, Ex-1028 (Obaro), 3–4; Ex-1033 (Kniskern), 4; Ex-1039 (Lesinski), 3. The more robust stimulation of the B cells results in the production of memory B cells (which not only persist for long periods of time, but are also fast-responding), and generates IgG antibodies (which are much longer-lasting than IgM antibodies). *See, e.g.*, Ex 1028 (Obaro), 3–4; Ex-1033 (Kniskern), 4; Ex-1039 (Lesinski), 3.

40. The differences in the immune cell activation between capsular polysaccharides and polysaccharide protein conjugates is illustrated in the diagram below (from Mazmanian and Kasper, “The love–hate relationship between bacterial polysaccharides and the host immune system,” *Nat. Rev. Immunol.* 6:849–858 (2006) (Ex-1025, 3)):



41. This approach of polysaccharide–protein conjugation was used with great success for the development of the now widely used *Haemophilus influenzae* type b vaccine which was studied in the 1980s and 1990s. *See, e.g.*, Ex-1028 (Obaro), 4; Ex-1032 (Anderson 1987), 1; Ex-1033 (Kniskern), 3–5; Ex-1039 (Lesinski), 3.

42. By March 2016, conjugate vaccines were considered “the golden standard” for measuring the success of clinical immunology because “the advent of conjugate vaccines for prevention of *H. influenzae*, *N. meningitidis*, and *S. pneumoniae* had dramatically improved the quality of life of the [pediatric] population in the western world.” Ex-1005 (Porro), 1:22–28; *see also* Ex-1011 (Plotkin), 8. As a result, there are a variety of well-known and thoroughly-researched strategies for developing effective conjugate vaccines. Specifically, there were

myriad techniques for conjugating specifically-selected antigen polysaccharides to carrier proteins in order to improve opsonophagocytic response (i.e., the body's immune response against all gram positive and some gram negative bacterial pathogens) available for use before 2016. *E.g.*, Ex-1007 (Siber), 7:54–67; Ex-1035 (Caulfield), 8–9; Ex-1005 (Porro), 32:28–33:6; Ex-1006 (Mekalanos); Ex-1010 (Gu), 1.

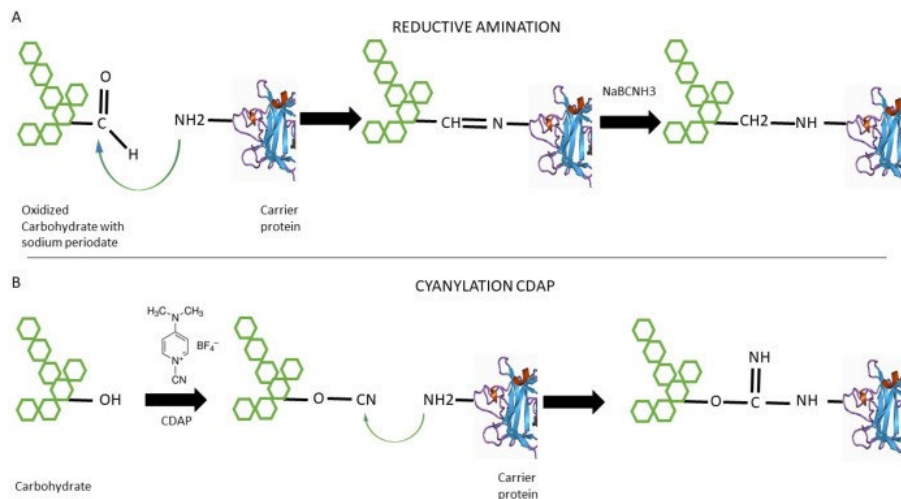
43. By March 2016, numerous polysaccharide-polypeptide conjugate vaccines were in development and described in the literature. *See, e.g.*, Ex-1011 (Plotkin), 15–16, Table 25-2 (providing “representative immunogenicity data” from “select pivotal trials” for pneumococcal conjugate vaccines); Ex-1038 (Payton), 4–8, Table 11.1 (listing various vaccines approved in the U.S., including certain conjugate vaccines); Ex-1039 (Lesinski), 3–4; Ex-1041 (Finn), 5, Table 1 (listing “Some PS-protein conjugate vaccines currently or previously used or approaching licensure”). My lab, for example, had been developing conjugate vaccines against group B *Streptococcus*, and others had explored conjugate vaccines against, for example, *Staphylococcus aureus* and *Salmonella typhi*. Ex-1042 (Kasper 1996); Ex-1043 (Shinefield), 1; Ex-1044 (Lin).

44. As of March 2016, common carrier proteins for polysaccharide-polypeptide conjugates included bacterial toxins or toxoids (inactivated toxins). *E.g.*, Ex-1007 (Siber), 6:63-7:53; Ex-1033 (Kniskern), 5–6 (listing mutant diphtheria

toxin (CRM<sub>197</sub>), diphtheria toxoid, outer membrane protein complex, and tetanus toxoid as protein carriers used on licensed *H. influenzae* Type B conjugate vaccines); Ex-1034 (Emini), 21. Examples of bacterial toxin-derived polypeptide carriers that were commonly used for polysaccharide-polypeptide conjugate vaccines include “the diphtheria and tetanus toxoids, and variants thereof (e.g., DT, DT CRM<sub>197</sub>, TT), cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A or a derivative thereof, pneumococcal adhesion protein A or a derivative thereof, C5a peptidase [from group A or group B] *streptococcus* or a derivative thereof, non-typable *H. influenzae* P4 protein or a derivative thereof, non-typable *H. influenzae* P6 protein or a derivative thereof, *M. catarrhalis* uspA or a derivative thereof, keyhole limpet haemocyanin (KLH), OMPC from *N. meningitidis*, the purified protein derivative of tuberculin (PPD), and protein D from *Haemophilus influenzae* (EP594610-B), or fragments of any of the foregoing.” Ex-1007 (Siber), 7:29–42. In particular, CRM<sub>197</sub>, a non-toxic variant (i.e., toxoid) of diphtheria toxin, was used in multiple commercial and developmental polysaccharide-polypeptide conjugate vaccines prior to 2016. *E.g.*, Ex. 1007 (Siber), 7:45–53; Ex-1033 (Kniskern), 5–6.

45. Additionally, numerous chemical methods of conjugating polysaccharides to carrier polypeptides were known prior to March 2016. *E.g.*, Ex-1007 (Siber); Ex-1035 (Caulfield), 8–9 (describing “known coupling

techniques” for pneumococcal vaccines). Among them are the traditional and widely used reductive amination and activation by cyanogen bromide or related groups as 1-Cyano-4-Dimethylaminopyridine Tetrafluoroborate (CDAP). *E.g.*, Ex-1007 (Siber), 7:55–67 (stating “[a] variety of strategies for coupling polysaccharide antigens to polypeptides are known in the art,” and listing “CDAP” as one method) (citing Ex-1036 (Anderson 1994), which describes conjugation by reductive amination)). The figures below illustrate the reductive amination and CDAP conjugation methods. Ex-1045 (Morais), 4.



46. In addition to these traditional conjugation methods, by March 2016 many other methodologies had been applied in order improve conjugation of capsular polysaccharides to carrier proteins. For example, linkers, including sortase-mediated linkers, could be employed to insert chemical handles for conjugation. *See, e.g.*, Ex-1006 (Mekalanos) (describing conjugation with sortase linker); Ex-1010

(Gu), 1 (describing conjugation with ((2-oxoethyl)thio) spacer or linker). In other conjugation methods, multiple capsular polysaccharides are linked to a carrier protein. Ex-1005 (Porro), 32:28-33:6 (describing coupling three different carbohydrate structures to a carrier protein “via reductive amination”).

## **2. Multivalent Polysaccharide-Polypeptide Conjugate Vaccines**

47. Capsular polysaccharides have characteristic chemical structures, which form the basis of serogroups and serotypes. *E.g.*, Ex-1028 (Obaro), 2; Ex-1029 (Mäkelä), 3. Specifically, strains of a species of extracellular bacteria, called “serotypes” or “serogroups,” are characterized by the particular capsular polysaccharides displayed on their surface, which have different repeating units of sugars. *See, e.g.*, Ex-1028 (Obaro), 2; Ex-1012 (Nahm). In general, antibodies recognize the specific structure and conformation of a polysaccharide, and are therefore serotype-specific. *See, e.g.*, Ex-1011 (Plotkin), 8; Ex-1028 (Obaro), 2–3. Although there may be some cross-reactivity to other similar polysaccharides, antibodies against a polysaccharide from one serotype are generally not cross-protective against structurally-unrelated serotypes. *E.g.*, Ex-1011 (Plotkin), 8, 39; Ex-1028 (Obaro), 2-3; Ex-1039 (Lesinski), 3-4. Because of this lack of cross-protection, vaccines are frequently multivalent, i.e., they include polysaccharides from more than one serotype. *See, e.g.*, Ex-1011 (Plotkin), 8, 39; Ex-1028 (Obaro), 2-3; Ex-1039 (Lesinski), 3-4.

48. There is a natural progression in the development of multivalent vaccines. The earliest version of multivalent vaccines utilizes the most prevalent polysaccharide serotypes. Over time, later versions of the vaccines will incorporate additional clinically-relevant serotypes for broader protection. *E.g.*, Ex-1011 (Plotkin), 10–12.

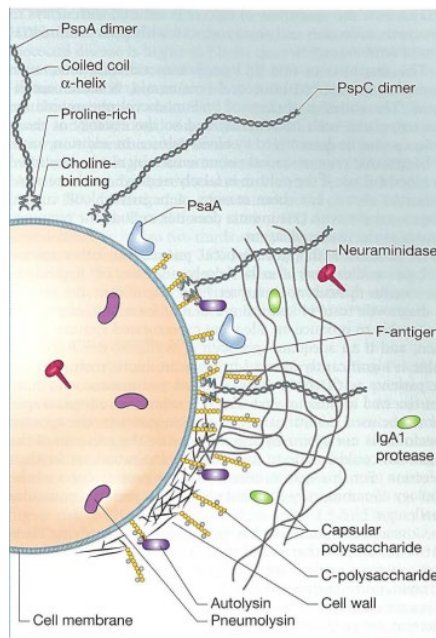
49. For example, since the early 1990s, my group has worked on group B *Streptococcus* conjugate vaccines. We sequentially studied the 4 most virulent serotypes (III, Ia, Ib, II) for newborn children before combining those 4 into a multivalent version. Ex-1047 (Paoletti and Kasper 1994). By the mid-1990s, serotype V had become another prominent cause of infection, and the approach we took was to add a serotype V conjugate to the vaccine.

#### **B. Pneumococcal Vaccines**

50. *S. pneumoniae* (pneumococcus) is an encapsulated gram-positive bacterium and is an asymptomatic colonizer of the nasopharynx. Ex-1011 (Plotkin), 8–9, 47. It is a major cause of a diverse array of infections, including pneumonia, meningitis, bacteremia, sinusitis, and otitis media. *Id.* Infections caused by *S. pneumoniae* are a major cause of morbidity and mortality among children and adults worldwide. *Id.*; *see also* Ex-1026 (Bentley), 1; Ex-1048 (Johnson), 1; Ex-1049 (Burton), 1. *S. pneumoniae* and pneumococcal infections have been a focus of research study for over a century and have served as a “biological model” for

understanding infectious diseases caused by bacteria. Ex-1028 (Obaro), 1; Ex-1011 (Plotkin), 46.

51. The capsular polysaccharide on the cell surface is one of the primary factors responsible for virulence of *S. pneumoniae* in a host. *E.g.*, Ex-1011 (Plotkin), 47; Ex-1026 (Bentley), 1. As of March 2016, there were over 90 recognized serotypes of *S. pneumoniae*. Ex-1011 (Plotkin), 10; Ex-1012 (Nahm), 9; Ex-1026 (Bentley), 1–2. The figure below shows a representation the cell membrane, cell wall, and capsule of *S. pneumoniae*. (reproduced from Ex-1011 (Plotkin), 47).



52. Beginning in the early 1900s, researchers attempted to use inactivated pneumococci as vaccines—these were inactivated “whole cell” bacterial vaccines that included not only the capsular polysaccharides that were serotype-specific, but also the non-capsular components. Ex-1011 (Plotkin), 46; Ex-1050 (Malley), 1.

However, even decades later, the effectiveness of using non-capsular antigens (or “whole cells”) in bacterial vaccines was uncertain. By contrast, capsular polysaccharides were widely understood to be the most effective targets for pneumococcal vaccines, due to their ability to confer broad protection against infection if the correct combination of serotypes were selected. *See* Ex-1050 (Malley), 3; Ex-1011 (Plotkin), 42. Moreover, whole cell vaccines have greater potential for toxicity and adverse events compared to capsular polysaccharides due to their complexity.

53. Beginning in the 1940s, researchers began developing pneumococcal vaccines containing individually extracted purified capsular polysaccharides (“pneumococcal polysaccharide vaccines” or “PPVs”). Ex-1028 (Obaro), 3; Ex-1011 (Plotkin), 46. In 1977, a 14-valent (containing 14 *S. pneumoniae* serotypes) was licensed in the United States for persons of two years or older. Ex-1011 (Plotkin), 46; Ex-1028 (Obaro), 3; Ex-1053 (PDR 1979 Pneumovax®). In 1983, that vaccine was replaced with a 23-valent PPV (containing 23 *S. pneumoniae* serotypes). Ex-1011 (Plotkin), 46; Ex-1028 (Obaro), 3; Ex-1054 (PDR 1990 Pneumovax® 23).

54. To improve the immune response to capsular polysaccharides in younger children, researchers began developing and testing pneumococcal vaccines in which the capsular polysaccharides were conjugated to various carrier proteins.

*See, e.g.*, Ex-1011 (Plotkin), 46. These efforts culminated in the development of a 7-valent pneumococcal conjugate vaccine (“PCV”), Prevnar®, that was approved in 2000, and was shown to be effective in younger children. *Id.* The Prevnar® vaccine contained *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F—believed to be the seven most prevalent disease-causing serotypes at that time—conjugated to the CRM197 carrier protein. *See* Ex-1005 (Porro), 2:5–16, 13:20-22; Ex-1011 (Plotkin), 11, 46. In 2009, a “[t]en valent pneumococcal vaccine was approved under the trade name Synflorix® containing polysaccharide serotypes 1, 4, 5, 6B, 7, 9, 14, 23F conjugated to protein D (PD), serotype 18C conjugated to tetanus toxoid (TT) and serotype 19F conjugated to diphtheria toxoid (DT).” Ex-1009 (Matur), 3; Ex-1011 (Plotkin), 11–12. Then in 2010, Prevnar 13®, a 13-valent PCV containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F each conjugated to CRM197 was approved. Ex-1011 (Plotkin), 508, 46; Ex-1005 (Porro), 32:5–16; Ex-1006 (Mekalanos), 30:1–14; Ex-1016 (PDR 2011 Prevnar 13®).

### **1. Serotype Selection Was Dictated by Disease Prevalence**

55. As described above, there were over 90 recognized serotypes of *S. pneumoniae* as of March 2016. Ex-1011 (Plotkin), 10; Ex-1012 (Nahm), 9; Ex-1026 (Bentley), 1–2. Skilled artisans understood that the immune response for a pneumococcal vaccine is generally serotype specific, and the serotypes to include in a vaccine should be determined by disease prevalence and virulence. *E.g.*, Ex-1011

(Plotkin), 46; Ex-1028 (Obaro), 2. Skilled artisans also understood that multiple (or plurality of) pneumococcus serotypes needed to be included in a vaccine to cover a meaningful percentage of disease caused *S. pneumoniae*. *See, e.g.*, Ex-1011 (Plotkin), 8, 39; Ex-1028 (Obaro), 2–3; Ex-1005 (Porro), 2:5–16, 67:10–12 (noting that “presently licensed 13-valent [i.e., includes 13 serotypes] vaccine covers about 61% of IPD in children younger than 5 years”).

56. POSITAs understood that different pneumococcal serotypes vary in prevalence and virulence, depending on a multitude of factors, including host, age, region and country. *See, e.g.*, Ex-1028 (Obaro), 2; Ex-1011 (Plotkin), 10-11. Their distribution is temporal and varies by geographic location. Ex-1028 (Obaro), 2; Ex-1011 (Plotkin), 10–11. As a result, skilled artisans routinely monitored serotypes most likely to cause disease in order to identify polysaccharide candidates from key serotypes for inclusion in vaccines. *E.g.*, Ex-1011 (Plotkin), 10 (“Candidates for conjugate vaccines have therefore been designed based on knowledge about the relative importance of disease-causing serotypes.”); Ex-1026 (Bentley), 1 (“[P]olyvalent polysaccharide vaccines have been developed in which CPS [polysaccharides] from the serotypes most commonly associated with invasive disease in children are linked to a protein carrier, and a seven-valent conjugated polysaccharide vaccine has been introduced and shown to be highly effective”).

57. This concept is illustrated by the progression of commercial pneumococcal vaccines. Initial unconjugated PPVs from the 1970s and 1980s expanded from 14-valent to 23-valent to cover the most common invasive serotypes in adults. Then conjugated PCVs were approved for pediatric use in 2000 as first 7-valent PCV7 (which included serotypes 4, 6B, 9V, 14, 18C, 19F, 23F), then extended to 10-valent and 13-valent formulations as surveillance data revealed additional important serotypes.

58. Accordingly, it was well known that a POSITA would inevitably update conjugate vaccine formulations to include prevalent serotypes to optimize disease coverage. Indeed, it was well known that “serotypes could be substituted [in a vaccine] depending on the age of the recipient receiving the vaccine and the geographical location where the vaccine will be administered.” *E.g.*, Ex-1052 (Bertaud), 10 (“[O]ne or two other serotypes could be substituted depending on the age of the recipient receiving the vaccine and the geographical location where the vaccine will be administered.”); Ex-1034 (Emini), 19 (“[T]here is a need to address remaining unmet medical need for coverage of pneumococcal disease due to serotypes not found in PREVNAR 13® and potential for serotype replacement over time”); Ex-1021 (Blay), 12; Ex-1011 (Plotkin), 10–11.

59. In other words, well before March 2016, it was routine for POSITAs to determine serotypes to be included in a pneumococcal vaccine based on serotype

prevalence and virulence in the population at the time a vaccine is developed because serotypes in commercial vaccines must be updated over time to optimize protection of the population. Moreover, epidemiological studies were the field's accepted basis to expand coverage of a pneumococcal vaccine. Accordingly, a POSITA would have known to look to recently-published sero-epidemiological studies to identify key serotypes to include in a conjugate vaccine. *E.g.*, Ex-1005 (Porro), 66:28–67:9 (describing that new vaccines should be based on “[n]ew emerging serotypes of *S. pneumoniae* according to the public available data on epidemiology and antibiotic resistance”) (citing Ex-1057 (Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract)). This is evidenced by the multiple references expressly identifying serotypes 23A, 23B, and/or 35B for inclusion in PCVs. *Infra* §IV.B.2.

## 2. Serotypes 23A, 23B, and 35B Were Known Vaccine Targets

60. Prior to March 2016, multiple epidemiological studies from a variety of geographic locations identified *S. pneumoniae* serotypes 23A, 23B, and/or 35B to have increased disease potential in various populations.

61. For example, a 2009 study in the United States stated that though “PCV7 [serotypes] account for only about one-third of pneumococcal isolates recovered from [acute COPD] patients .... [i]f the vaccine were to offer protection against cross-reactive serotypes (such as **23A/B** and 9L/N) then this could be

extended to about two-thirds of exacerbation-associated isolates.” Ex-1018 (Dransfield), 6. Another study in the United States published in 2014 reported that “[a]mong the [penicillin non-susceptible *S. pneumoniae*] subset, serotypes showing a proportional increase were **35B**, 15B, and **23B** .... [and among multidrug resistant] strains, the largest proportional increases were observed in serotypes **35B**, 15B, and **23A**.” Ex-1020 (Richter 2014), 1.

62. Similarly, a German study published in 2015 observed that “[n]on-PCV13 serotypes which increased among adults following the introduction of childhood-vaccination were 6C, 12F, 15B, 15C, 22F, **23A**, **23B** and **35B**.” Ex-1023 (Imöhl), 4. A 2015 study from Spain also reported that “[s]urveillance program results suggest that pneumococci of various serogroups/serotypes not included in PCV13 (e.g., 11, 12, 15, 22F, **23A**, **23B**, 33F, 24, 34, and **35B**) are rapidly increasing in prevalence worldwide.” Ex-1019 (Domenech), 2. Likewise, a Netherlands study published in 2015 found “[s]everal serotypes (e.g., 6A, 6B, **23A** and **23B**) are associated with a significantly higher propensity to cause disease in high risk patients.” Ex-1017 (Wagenvoort), 1, 5. Additionally, a 2008/2009 study in England identified that serotypes **23A** and **23B** (among others) increased significantly in certain populations of children as compared to pre-vaccinated children sampled in 2001/2002. *See* Ex-1024 (Flasche), 2, 4.

63. In my opinion, based on these epidemiological studies, a person of skill in the art would have understood that serotypes 23A, 23B, and 35B were all likely vaccine targets as of 2015, and would have been motivated to include them in pneumococcal vaccines due to their increasing prevalence in various populations.

64. Additionally, multiple prior art references also specifically proposed including serotypes 23A, 23B, and/or 35B in PCVs. In 2006, for example, Nierop taught methods for expression of capsular polysaccharides for use in both conjugated and unconjugated polysaccharide vaccines, recommending inclusion of *S. Pneumonia* serotypes 23A, 23B, and 35B. Ex-1022 (Nierop), 2, 11. Specifically, Nierop states:

The use of type specific genes from pneumococcal serotypes (Danish nomenclature) 1, 2, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10C, 11A, 11B, 11C, 11F, 12B, 12F, 13, 14, 15F, 15A, 15B, 15C, 16F, 16A, 17F, 17A, 18A, 18B, 18C, 19F, 19A, 19B, 19C, 20, 21, 22F, 22A, **23A**, **23B**, 24F, 24A, 24B, 25F, 25A, 27, 28F, 28A, 29, 33F, 33A, 33B, 33C, 10F, 11D, 12A, 18F, 23F, 31, 32F, 32A, 33D, 34, 35F, 35A, **35B**, 35C, 36, 38, 39, 40, 41F, 41A, 42, 43, 44, 45, 46, 47F, 47A, 48 are particularly preferred embodiments of the invention.

*Id.* at 11.

65. That same year, Blay suggested inclusion of *S. Pneumoniae* serotypes in a conjugate vaccine to protect against influenza. Ex-1021 (Blay), 10 (describing “capsular saccharides from *Streptococcus pneumoniae* covalently bound to a carrier protein.”). Blay explains:

[A] skilled artisan will recognize that it would be possible to create new vaccine variations with the inclusion or omission of polysaccharides from a variety of pneumococcal serotypes. For example, an anti-influenza vaccine according to the present invention can be manufactured using polysaccharides from all known serotypes of *Streptococcus pneumoniae*. In general, it is only required to include the polysaccharides necessary to elicit the anti-influenza response.

*Id.* at 11.

66. In my opinion, although pneumococcal polysaccharides have not been established to elicit an anti-influenza response, Blay demonstrates that skilled artisans had contemplated inclusion of serotypes 23A and 23B in conjugate vaccines. Indeed, Blay also taught that serotypes 23A and 23B might be substituted for 23F in conjugate vaccine formulations:

A skilled artisan will recognize that it is possible to substitute certain serotypes without compromising efficacy of the vaccine. Thus, in one preferred embodiment, *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6B (6A), 7F (7C), 8, 9N (9A), 9V, 10A, 11A (11B), 12F, 14, 15B (15A, 15C, 15F), 17F, 18C (18A, 18B), 19F (19B), 19A, 20, 22F (22A), 23 F (**23A**, **23B**), and 33F (33C) could be used to manufacture the anti-Influenza vaccine of the present invention. The numbers in parentheses refer to serotype substitutions that reflect alternative embodiments of the vaccine. For example, as indicated in parentheses above, the *S. pneumoniae* serotype 6B could be substituted with serotype 6A; similarly, *serotype 23 F could be substituted with either 23A or 23B*.

*Id.* at 11–12. In my opinion, this represents the concept that while certain serotypes may show cross-reactivity, this cross-reactivity might not confer full cross-protection. However, Blay suggests some vaccine developers would be motivated to at least test cross-reactive serotypes for potential substitution.

67. In 2014, Porro described pneumococcal conjugate vaccines that linked up to three polysaccharides to a single carrier protein. Porro specifically taught inclusion of serotypes 23A and 35B in its vaccine compositions:

According to preferred embodiments of the antigenic multivalent molecular construct of the invention the carried carbohydrate structures are selected among, but not limited to, Ps [polysaccharide] of *Streptococcus pneumoniae* (type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8, 9N, 9V, 10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19A, 19F, 20, 22F, **23A**, 23F, 33F, **35B**, ...”

Ex-1005 (Porro), 14:26–15:3.

68. In 2015, Gu taught pneumococcal conjugate vaccines in which the conjugation process included the use of a spacer. Ex-1010 (Gu), 1. Specifically, Gu states:

In some embodiments, the oxo-eT linked glycoconjugate comprises a pneumococcal (Pn) capsular polysaccharide derived from *Streptococcus pneumoniae*. In specific embodiments, 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, 11A, 12F, 14, 15A, 15B, 17F, 18C, 19A, 19F, 20, 22F, **23A**, **23B**, 23F, 33F and **35B** capsular polysaccharides. ... In specific embodiments, the Pn capsular polysaccharide is selected from the group consisting of Pn-serotype 2, 9N, 15A, 17F, 20, **23A**, **23B** and **35B** capsular polysaccharides.

Ex-1010 (Gu), 12.

69. In 2015, Mekalanos described pneumococcal conjugate vaccines, manufactured using a sortase-mediated conjugation process, comprising, *inter alia*,

serotypes 35B and 23B. Ex-1006, 3:20–25; Ex-1013, 6; *Infra* §§IX.B. (Ground 2), IX.C. (Ground 3). Specifically, Mekalanos taught:

The *Streptococcus pneumoniae* polysaccharide of the immunogenic composition may be a capsular type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22F, 23B, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33D, 33F, 34, **35A, 35B**, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48.

Ex-1006, 3:20–25; *see also*, Ex-1013, 6 (same).

70. In 2016, Matur also described inclusion of *S. pneumoniae* 23A, 23B, and 35B in pneumococcal conjugate vaccine formulations. Specifically, Matur taught:

The present invention also provides an immunogenic multivalent serotype composition, wherein the capsular polysaccharides from serotypes 1, 3, 4, 5, 6B, 7F, 9N, 9V, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F of *S. pneumoniae* are conjugated to a carrier protein CRM197, wherein the composition does not contain capsular polysaccharide from serotype 6A. Further, the present invention may additionally contain one or more serotypes selected from 6C, 8, 10A, 11A, 12F, 15A, **23A, 23B and 35B** of *S. pneumoniae*.

Ex-1009 (Matur), 10.

71. Separately, Babb discloses incorporation of the claimed serotypes in deactivated whole cell pneumococcal vaccines. Ex-1008, 19 (“Vaccines of the present invention may comprise photon-irradiated (e.g. gamma-irradiated and/or X-irradiated) streptococcal derivatives.”)

72. Specifically, Babb states:

In some embodiments, vaccines of the invention comprise one or more serotypes of *Streptococcus pneumoniae*. Accordingly, the vaccines may comprise any one of more of *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10C, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22A, 22F, **23A**, **23B**, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33C, 33D, 33F, 34, 35A, **35B**, 35C, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47 A, 47F, and/or 48.

*Id.*

73. In my opinion, the reasons for including particular serotypes in a pneumococcal whole cell vaccine are the same as those for including them in a PCV (i.e., based on prevalence and virulence in the targeted population).

### **C. Immunogenicity and Protective Capacity**

74. One method researchers use to assess a bacterial vaccine's immunogenicity is by measuring anti-capsular antibody levels with the use of a well-known enzyme-linked immunosorbent assay (ELISA). Ex-1049 (Burton), 1; Ex-1011 (Plotkin), 12.

75. Researchers also measure protective capacity of a vaccine to determine its efficacy. Protective capacity refers to the vaccine's ability to prevent disease. The opsonophagocytic killing assay ("OPA" or "OPKA") is a widely accepted reference method for measuring the protective capacity of pneumococcal antibodies. Ex-1049

(Burton), 1; Ex-1011 (Plotkin), 13. It is used to quantify opsonic antibody activity present in blood serum samples.

76. Opsonization is the process where “opsonins” such as antibodies or complement proteins coat that antigen, effectively tagging them to make them more susceptible for destruction by macrophages and neutrophils through phagocytosis. Phagocytosis is the engulfment of the antigen by macrophages and other phagocytic cells like neutrophils after the bacteria is opsonized. Ex-1055 (Mantis), 36. A POSITA would have understood “opsonophagocytosis” or an “opsonophagocytic response” to be the combined mechanism of first coating (opsonizing) the antigens with opsonins, which are primarily antibodies and complement, and subsequent engulfment by phagocytic cells (phagocytosis) that results in killing the bacteria.

77. An OPA assay attempts to quantify this process by incubating a known number of pathogenic bacteria with a sample of freshly drawn blood or serum along with a source of antibodies. After a specified incubation period, the number of surviving bacteria is determined and compared to the number present at the start of the assay to calculate the percentage of killing. This measured percentage of killing provides a direct measure of the functional activity of antibodies against a specific pathogen, which is a key indicator of a vaccine's potential to provide protection. *See* Ex-2011 (Plotkin), 13.

**D. Dosage and Administration of PCVs**

78. By 2016, POSITAs understood that under some circumstances, such as conditions of greater immune deficiency or immune immaturity, multiple administrations of a vaccine—for example, an initial dose and a second dose of the same or different composition—may improve immunogenicity. Indeed, a multiple dose schedule is frequently used in conditions such as immune deficiency or immune immaturity. *See, e.g.*, Ex-1007 (Siber), 10:33–11:3; Ex-1011 (Plotkin), 14–15; Ex-1021 (Blay), 3.

79. A person of skill in the art also would have understood that a second dose could comprise administration of a vaccine composition that is identical to the previously received first dose or, alternatively, a second dose may comprise administration of a vaccine composition that is distinct from the previously received first dose. *See, e.g.*, Ex-1007 (Siber), 10:33–11:3; Ex-1056 (Sigurdardottir), 1. A person of skill might choose the former in order to increase antibody production or might choose the latter to increase serotype coverage by including one or more additional serotypes in the second composition.

80. A person of skill in the art would additionally have understood that the interval between doses is subject to change based on variables like recipient age and health or due to requirements of different vaccine compositions or combinations of compositions. The interval between doses in a given schedule may be as little as

about two weeks or as long as a year, depending on the characteristics of the vaccine and/or its recipient. *See* Ex-1007 (Siber), 11:4–12:5. For example, Siber teaches that “[i]n immunization schedules of the present invention, once a first vaccine dose has been administered, there is a first interval before administration of a subsequent dose,” which might be “at least about two weeks, one month, six weeks, two months, three months, six months, nine months, 12 months, or longer.” *Id.* at 11:10–13.

81. By March 2016, based on commercially available pneumococcal vaccines, a person of skill in the art would have understood that a “dose” of a pneumococcal conjugate vaccine is typically 0.5 mL. *See, e.g.*, Ex-1011 (Plotkin), 51; Ex-1016 (PDR 2011 Prevnar 13®); Ex-1006 (Mekalanos), 26:8–9. Additionally, the composition of a 0.5 mL dose (i.e., the amount of specific polysaccharide serotypes and/or carrier protein in a single dose) is typically reported in µg—unlike the percent weight values recited in the ’757 Patent. Ex-1016 (PDR 2011 Prevnar 13®). The weight percent may be estimated, however, by making certain assumptions, as described in greater detail below. *Infra* §IX.C.2.b–c.

## **VII. THE ’757 PATENT**

### **A. Specification**

82. The ’757 Patent is broadly directed to pneumococcal saccharide-polypeptide conjugate vaccines. Ex-1001. The specification describes well-known examples of pneumococcal conjugate vaccine constructs and methods of making

them that had been used widely in commercial vaccines. For example, it describes a variety of known methods of isolating and purifying polysaccharides, provides a broad list of potential carrier polypeptides, and describes several known techniques for conjugating polysaccharides to carrier polypeptides. Ex-1001, 15:40–17:20, 18:22–52, 22:44–26:43.

83. It also describes vaccine compositions encompassing saccharides “from any bacteria and fungi that can incorporate saccharides into their surface structure,” including from *S. pneumoniae*. Ex-1001, 7:14–16. The specification further states that “[s]ome non-limiting examples of saccharides from a *S. pneumoniae* serotype include, but are not limited to 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19F, 19A, 22F, 23F, **23A**, **23B**, 24F, 24B, 31, 33F, 34, 35F, **35B**, 38, and Serogroup 20. Serogroup 20 can comprise serotype 20A and serotype 20B.” Ex-1001, 8:3–10 (emphasis added).

84. Notably, the specification does not provide any particular reason that the claimed serotypes (e.g., 23A, 23B and/or 35B) should be targeted over any of the other listed serotypes. Ex-1001.

## **B. Claims**

85. As I prefaced above, Claim 1, the only independent claim of the ’757 Patent, does not recite any particular carrier protein or conjugation technique. Ex-1001, Cl. 1. Accordingly, I understand that independent Claim 1 encompasses

pneumococcal conjugate vaccines utilizing any suitable carrier polypeptide and/or any available conjugation method.

86. Based on this understanding, in my opinion, the only discernable difference between the claims of the '757 Patent and the prior art vaccines is the inclusion of specific polysaccharide serotypes (*S. pneumoniae* serotypes 23A, 23B, and/or 35B). The dependent claims merely recite additional known serotypes, known aspects of pneumococcal-conjugate vaccines (excipients, adjuvants, carriers), or known methods of administration.

### **C. Prosecution History**

87. The '757 Patent was filed on September 27, 2018. Ex-1001. As shown in its prosecution history, the '757 Patent claims priority to PCT application No. PCT/US2017/025621 (filed on March 31, 2017) ("757 PCT"), which claims priority to provisional application No. 62/373,807 (filed on August 11, 2016), provisional application No. 62/372,263 (filed on August 8, 2016), provisional application No. 62/330,245 (filed on May 2, 2016), and provisional application No. 62/316,555 (filed on March 31, 2016). Ex-1001; Ex-1004.

88. It appears that the '757 PCT was originally filed with 295 claims. Ex-1004, 254–282. However, after a preliminary amendment and response to a restriction requirement, most of the claims were cancelled, and the only remaining independent claim under examination stated:



90. Six days later, on March 10, 2021, the examiner issued a Notice of Allowance amending the Markush listing to just 23A, 23B, and 35B (from the 38 serotypes originally listed), and explained allowance because those recited vaccines were “novel and nonobvious.” Ex-1004, 1241–42. The allowed claim, showing the amendment, is reproduced below.

A pharmaceutical composition comprising a plurality of at least two unique an immunogenic saccharide-polypeptide conjugates, each comprising, individually a, at least two unique capsular polysaccharides, fragments thereof, or combinations thereof, conjugated to a polypeptide, wherein each of the at least two unique capsular polysaccharides, or fragments thereof, is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 1, 2, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18G, 19A, 19F, 23F, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15G, 16F, 17F, 20A, 20B, 22F, 23A, 23B, 24F, 24B, 31, 33F, 34, 35F, and 35B, and 38.

Ex-1004, 1240.

91. In my opinion, the examiner’s conclusions were inconsistent with the prior art. *See Supra* §VI.B.2. As described above, multiple prior art references identified the claimed serotypes (*e.g.*, 23A, 23B, and/or 35B) for inclusion in pneumococcal conjugate vaccines. *See Supra* ¶¶64–70 (discussing Ex-1022 (Nierop), 11; Ex-1021 (Blay), 10–12; Ex-1005 (Porro), 14:26–15:3; Ex-1010 (Gu), 12; Ex-1006 (Mekalanos), 3:20–25; Ex-1009 (Matur), 10). Additionally, Babb taught use of serotypes 23A, 23B, and/or 35B in whole cell pneumococcal vaccines. *See Supra* ¶¶71–72. I understand from counsel that at least Babb and Matur were

considered during prosecution of the '757 Patent, which is directly contrary to the examiner's assertion that serotypes 23A, 23B, and 35B were "free of prior art."

92. Moreover, in my opinion, multiple references not found by the examiner, including Porro, Mekalanos, Nierop, Blay, and/or Gu each of which directly teaches pneumococcal conjugate vaccines and expressly listing at least one or more of 23A, 23B, and/or 35B. *See Supra* ¶¶64–70.

93. I additionally understand from counsel that Porro was identified by a different examiner during prosecution of similar claims in a related continuing application. Additionally, I understand from counsel that the other examiner found similar claims in a related continuation application to be anticipated by Porro. *See Ex-1005; Ex-1006; see also* §VI.B.2.

## **VIII. OVERVIEW OF THE APPLIED PRIOR ART REFERENCES**

### **A. Porro (Ex-1005)**

94. WO 2014/118201 ("Porro"), titled "Multivalent Glycoconjugate Vaccines," is the WIPO publication of PCT International Application No. PCT/EP2014/051670 that designated the United States, published on August 7, 2014. *See Ex-1005* at Title, Cover. I have been informed by counsel that Porro is prior art to the '757 Patent.

95. Porro states that it "opens new avenues in the field of clinical immunology and vaccinology." *Id.* at 11:19–20. Specifically, Porro relates to

improving conventional conjugate vaccines by inventing “a new category of conjugate antigens which feature the expression of multiple carbohydrate specificities” to decrease “the amount of carrier protein needed in the [already] available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer.” *Id.* at 4:6–24.

96. Porro also teaches that a POSITA would have looked to include “emerging serotypes” in new “broad-spectrum vaccines” based on “available data on epidemiology and antibiotic resistance.” *Id.* at 66:28–67:9 (citing Ex-1057 (Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract)). Porro explains that a POSITA would have been motivated to include “newly emerging types of *S. pneumoniae*” in order to “elevate the bar on coverage.” *Id.* at 67:9–25.

97. Porro teaches that compositions including those “emerging serotypes,” which would be determined from available data corresponding to contemporary sero-epidemiological studies, are “preferred embodiments” for its multi-valent vaccine:

According to preferred embodiments of the antigenic multivalent molecular construct of the invention the carried carbohydrate structures are selected among, but not limited to, Ps of *Streptococcus pneumoniae* (type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8, 9N, 9V, 10A, 11A, 11B, 11C,

11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19A, 19F, 20, 22F, **23A**, 23F, 33F, **35B** ...).

*Id.* at 14:26–15:3.

**B. Mekalanos (Ex-1006)**

98. WO 2017/011338 (“Mekalanos”), titled “Sortase-Mediated Coupling of Immunogenic Polysaccharide-protein Conjugates and Their Use,” was filed on July 8, 2016, and published on January 19, 2017. Ex-1006 at Title, Cover. I understand that Mekalanos claims priority to a U.S. provisional application filed on July 10, 2015. Ex-1006, Ex-1013. I understand from counsel that Mekalanos is prior art to the ’757 Patent.

99. Mekalanos relates to immunogenic vaccine compositions comprising “immunogenic polysaccharide-protein conjugates, a novel sortase-mediated method of making immunogenic polysaccharide-protein conjugates, and methods of administering immunogenic polysaccharide-protein conjugates.” *Id.* at 1:9–11.

100. Mekalanos teaches that its vaccine compositions “may include a *Streptococcus pneumoniae* polysaccharide.” *Id.* at 3:16–17. It further teaches that “[t]he *Streptococcus pneumoniae* polysaccharide of the immunogenic composition may be a capsular type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22F, **23B**,

23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33D, 33F, 34, 35A, **35B**, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48.” *Id.* at 3:20–25.

101. Accordingly, Mekalanos teaches that its immunogenic vaccine compositions may comprise the *Streptococcus pneumoniae* polysaccharide serotypes recited in the claims of the ’757 Patent, including serotypes 23B and 35B. *See id.*

102. Mekalanos also teaches that its immunogenic composition, “when administered to a mammal, elicits a T-cell dependent immune response in the mammal.” *Id.* at 4:23-25. Mekalanos further teaches that “[a]dministering desirably includes parenteral administration (for instance, by subcutaneous, intramuscular, intravenous, or intradermal injection)” and that “[t]ypically the immunogenic conjugate is in a volume of about 0.5 ml for subcutaneous injection, 0.1 ml for intradermal injection, or 0.002-0.02 ml for percutaneous administration.” *Id.* at 6:5–6, 26:7–8.

**C. Siber (Ex-1007)**

103. U.S. Patent No. 8,808,707 (“Siber”), titled “Pneumococcal Dosing Regimen,” was filed on April 26, 2007, and issued on August 19, 2014. Ex-1007 at Title, Cover. I understand from counsel that Siber is prior art to the ’757 Patent.

104. Siber teaches “methods of immunizing older adult subjects against *Streptococcus pneumoniae* infection” wherein an “initial” immunization “with a conjugated pneumococcal polysaccharide vaccine” is later followed by one or more “additional immunization doses comprising conjugated pneumococcal polysaccharide vaccine or unconjugated pneumococcal polysaccharide vaccine composition.” *Id.* at Abstract.

105. Siber teaches a wide variety of conjugated pneumococcal vaccines that generally comprise polysaccharides of different *S. pneumoniae* serotypes conjugated to several different carrier polypeptides. *See generally id.* at 3:33–6:42 (describing *S. pneumoniae* capsular polysaccharide antigens), 7:3–67 (describing carrier proteins and conjugation methods), 8:1–9:11 (describing existing PCVs). These carrier proteins include diphtheria toxoids (CRM197 and Aventis 4vPnD), Protein D of *H. influenzae*, or tetanus toxoid. *See, e.g., id.* at 8:36–47, 7:3–67 (detailing suitable carrier proteins and conjugation methods), Cls. 17, 35.

106. Siber also teaches that while available pneumococcal vaccines accounted “for about 90% of pneumococcal blood isolates [then] identified as relevant for infection,” pneumococcal vaccines “could be modified so as to include additional and/or different combinations of serotype specific polysaccharides” as “infectious serotypes may shift over time, and/or various serotypes may be particularly relevant for specific populations.” *Id.* at 5:31–42.

107. Siber additionally teaches that administration of an initial dose, followed by a booster dose of either (1) the same conjugated or unconjugated pneumococcal vaccine or (2) a different conjugated or unconjugated pneumococcal vaccine may provide “beneficial immunoprotective” effects. *Id.* at 2:46–51 (“an initial immunization dose with conjugate vaccine followed by at least one additional immunization dose with either conjugate or unconjugated polysaccharide vaccine gives a beneficial immunoprotective effect”); *see also id.* at 10:23–11:14 (further explaining the immunological benefits of administering multiple vaccine doses to the same recipient).

## **IX. DETAILED EXPLANATION OF THE UNPATENTABILITY GROUNDS**

### **A. Ground 1: Claims 1, 3, and 12 are Anticipated by Porro**

108. In my opinion, at least Claims 1, 3, and 12 of the ’757 Patent are anticipated by Porro. As described in further detail below, in my opinion, Porro discloses pneumococcal conjugate vaccine compositions that meet all of the limitations of at least Claims 1, 3, and 12.

**1. Independent Claim 1**

**a. Element 1[pre]: A pharmaceutical composition comprising**

109. In my opinion, Porro discloses a pharmaceutical composition. Specifically, Porro discloses “glycoconjugate vaccines and formulations containing the same.” Ex-1005, 1:8–9.

**b. Element 1[a]: a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide,**

110. In my opinion, Porro discloses a pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide.

**(1) Immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide**

111. Porro discloses immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide.

112. Porro discloses “an antigenic multivalent molecular construct consisting of a basic unit comprising a helper-T dependent carrier protein covalently bound to a minimum of three carbohydrate structures of different serological specificity.” Ex-1005, 11:29–12:5. And, according to Porro, “the term carbohydrate

structures is intended to comprise ... polysaccharides (such as capsular polysaccharides).” Ex-1005, 12:19–22.

113. Although Porro’s “multivalent molecular construct” comprises “a minimum of three carbohydrate structures” covalently bound (i.e., conjugated) to each “carrier protein,” I have been informed by counsel that the term “comprising” means a claim limitation covers the structural elements recited plus additional elements. Based on this understanding, in my opinion, Porro’s multivalent molecular construct falls within Element 1[a], which states “each comprising individually a capsular polysaccharides conjugated to a polypeptide.”

114. Additionally, Porro discloses that in “preferred embodiments ... the helper-T dependent carrier protein ... is selected between the group of natural diphtheria mutant protein CRM 197 ..., tetanus toxoid, [and others].” Ex-1005, 13:4–19. Porro’s carrier proteins are the same polypeptides/carrier proteins disclosed by the ’757 Patent. Ex-1001, 17:31–50 (“[a] polypeptide ... can be a carrier protein” such as “CRM197, tetanus toxoid, a cholera toxoid,” among others).

**(2) A plurality of at least two ... conjugates**

115. Porro discloses a pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates.

116. Porro discloses “one or ***more than one*** antigenic multivalent molecular construct ... in a vaccine for the protection of a subject (preferably belonging to the

human [pediatric]population) from the infections due to at least one agent” from *S. pneumoniae*. Ex-1005, 25:6–11 (emphasis added); *see also id.* at 1:6–16 (“The present invention refers to new conjugate antigens expressing built-in multiple epitopes and to polyvalent glycoconjugate vaccines and formulations containing the same. In addition, the present invention concerns the use of these vaccines in particular for the protection of the human population, and in particular for the protection of the [pediatric] population from pulmonary and systemic infections due to *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *K. pneumoniae*, *M. tuberculosis*, *S. aureus*, or from intestinal infections due to *S. typhi*, *V. cholerae* and *E. coli*.”) (emphasis added).

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

117. In my opinion, Porro discloses including serotypes 23A and 35B in a conjugated vaccine. Specifically, Porro explains that “[n]ew emerging serotypes of *S. pneumoniae* according to the [publicly] available data on epidemiology and antibiotic resistance, are ... type **23A** ... and 35 (type **35B**) (Swanson D., IDSA meeting, Boston, 2011)” and that “such antigen [Polysaccharides] might be likely included in a further up-dated broad-spectrum vaccine formulation prepared

according to the molecular construct disclosed.” Ex-1005, 66:28–67:9 (citing Ex-1061 (IDSA Abstract)).

118. Porro additionally discloses that these pneumococcal polysaccharide serotypes are “preferred” for its multivalent vaccine:

According to *preferred embodiments* of the antigenic multivalent molecular construct of the invention the carried carbohydrate structures are selected among, but not limited to, Ps of *Streptococcus pneumoniae* (type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8, 9N, 9V, 10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19A, 19F, 20, 22F, **23A**, 23F, 33F, **35B**...

Ex-1005, 14:26–15:3 (emphases added).

119. I understand from counsel that because this limitation is written in Markush format, this limitation is anticipated even though Porro does not specifically list serotype 23B. *Supra* §IV.B.

2. **Dependent Claims 3 and 12**

- a. **Claim 3: The pharmaceutical composition of claim 1, wherein at least one polypeptide of the plurality comprises CRM<sub>197</sub>, 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.**

120. In my opinion, Porro also discloses the pharmaceutical composition of claim 1, wherein at least one polypeptide of the plurality comprises CRM<sub>197</sub>.

121. For example, Porro specifically discloses using CRM<sub>197</sub> for use as a carrier protein in a pneumococcal conjugate vaccine. Ex-1005, 2:5–11 (“For instance, vaccines like ‘Pevnar’, present in the western markets since the year 2000 (formerly in its 7-valent formulation and now in its 13-valent formulation, both formulations containing single type-specific polysaccharide (Ps) of *S. pneumoniae* covalently conjugated to the *carrier protein CRM197*) is nowadays recommended by WHO to all countries of the world”), 13:4–9 (“According to preferred embodiments of the present invention the helper-T dependent carrier protein ... is selected between the group of natural diphtheria mutant protein *CRM197* ... ”),

13:20–22 (“According to the most preferred embodiment of the present invention the carrier protein is the natural diphtheria mutant protein *CRM197*.”).

- b. Claim 12: The pharmaceutical composition of claim 1, 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.**

122. In my opinion, Porro discloses 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.

123. Specifically, Porro discloses that “[a]ccording to preferred embodiments of the antigenic multivalent molecular construct of the invention the carried carbohydrate structures are selected among, but not limited to, Ps of *Streptococcus pneumoniae* (type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8, 9N, 9V, 10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19A, 19F, 20, 22F, 23A, 23F, 33F, 35B.” Ex-1005, 14:26–15:3 (emphases added).

**B. Ground 2: Claims 1-5, 8-9, 11-12, 15, and 18-19 are Anticipated by Mekalanos**

124. In my opinion, at least Claims 1–5, 8–9, 11–12, 15, and 18-19 of the ’757 Patent are anticipated by Mekalanos.

125. As I explained above, Mekalanos is directed to a “sortase-mediated coupling of immunogenic polysaccharide-protein conjugates and their use.” Ex-1006, Title, 2:1–9.

126. Mekalanos explains that it sought to improve conventional pneumococcal conjugate vaccines, which could be “difficult to produce cheaply because of the highly specialized chemistry required for each antigen-protein conjugate.” Ex-1006, 11:5–10. Specifically, Mekalanos explains that “in the case of pneumococcal disease where each of the 90+ known serotypes has a different PS [polysaccharide] structure [] one single conjugation method may not be appropriate for all serotypes.” Ex-1006, 14:28–36. In order to combat this challenge, Mekalanos proposes an alternative chemical method of conjugating antigens to carrier polypeptides that does not require “utilizing differing chemical linkages specialized to produce each combination” of polysaccharide-polypeptide conjugate. Ex-1006, 16:14–18.

127. As described above, since the ’757 Patent claims are not limited to a particular conjugation method, Mekalanos’s sortase-mediated conjugation method falls within the challenged claims. *Supra* §§VII.B, VIII.B. As described in further detail below, Mekalanos discloses pneumococcal conjugate vaccine compositions that meet all of the limitations of at least Claims 1–5, 8–9, 11–12, 15, and 18–19.

**1. Independent Claim 1**

**a. Element 1[pre]: A pharmaceutical composition comprising**

128. In my opinion, Mekalanos discloses “a pharmaceutical composition” as required by the preamble of Claim 1 of the ’757 Patent.

129. Specifically, Mekalanos discloses “pharmaceutical compositions” comprising “immunogenic compositions containing a polysaccharide-sortase conjugate” and “a pharmaceutically acceptable excipient.” Ex-1006, Abstract; *see also id.* at 25:30–27:6 (describing “Immunogenic Conjugate Compositions: antigenic PS [polysaccharide]-carrier protein”).

**b. Element 1[a]: a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide,**

**(1) Immunogenic saccharide-polypeptide conjugates**

130. In my opinion, Mekalanos discloses two main embodiments, each of which comprises immunogenic saccharide-polypeptide conjugates. Ex-1006, 2:1–9, 16:33–35.

131. In the first embodiment of Mekalanos, the “immunogenic conjugates ... include a polysaccharide antigen conjugated to a sortase carrier protein capable of stimulating an immune response.” Ex-1006, 16:32–33. A POSITA would have understood that, for this embodiment, the “sortase carrier protein” is a “polypeptide.”

Ex-1006, 23:13–15 (“For example, some embodiments of the invention provide a sortase comprising a polypeptide sequence of *S. aureus* Sortase A (SEQ ID NO: 1).”).

132. In the second embodiment of Mekalanos, the “immunogenic conjugates ... include a polysaccharide antigen conjugated to a carrier protein capable of stimulating an immune response.” Ex-1006, 16:33–35. For this second embodiment, Mekalanos also discloses that the non-sortase carrier proteins include “CRM 197,” “tetanus toxoid,” and “cholera toxin B.” Ex-1006, 20:22–41. Mekalanos’s non-sortase carrier proteins are the same polypeptides/carrier proteins disclosed by the ’757 Patent. Ex-1001, 17:31–43 (“[a] polypeptide ... can be a carrier protein” such as “CRM197, tetanus toxoid, a cholera toxoid,” among others).

133. Based on these disclosures, a POSITA would have understood that Mekalanos discloses the claimed saccharide-polypeptide conjugates.

**(2) Each comprising individually a capsular polysaccharides conjugated to a polypeptide**

134. Mekalanos discloses that the pharmaceutical composition comprises capsular polysaccharides.

135. Mekalanos discloses that its “polysaccharide antigen[s]” are polymers “of saccharides (sugars) derived from *capsules* of encapsulated bacterial pathogens such as *Streptococcus pneumoniae*.” Ex-1006, 9:25–26 (emphasis added); *see also*

Cl. 37 (“[t]he immunogenic composition of claim 34 wherein said polysaccharide is a *Streptococcus pneumonia* polysaccharide”). Moreover, a POSITA would have understood that, in general, bacterial polysaccharides used to create vaccines are capsular polysaccharides. *Supra* §VI.A (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 46–47, 50–51; Ex-1028 (Obaro), 2; Ex-1029 (Mäkelä), 2–3).

136. Accordingly, in my opinion, Mekalanos discloses immunogenic saccharide-polypeptide conjugates comprising individually a capsular polysaccharide conjugated to a polypeptide.

**(3) A plurality of at least two ... conjugates**

137. In my opinion, Mekalanos discloses that the pharmaceutical composition comprises “at least two” capsular saccharide-polypeptide conjugates.

138. First, Mekalanos states that “[t]he immunogenic conjugates of the invention *may be used in combination*, for example, in pediatric immunizations.” Ex-1006, 25:29–31. Mekalanos also discloses polysaccharide conjugate compositions that contain more than one antigen of interest and more than one carrier protein, stating that “[t]he immunogenic conjugate formulation desirably includes *at least one* carrier protein, *at least one* antigen of interest.” *See* Ex-1006, 25:38–40. In my opinion, a POSITA would have read these disclosures of “in combination” or “at least one” as disclosing one *or more* (e.g., two) such antigens, since “two” is included in “at least one.” I also note that both of these disclosures appear under a

section titled “Immunogenic Conjugate Compositions: antigenic PS-carrier protein,” which a POSITA would have understood to refer to multivalent conjugate vaccines, which included multiple polysaccharide-protein conjugates. *Id.* at 25:29. *See also Supra* §VI.A.2 (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 8, 10–12, 39; Ex-1028 (Obaro), 2–3; Ex-1039 (Lesinski), 3–4; Ex-1029 (Mäkelä), 3; Ex-1012 (Nahm); Ex-1047 (Paoletti and Kasper 1994)). Accordingly, in my opinion, Mekalanos discloses a plurality or at least two capsular saccharide-polypeptide conjugates for use in a PCV as recited in the claims.

139. Second, Mekalanos explains that its invention is an incremental improvement on conventional vaccines, such as Prevnar 13®, which includes an arrangement of two or more conjugates. Specifically, Mekalanos discloses Prevnar 13® as a “mixture of 13 different conventional conjugate PS vaccines coupled to CRM197.” Ex-1006, 31:12–14. Prevnar 13® was well-known to contain pneumococcal polysaccharides from 13 different serotypes (i.e., at least two as recited in the claims), which are each individually conjugated to a carrier protein. Thus, in my opinion, Mekalanos sought to improve vaccines like Prevnar 13®, which were multivalent and included a plurality of at least two polysaccharide-protein conjugates, the same configuration recited in the challenged claims. Ex-1006, 14:30–32, 16:14–18.

140. Third, Mekalanos explicitly recites claims directed to compositions containing two or more pneumococcal polysaccharide-protein conjugates:

The immunogenic composition of any one of claims 1 to 43, wherein *said immunogenic composition further comprises a second antigen of interest*.

Ex-1006, Cl. 44 (emphasis added); *see also id.* at Cls. 37, 34, 2, 1.

141. Taking the above disclosures together, in my opinion, Mekalanos claims and discloses a pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide.

142. And to the extent not expressly disclosed, in my opinion, a POSITA would have immediately envisaged a pharmaceutical composition comprising a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide based on these disclosures in Mekalanos.

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

143. In my opinion, Mekalanos discloses that each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B.

144. Mekalanos discloses that “[t]he polysaccharide of the immunogenic composition may include a *Streptococcus pneumoniae* polysaccharide,” which “may be a *capsular* type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11 A, 11 B, 11 C, 11 D, 11 F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22F, **23B**, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33D, 33F, 34, 35A, **35B**, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48.” Ex-1006, 3:16–26 (emphases added).

145. Mekalanos also claims such pharmaceutical compositions:

The immunogenic composition of claim 34, wherein said *Streptococcus pneumoniae polysaccharide is capsular type* 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11A, 11B, 11C, 11D, 11F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22F, **23B**, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33D, 33F, 34, 35A, **35B**, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48.

Ex-1006, Cl. 37 (emphases added).

146. Though Mekalanos discloses 23B and 35B among a list of 84 other serotypes, Mekalanos also discloses that “[t]he methods of making immunogenic compositions described herein *may be used with any antigenic polysaccharide* capable of being covalently linked by a free carboxyl group, e.g., any capsular polymer or any polymer, attached to a sortase recognition peptide, and any carrier

protein capable of being covalently-linked by a free amino group, e.g., carrier proteins attached to a polyglycine motif.” Ex-1006, 17:30–34 (emphasis added).

147. Mekalanos also specifically lists and claims 23B and 35B as serotypes to be included in its immunogenic conjugates. *E.g.*, Ex-1006, 3:16–26, Cl. 37. I understand from counsel that because this limitation is written in Markush format, this limitation is anticipated even though Mekalanos does not specifically list serotype 23A. *Supra* §IV.B.

148. Moreover, as I have described above, a POSITA would have understood that the specific serotypes in commercial vaccines were selected by prevalence and virulence in the population at the time a vaccine is developed. *Supra* §VI.B.1 (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 10-11, 46; Ex-1012 (Nahm), 9; Ex-1026 (Bentley), 1-2; Ex-1028 (Obaro), 2-3; Ex-1005 (Porro), 2:5-16, 66:28-67:9; Ex-1057(Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract); Ex-1052 (Bertaud), 10; Ex-1034 (Emini), 19; Ex-1021 (Blay), 12). Indeed, Mekalanos itself repeatedly relies on the Bentley article, cited in the Technology Background section of my Declaration (§VI.B), which states that “polyvalent polysaccharide vaccines have been developed in which CPS [capsular polysaccharides] from the *serotypes most commonly associated with invasive disease* in children are linked to a protein carrier.” Ex-1026 (Bentley), 1 (emphasis added); Ex-1006 (Mekalanos), 24:22–23 (citing Bentley). I note that the

'757 Patent also cites the same reference for identifying *S. pneumoniae* serotype structures. Ex-1001, 8:17–20 (citing Bentley).

149. Selecting an appropriate subset of serotypes from a larger list was well within the level of skill in the art, as a POSITA would have selected relevant serotypes based on concurrent sero-epidemiologic data identifying prevalent serotypes in the population. *Supra* §VI.B.1 (Technology Background) (citing, e.g., Ex-1005 (Porro), 66:28–67:9; Ex-1057(Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract).

**2. Dependent Claims 2-5, 8-9, 11-12, 15, and 18-19**

**a. Claim 2: The pharmaceutical composition of claim 1, wherein at least one polypeptide comprises a mixture of polypeptides.**

150. As I explained above in Section §IX.B.1, Mekalanos discloses that the carrier protein is a polypeptide. *See, e.g.*, Ex-1006, 2:13–15, 20:40–41.

151. In my opinion, Mekalanos also discloses that at least one polypeptide comprises a mixture of polypeptides, as Mekalanos discloses that “a mixture of carrier proteins can be conjugated to the antigenic [polysaccharide] PS in a single reaction or multiple sequential reactions.” Ex-1006, 17:19–20.

152. Mekalanos also discloses that “[i]n the immunogenic conjugates of the invention, an antigen of interest, e.g., PS or capsular organic polymers, is covalently linked by a thioester bond to a sortase which is then optionally capable of coupling

the antigen with a carrier protein by a peptide bond.” Ex-1006, 16:20–22. A POSITA would have understood that the sortase itself is also a carrier protein. *Supra* §VI.A.1 (Technology Background) (citing, e.g., Ex-1006 (Mekalanos) (describing conjugation with sortase linker); Ex-1010 (Gu), 1). Thus, Mekalanos discloses a mixture of polypeptides.

- b. Claim 3: The pharmaceutical composition of claim 1, wherein at least one polypeptide of the plurality comprises CRM<sub>197</sub>, 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.**

153. In my opinion, Mekalanos discloses that at least one polypeptide of the plurality comprises CRM<sub>197</sub>, tetanus toxoid, diphtheria toxoid, cholera toxoid, pneumolysin, KLH, any fragment thereof, or any combination thereof.

154. Mekalanos discloses that “[v]arious carrier proteins of the invention include, e.g., toxins and toxoids (chemical or genetic), which may or may not be mutant, such as ... diphtheria toxoid (Massachusetts State Biological Labs; Serum Institute of India, Ltd.) or CRM 197, tetanus toxin, tetanus toxoid (Massachusetts

State Biological Labs; Serum Institute of India, Ltd.), tetanus toxin fragment Z, ... pneumolysin,” and that “[d]esirably, the carrier protein is the cholera toxin B subunit (available from SBL Vaccin AB), diphtheria toxin (Connaught, Inc.),” or “tetanus toxin Fragment C (available from Sigma Aldrich).” Ex-1006, 20:22–33.

155. Mekalanos further discloses that “keyhole limpet hemocyanin (KLH)” has been commonly used as a carrier “in the development of immunogenic compositions.” Ex-1006, 20:40–41.

156. Mekalanos also specifically claims the specific carrier proteins listed in Claim 3 of the ’757 Patent. *See, e.g.*, Ex-1006, Cls. 26 (“Vibrio cholerae flagellin protein”), 28 (“pneumolysin”), 30 (“diphtheria toxin”), 31 (“diphtheria toxoid”), 32 (“tetanus toxin”), 33 (“tetanus toxoid”).

- c. Claim 4: The pharmaceutical composition of claim 1, 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.**

157. In my opinion, Mekalanos discloses that the pharmaceutical composition further comprises an adjuvant, an emulsifier, or a salt, or a combination thereof.

158. Mekalanos discloses that “[t]he immunogenic conjugate formulation desirably includes at least one carrier protein, at least one antigen of interest, and a pharmaceutically acceptable carrier or excipient (e.g., aluminum phosphate, sodium

chloride, or sterile water).” Ex-1006, 25:38–40. A POSITA would have understood that both aluminum phosphate and sodium chloride are salts.

159. Mekalanos also discloses that the “immunogenic conjugate composition may also include an adjuvant system for enhancing the immunogenicity of the formulation, such as oil in a water system and other systems known in the art or other pharmaceutically acceptable excipients.” Ex-1006, 25:40–26:2; *see also id.* at 31:23–27 (“The PS [polysaccharide] carrier protein immunogenic conjugate can be modified to further stimulate the immune response, and ultimately improve the efficacy of the immunization, by addition of an adjuvant. The immunogenic conjugate can be absorbed by an alum adjuvant such as aluminum hydroxide gel. Additionally, the immunogenic conjugate can be combined with an emulsion adjuvant such as squalene based oil in water nano emulsion.”).

- d. Claim 5: The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.**

160. In my opinion, Mekalanos discloses that the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, or subcutaneously injectable composition.

161. Mekalanos discloses that “the immunogenic conjugates of the invention may be administered to a subject, e.g., by intramuscular injection, intradermal injection, or transcutaneous immunization with appropriate immune adjuvants.” Ex-1006, 26:21–23; *see also id.* at 6:5–6 (“Administering desirably includes parenteral administration (for instance, by subcutaneous, intramuscular, intravenous, or intradermal injection).”).

- e. **Claim 8: The pharmaceutical composition of claim 1, 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.**

162. In my opinion, Mekalanos discloses that the immunogenic saccharide-polypeptide conjugates comprise the capsular polysaccharide chemically cross-linked to the polypeptide and/or the capsular polysaccharide at least partially chemically cross-linked to the polypeptide.

163. Mekalanos discloses that “[i]n the immunogenic conjugates of the invention, an antigen of interest, e.g., PS [polysaccharide] or capsular organic polymers, is covalently linked by a thioester bond to a sortase which is then optionally capable of coupling the antigen with a carrier protein by a peptide bond.” Ex-1006, 16:20–22.

164. Mekalanos states that “[t]he novel PS-sortase conjugate may be enzymatically stabilized by **chemical cross-linking**, for example, such that sortase is the carrier protein of the immunogenic conjugate.” Ex-1006, 16:25–26 (emphasis added).

165. Mekalanos additionally discloses that “[m]ethods of enzymatic stabilization by ... **chemical cross-linking**, e.g., formaldehyde, glutaraldehyde, and formaldehyde/glutaraldehyde cross-linking, are well known in the art.” Ex-1006, 16:41–17:1 (emphasis added).

166. Moreover, Mekalanos explains that this is desirable because “[o]nce the PS-sortase immunogenic conjugate is formed, treatment with, for instance, a chemical cross-linker such as formaldehyde, crosslinks the basic amino acid lysine residues of sortase, further stabilizing the enzymatic conjugate.” Ex-1006, 17:1–4; *see also id.* 28:36–39 (“the PS-sortase conjugate may be enzymatically stabilized by treatment with a chemical cross-linking agent such as formalin or glutaraldehyde, further entrapping the antigenic polysaccharide to form a protein cross-linked cage or mesh”).

167. Based on these disclosures, a POSITA would have understood that the conjugates disclosed in Mekalanos are cross-linked to the carrier protein.

**f. Claim 9: The pharmaceutical composition of claim 1, wherein a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated.**

168. In my opinion, Mekalanos discloses that a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated.

169. As I explained in Section §IX.B.2.b, Mekalanos discloses that at least one polypeptide of the plurality comprises tetanus toxoid, diphtheria toxoid, or cholera toxoid. Moreover, Mekalanos discloses: “Tetanus toxoid is one possible carrier protein. This toxin is detoxified by treatment with formaldehyde, a reagent that reacts with amino groups of proteins.” Ex-1006, 17:34–35.

170. Tetanus toxoid is also claimed by Mekalanos. Ex-1006, Cl. 33 (“tetanus toxoid”).

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

171. In my opinion, Mekalanos discloses administering the pharmaceutical composition (i.e., first composition) to a subject.

172. Mekalanos discloses that “the use of the immunogenic composition of the invention to generate an immune response in a subject including administering the pharmaceutical composition of the invention to a subject where the immunogenic composition elicits a T-cell dependent immune response in the subject.” Ex-1006, 5:8–10.

173. Mekalanos also discloses that “[a]dministering may involve a single administration of an immunogenic conjugate or administering an immunogenic conjugate in multiple doses.” Ex-1006, 6:11–13.

- h. Claim 12: The pharmaceutical composition of claim 1, 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.**

174. In my opinion, Mekalanos discloses that the pharmaceutical composition further comprises at least one additional immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide.

175. As I have explained above §IX.B.1, Mekalanos discloses that its pharmaceutical compositions comprise immunogenic conjugates “used in combination.” Ex-1006, 25:29–31.

176. Mekalanos also discloses polysaccharide conjugate compositions that contain more than one antigen of interest and more than one carrier protein. *See* Ex-1006, 25:30–40 (“The immunogenic conjugate formulation desirably includes at least one carrier protein, at least one antigen of interest.”); *see also id.* at Cl. 45 (limiting Claim 1’s “immunogenic composition comprising a polysaccharide-sortase conjugate” to “further comprise[] a third antigen of interest”). Mekalanos thus discloses a pharmaceutical composition further comprising at least one additional

immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide.

177. Mekalanos also discloses that “[t]he *Streptococcus pneumoniae* polysaccharide of the immunogenic composition may be a capsular type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, **8**, 9A, 9L, **9N**, 9V, **10A**, 10B, 10F, **11A**, 11B, 11C, 11D, 11F, 12A, 12B, **12F**, 13, 14, **15A**, **15B**, **15C**, 15F, 16A, **16F**, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, **20**, 21, 22F, 23B, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, **32F**, 33A, 33B, 33D, 33F, **34**, 35A, 35B, 35F, 36, 37, 38, 39, 40, 41 A, 41 F, 42, 43, 44, 45, 46, 47A, 47F, and 48.” Ex-1006, 3:20–26 (emphases added), Cl. 37.

178. A POSITA would have understood that serotype 20 comprises serotypes 20A and 20B. *See* Ex-1001, 1:38.

- i. Claim 15: The method of claim 11, wherein the pharmaceutical composition is administered intramuscularly.**

179. In my opinion, Mekalanos discloses that “the immunogenic conjugates of the invention may be administered to a subject, e.g., by intramuscular injection.” Ex-1006, 26:21–22.

- j. Claim 18: The method of claim 11 wherein the subject is a human.**

180. In my opinion, Mekalanos discloses that the subject is a human. *See, e.g.*, Ex-1006, 10:13–14 (“Desirably, a subject is a mammal such as a human.”).

**k. 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.**

181. In my opinion, Mekalanos discloses a method of making a composition comprising contacting the plurality of immunogenic saccharide-polypeptide conjugates with an excipient, an adjuvant, or any combination thereof.

182. As I have explained above, Mekalanos discloses that “[t]he immunogenic conjugate formulation desirably includes at least one carrier protein, at least one antigen of interest, and a pharmaceutically acceptable carrier or excipient (e.g., aluminum phosphate, sodium chloride, or sterile water).” Ex-1006, 25:38–40.

183. Mekalanos discloses that the “composition may also include an adjuvant system for enhancing the immunogenicity of the formulation, such as oil in a water system and other systems known in the art or other pharmaceutically acceptable excipients.” Ex-1006, 25:40–26:2. Specifically, in Example 5, Mekalanos discloses combining the immunogenic conjugate “with an emulsion adjuvant such as squalene based oil in water nano emulsion ... to create a delivery system for the immunogenic conjugate” and “to create depots that trap the conjugated antigen-carrier protein at the site of injection to allow for its slow release.” Ex-1006, 31:22–31.

184. Because Mekalanos explains that its invention is an incremental improvement on conventional vaccines, which themselves are mixtures of immunogenic conjugates, comprising an adjuvant, a POSITA would have understood that these teachings would also apply to pharmaceutical compositions comprising a plurality of immunogenic saccharide-polypeptide conjugates. *See, e.g., id.* at 4:1–2 (“The immunogenic composition may further include, e.g., a second antigen of interest.”), 16:14–18, 14:30–32, 31:12–14 (disclosing Prevnar 13® as an “alum absorbed mixture of 13 different conventional conjugate PS vaccines coupled to CRM197”).

**C. Ground 3: Claims 1-12, 15, and 18-19 are obvious over Mekalanos**

**1. Independent Claim 1**

185. As I explained above in Section §IX.B.1, Mekalanos teaches each limitation of Element 1[pre], Element 1[a], and Element 1[b] and I incorporate by reference my analysis from above. For the additional reasons below, Claim 1 is also obvious.

**a. Element 1[a]: a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide conjugated to a polypeptide**

186. In my opinion, a POSITA would have found it obvious to include at least two unique capsular polysaccharide-polypeptide conjugates in a single composition in view of Mekalanos.

187. As I explained above, a POSITA would have been motivated to make a vaccine composition comprising two capsular polysaccharides, each conjugated to a polypeptide, in the composition because saccharide-polypeptide conjugates were known to enhance immune response and improve effectiveness. Section §VI.A.1 (Technology Background) (citing, e.g., Ex-1029 (Mäkelä), 2; Ex-1030 (Rappuoli), 1; Ex-1028 (Obaro), 3–4; Ex-1031 (Avery); Ex-1033 (Kniskern), 3–6; Ex-1039 (Lesinski), 3; Ex-1025 (Mazmanian and Kasper), 3; Ex-1032 (Anderson 1987), 1; Ex-1005 (Porro), 1:22–28, 32:28–33:6; Ex-1011 (Plotkin), 8, 15–16, Table 25-2; Ex-1007 (Siber), 6:63–7:67; Ex-1035 (Caulfield), 8–9; Ex-1010 (Gu), 1; Ex-1038 (Payton), 4–8, Table 11.1; Ex-1041 (Finn), 5, Table 1; Ex-1042 (Kasper 1996); Ex-1043 (Shinefield), 1; Ex-1044 (Lin); Ex-1034 (Emini), 21; Ex-1036 (Anderson 1994)). Moreover, multivalent conjugate vaccines targeting *S. pneumoniae* (e.g. Prevnar13®) were commonly used to vaccinate certain populations, including young children and the elderly. Section §§VI.A.2 (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 8, 10–12, 39; Ex-1028 (Obaro), 2–3; Ex-1039 (Lesinski), 3–4; Ex-1012 (Nahm), VI.B (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 11–12, 46, 508; Ex-1028 (Obaro), 3; Ex-1005 (Porro), 2:5–16, 32:5–16; Ex-1009 (Matur), 3; Ex-1016 (PDR 2011 Prevnar 13®); Ex-1026 (Bentley), 1; Ex-1006 (Mekalanos), 30:1–14).

188. Further, Mekalanos itself teaches, “‘immunogenic conjugates’ more efficiently promote the induction of B-cell maturation and isotype switching leading to much higher levels of antibody with the correct anti-PS [polysaccharide] protective profile.” Ex-1006, 12:37–39. Additionally, the “[p]rotective antibodies have high affinity for their PS antigens, and typically are of the Immunoglobulin G (IgG) subclass, a long-lived antibody with complement fixing and opsonic effector.” Ex-1006, 12:37–41.

189. Additionally, as I have laid out above, Mekalanos explains that its invention is an incremental improvement on conventional vaccines, such as Prevnar 13®, which themselves include an arrangement of at least two polysaccharides conjugated to carrier proteins. *Supra* §§VIII.B, IX.B.1. Based on the teachings in Mekalanos, in my opinion, a POSITA would have been motivated with a reasonable expectation of success in including at least two of the immunogenic conjugates in the pharmaceutical composition, as Mekalanos explains that its conjugation technique could be used to replace conventional conjugation techniques in conventional multivalent conjugate vaccines.

190. Accordingly, a POSITA would have followed Mekalanos’ teachings to implement the pharmaceutical composition with a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide.

- b. Element 1[b]: wherein each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B.**

191. Additionally, in my opinion, a POSITA would have found it obvious to make a pneumococcal vaccine composition comprising *S. pneumoniae* serotypes 23A, 23B, and/or 35B, based on the teachings in Mekalanos.

192. As I explained above, Mekalanos discloses that “[t]he polysaccharide of the immunogenic composition may include a *Streptococcus pneumoniae* polysaccharide,” which “may be a capsular type 1, 2, 3, 4, 5, 6A, 6B, 7A, 7B, 7C, 7F, 8, 9A, 9L, 9N, 9V, 10A, 10B, 10F, 11 A, 11 B, 11 C, 11 D, 11 F, 12A, 12B, 12F, 13, 14, 15A, 15B, 15C, 15F, 16A, 16F, 17A, 17F, 18A, 18B, 18C, 18F, 19A, 19B, 19C, 19F, 20, 21, 22F, **23B**, 23F, 24A, 24B, 24F, 25A, 25F, 27, 28A, 28F, 29, 31, 32A, 32F, 33A, 33B, 33D, 33F, 34, 35A, **35B**, 35F, 36, 37, 38, 39, 40, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48.” Ex-1006, 3:16–26 (emphasis added); *see also* Cls. 37, 34, 44. *Supra* §IX.B.1.

193. Mekalanos also teaches that “[t]he methods of making immunogenic compositions described herein may be used with any antigenic polysaccharide capable of being covalently linked by a free carboxyl group, e.g., any capsular polymer or any polymer, attached to a sortase recognition peptide, and any carrier

protein capable of being covalently-linked by a free amino group, e.g., carrier proteins attached to a polyglycine motif.” Ex-1006, 17:30–34.

194. A POSITA therefore would have understood that any of the serotypes listed in Mekalanos could be used with Mekalanos’s conjugation techniques with a reasonable expectation of success.

195. A POSITA would have also understood that the particular serotypes selected for inclusion into a specific vaccine are typically chosen based on (1) the serotypes included in prior art vaccines and (2) the serotypes identified by sero-epidemiological studies as being prevalent in the population. *Supra* §VI.B.1 (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 10–11, 46; Ex-1012 (Nahm), 9; Ex-1026 (Bentley), 1–2; Ex-1028 (Obaro), 2–3; Ex-1005 (Porro), 2:5–16, 66:28–67:9; Ex-1057 (Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract); Ex-1052 (Bertaud), 10; Ex-1034 (Emini), 19; Ex-1021 (Blay), 12).

196. A POSITA would have been familiar with contemporary sero-epidemiological data and thus would have understood that each of the claimed serotypes—23A, 23B, and 35B—were known as potential targets for conjugated vaccines by 2016. *Supra* §VI.B.2 (Technology Background) (citing, e.g., Ex-1018 (Dransfield), 6; Ex-1020 (Richter 2014), 1; Ex-1023 (Imöhl), 4; Ex-1019 (Domenech), 2; Ex-1017 (Wagenvoort), 1, 5; Ex-1024 (Flasche), 2, 4; Ex-1022

(Nierop), 2, 11; Ex-1021 (Blay), 10–12; Ex-1005 (Porro), 14:26–15:3; Ex-1010 (Gu), 1, 12; Ex-1006 (Mekalanos), 3:20–25; Ex-1009 (Matur), 10; Ex-1008 (Babb), 19). A POSITA would have found it obvious to select those specific serotypes from the finite lists of options taught by Mekalanos because the sero-epidemiological data points directly to them. *Supra* §VI.B.2 (Technology Background). (citing, e.g., Ex-1019 (Domenech), 2 (“Surveillance program results suggest that pneumococci of various serogroups/serotypes not included in PCV13 (e.g., 11, 12, 15, 22F, 23A, 23B, 33F, 24, 34, and 35B) are rapidly increasing in prevalence worldwide.”); Ex-1023 (Imöhl), 4 (“Non-PCV13 serotypes which increased among adults following the introduction of childhood-vaccination were 6C, 12F, 15B, 15C, 22F, 23A, 23B and 35B.”); Ex-1017 (Wagenvoort) ), 1, 5 (“Several serotypes (e.g. 6A, 6B, 23A and 23B) are associated with a significantly higher propensity to cause disease in high risk patients.”); Ex-1018 (Dransfield), 6 (“If the [PCV7] vaccine were to offer protection against cross-reactive serotypes (such as 23A/B and 9L/N) then this could be extended to about two-thirds of exacerbation-associated isolates”)).

197. A POSITA would therefore have been motivated to make vaccine compositions comprising the claimed *S. pneumoniae* serotypes, each conjugated to a carrier protein based on Mekalanos.

## 2. Dependent Claims

198. As I explained above in Section §IX.B.2, Mekalanos teaches each limitation of Claims 2–5, 8–9, 11–12, 15, and 18–19 and I incorporate by reference my analysis from above. For the additional reasons below, Claims 6-7 and 10 are also obvious.

- a. **Claim 6: The pharmaceutical composition of claim 1, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.**

199. In my opinion, Mekalanos teaches that at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response. As described above, an opsonophagocytic response is the process by which the immune system kills pathogens, first by opsonization (coating of the antigen by antibodies or complement proteins) then phagocytosis (engulfment of the coated antigen by phagocytic cells that then destroy the antigen). *Supra* §VI.C (Technology Background) (citing, e.g., Ex-1049 (Burton), 1; Ex-1011 (Plotkin), 13; Ex-1055 (Mantis), 36). Determining whether vaccine induced antibodies can kill the bacteria targeted by the vaccine in *in vitro* opsonophagocytic assays is a routine test conducted during vaccine development. *Supra id.*

200. Mekalanos teaches that an opsonophagocytic response is expected for an effectively conjugated immunogenic saccharide-polypeptide conjugate. More specifically, Mekalanos teaches that “A T-cell independent antigen such as PS can

be converted to a T-cell dependent antigen by chemical coupling of PS to protein” during the conjugation process. Ex-1006, 12:34–37. The resulting “immunogenic conjugates” “more efficiently promote the induction of B-cell maturation and isotype switching leading to much higher levels of antibody with the correct anti-PS protective profile.” Ex-1006, 12:37–29.

201. Mekalanos also teaches that “[p]rotective antibodies have high affinity for their PS antigens, and typically are of the Immunoglobulin G (IgG) subclass, a long-lived antibody with complement fixing and opsonic effector activity.” Ex-1006, 12:34–41. A POSITA would have understood that “opsonic effector activity” is a precursor to achieving “opsonophagocytic response.” *Supra* §VI.C (Technology Background) (citing, e.g., Ex-1049 (Burton), 1; Ex-1011 (Plotkin), 13; Ex-1055 (Mantis), 36).

202. Mekalanos’s Example 4 also teaches testing immunogenic saccharide-polypeptide conjugates created from 23 serotypes for an opsonophagocytic response. Ex-1006, 30:3–20. It teaches that “[t]he functionality of the antibody responses induced with immunogenic conjugates can be assessed ... by measuring the ability of the anti-PS antibody to opsonize encapsulated *S. pneumococcus* and lead to bacterial killing after phagocytosis by macrophages.” Ex-1006, 31:16–19.

203. Mekalanos additionally teaches that “[p]rotection of animals from lethal challenge with *S. pneumococcus* is another way to demonstrate the efficacy of the immunogenic conjugate in immunized animals.” Ex-1006, 31:19–20.

204. While Example 4 relates to testing in mice and rabbits, Mekalanos teaches that an “animal” includes a human:

By ‘subject’ is meant an animal that can be infected by a microbe. Desirably, a subject is a mammal such as a human, monkey, dog, cat, mouse, rat, cow, sheep, goat, or horse. In a desirable embodiment, the subject is a human, such as a human child. Desirably, the subject is a human infant, toddler, pre-pubescent child, pubescent child, young adult, or adult under the age of 55 years old.

Ex-1006, 10:13–16; *See also id.* at 13:18–19 (the production of “high affinity antibodies ... can be easily monitored by measuring the levels of anti-PS IgG antibodies in the serum of an immunized subject, e.g., a human”).

205. A POSITA would have been motivated to test the pharmaceutical composition taught by Mekalanos for an opsonophagocytic response because doing so is a common way to determine if a vaccine elicits the desired therapeutic response. *Supra* §VI.C (Technology Background) (citing, e.g., Ex-1049 (Burton), 1; Ex-1011 (Plotkin), 13; Ex-1055 (Mantis), 36). A POSITA would do so by, for example, measuring serum levels in a human subject following administration of the pharmaceutical composition, as taught by Mekalanos. *See id.*

206. A POSITA would have had a reasonable expectation of success that an opsonophagocytic response would be elicited using the recited pharmaceutical composition based on Mekalanos's teachings because as long as critical epitopes are maintained through the conjugation process, the opsonophagocytic response should be preserved. *Supra* §VI.C (Technology Background) (citing, e.g., Ex-1049 (Burton), 1; Ex-1011 (Plotkin), 13; Ex-1055 (Mantis), 36).

207. Additionally, Mekalanos specifically teaches that “[t]he methods of making immunogenic compositions described herein may be used with any antigenic polysaccharide capable of being covalently linked by a free carboxyl group, e.g., any capsular polymer or any polymer, attached to a sortase recognition peptide, and any carrier protein capable of being covalently-linked by a free amino group, e.g., carrier proteins attached to a polyglycine motif.” Ex-1006, 17:30–34. And Mekalanos specifically identifies and claims compositions with serotypes 23B and/or 35B that elicit “a T-cell dependent immune response.” Ex-1006, 3:14–26, Cls. 37, 54.

**b. Claim 7: The pharmaceutical composition of claim 1, 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.**

208. In my opinion, Mekalanos teaches that 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.

209. By 2016, a POSITA would have understood the typical dose for a pneumococcal conjugate vaccine, such as the one taught by Mekalanos, was 0.5 ml. *Supra* §VI.D (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 51; Ex-1016 (PDR 2011 Prevnar 13®); Ex-1006 (Mekalanos), 26:8–9). Indeed, Mekalanos teaches that “[t]ypically the immunogenic conjugate is in a volume of about 0.5 ml for subcutaneous injection, 0.1 ml for intradermal injection, or 0.002-0.02 ml for percutaneous administration.” Ex-1006, 26:7–8. Mekalanos further states that “[i]n a desirable embodiment, *in a 0.5 ml dose*, approximately 10 µg of the antigen are conjugated with approximately 10 µg of the carrier protein.” Ex-1006, 26:11–12; *see also id.* at 26:31–40.

210. Mekalanos additionally teaches that “[a] 0.5 ml dose of the immunogenic conjugate may contain approximately 2-500 µg of the antigen covalently linked with approximately 2-500 µg of the carrier protein.” Ex-1006, 26:8–11.

211. Thus, a POSITA would have understood this to mean that, according to Mekalanos, the 0.5 ml dose may include an amount of conjugate in a range between 4 (2+2 µg) and 1000 µg (500+500 µg) of total immunogenic conjugate if the formulation included only two serotypes. Typically, dose is determined as amount of polysaccharide, because that is the main immunizing agent.

212. A POSITA would have further understood that 0.001% by weight of a 0.5 ml dose is about 10 µg/ml or 5 µg in about 0.5 ml. “At least” 5 µg of total conjugate in a 0.5 ml dose (i.e., 0.001 %) falls well within the maximum (1000 µg) of total conjugate described above.

213. Mekalanos also teaches that the “quantity of immunogenic conjugate dosage depends on the specific activity of the immunogenic conjugate and *can be readily determined by routine experimentation.*” Ex-1006, 26:25–28.

214. As I have already explained, determining an optimal dose would have been well within the capabilities of a POSITA. *Supra* §VI.D (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 51; Ex-1016 (PDR 2011 Prevnar 13®); Ex-1006 (Mekalanos), 26:8–9).

215. Accordingly, based on the teachings of Mekalanos, a POSITA would have been motivated with a reasonable expectation of success to optimize a dose that would include at least 0.001% by weight for the collective amount of immunogenic saccharide-polypeptide conjugate.

**c. Claim 10: The pharmaceutical composition of claim 1, 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.**

216. As I have explained above, in my opinion, Mekalanos teaches that 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.

*Supra* §IX.C.2.b.

217. As I explained above, 5 µg of each conjugate in a 0.5 ml dose (i.e., 0.001 %) falls within the 2-500 µg amount for each conjugate range described in Mekalanos. *Supra* §IX.C.2.b.

218. Moreover, Mekalanos teaches “[t]he frequency and quantity of immunogenic conjugate dosage depends on the specific activity of the immunogenic conjugate and can be readily determined by routine experimentation.” Ex-1006, 26:25–28. I agree with Mekalanos that a POSITA could determine the dose and frequency of administration of an immunogenic conjugate through routine experimentation.

219. As I explained above, a POSITA would have been motivated with a reasonable expectation of success to optimize a dose that would include at least 0.001%, by weight of each immunogenic saccharide-polypeptide conjugate.

**D. Ground 4: Claims 1-19 are obvious over Mekalanos in view of Porro and Siber**

220. As described above, both Mekalanos and Porro teach each element of independent Claim 1. *Supra* §§IX.A.1, IX.B.1. Dependent Claims 2–12, 15, and 18–19 recite routine and well-known vaccine components, formulation excipients, dosages, and administration methods, that were also taught by Mekalanos. *Supra*

§IX.B.2; *see also supra* §VI. Many of those elements were also taught by Porro and Siber. *Infra* §§IX.D.2–3.

221. Dependent Claims 13 and 14 merely recite specific serotypes, the combination of which was taught by Porro and Mekalanos. *Infra* §IX.D.3.k–m. Dependent Claims 16 and 18 are directed to administration of “a second composition,” administered “at least about four weeks before or about four weeks after” administration of a first compositions, which was taught by Siber. *Infra* §§IX.D.3.o–p.

- 1. A POSITA would have been motivated to combine the teachings of Mekalanos, Porro, and Siber and would have had a reasonable expectation of success.**

222. As described above, Mekalanos, Porro, and Siber each relate to similarly structured pneumococcal conjugate vaccines and methods of administering them. Ex-1005, Abstract (“The present invention refers to conjugate antigens expressing built-in multiple epitopes and to polyvalent glycoconjugate vaccines and formulations containing the same. In addition, the present invention concerns the use of these vaccines in particular for the protection of the human population, and in particular for the protection of the [pediatric] population from pulmonary and systemic infections due to *S. pneumoniae* ...”); Ex-1006, Abstract (“Also disclosed are immunogenic compositions containing a polysaccharide-protein conjugate, the conjugate containing a polysaccharide antigen and a carrier protein .... Also

disclosed are pharmaceutical compositions containing the immunogenic composition and a pharmaceutically acceptable excipient, methods of making the immunogenic compositions, and methods of generating immune response in a subject using the pharmaceutical composition.”); Ex-1007, Abstract (“Methods of immunizing older adult subjects against *Streptococcus pneumoniae* infection are provided .... Optionally, initial immunization may be followed by additional immunization doses comprising conjugated pneumococcal polysaccharide vaccine or unconjugated pneumococcal polysaccharide vaccine composition.”); *Supra* §§VI.A.1, VI.B, VIII.A–C.

223. Indeed, as described above, none of the ’757 Patent claims limit the particular conjugation chemistry employed, and therefore the conjugation methods used in Mekalanos, Porro, and Siber are all encompassed by the asserted claims. *Supra* §§ VII.B, VIII.A–C.

224. Specifically, Siber teaches “methods of immunizing (and re-immunizing) older adult subjects against pneumococcal infection,” by administering conjugate vaccines utilizing conventional conjugation methods such as CDAP and reductive amination that had been available for decades. Ex-1007, 2:52–54, 7:55–67; *see also* §VI.A.1 (Technology Background) (discussing conjugation methods such as reductive amination and CDAP) (citing, e.g., Ex-1007 (Siber); Ex-1035 (Caulfield), 8–9; Ex-1036 (Anderson 1994)). Siber additionally teaches that “a

polysaccharide vaccine could be modified so as to include additional and/or different combinations of serotype specific polysaccharides,” because it “may be desirable for example, as infectious serotypes may shift over time, and/or various serotypes may be particularly relevant for specific populations.” Ex-1007, 5:36–43.

225. Additionally, as I have already described in more detail above, Mekalanos and Porro each teach updated PCVs. *Supra* §§IX.A–C, VIII.A–B. Both of these references sought to improve previous commercial PCVs by employing alternative conjugation methods and including additional or different serotypes of *S. pneumoniae*. Ex-1005, 1:6–14, 4:20–5:20; Ex-1006, 11:5–10, 14:28–36.

226. Mekalanos teaches, for example, a novel sortase-mediated method of conjugating antigens to carrier polypeptides that improves manufacturability because the method does not require “utilizing differing chemical linkages specialized to produce each combination” of polysaccharide-polypeptide conjugates. Ex-1006, 16:14–18. Mekalanos also teaches vaccine compositions that include many of the specific serotypes of *S. pneumoniae* recited in Claims 1, 12, 13, and 14 of the ’757 Patent. Ex-1006, 3:14–26, 16:14–18.

227. Porro teaches conjugating multiple polysaccharides to a single carrier protein to decrease “the amount of carrier protein needed in the [already] available single-antigen-associated formulation, so that the immunogenic burden on the immune-system of the host will be significantly lower and, consequently, safer.”

Ex-1005, 4:6–26. Porro teaches vaccine compositions that include many of the specific serotypes of *S. pneumoniae* recited in Claims 1, 12, 13, and 14 of the '757 Patent. Ex-1005, 14:26-15:3.

228. Siber teaches conventional multivalent pneumococcal conjugate vaccines in which each polysaccharide is conjugated to a carrier protein. As I have explained above, the most common methods of conjugating polysaccharides to polypeptides are reductive amination and activation CDAP. *Supra* §VI.A.1 (Technology Background) (citing, e.g., Ex-1007 (Siber), 7:55–67; Ex-1035 (Caulfield), 8–9; Ex-1036 (Anderson 1994)). While Mekalanos and Porro teach alternative conjugation chemistries to those methods, a POSITA would have understood that the vaccines described by Mekalanos and Porro have the same general structure as the vaccines described in Siber—they are prepared by “linking isolated or purified polysaccharides with a polypeptide carrier.” Ex-1007, 3:23–36, 6:35–36. Accordingly, a POSITA would have understood the claimed serotypes could be incorporated into a PCV using any of the conjugation methods described in Siber, Mekalanos, and/or Porro.

229. For these reasons and the reasons provided below, a POSITA would have been motivated to use any of the conjugation methods, other vaccine manufacturing methods, vaccine components, and formulation excipients taught by Mekalanos, Porro, and Siber to make and use vaccine formulations containing any

of the *S. pneumoniae* serotypes taught by those references with a reasonable expectation of success in doing so.

230. Additionally, as described above, a POSITA would have been motivated with a reasonable expectation of success to include the claimed *S. pneumoniae* serotypes in a PCV based on routine epidemiological studies identifying prevalence and virulence in the population at the time to optimize protection of the population. *Supra* §VI.B (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 8–12, 42, 46–47, 508; Ex-1012 (Nahm), 9; Ex-1009 (Matur), 3; Ex-1006 (Mekalanos), 30:1–14; Ex-1026 (Bentley), 1-2; Ex-1028 (Obaro), 1-3; Ex-1005 (Porro), 2:5–16, 32:5–16, 66:28–67:9; Ex-1057(Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract). Moreover, epidemiological studies were the field’s accepted basis to expand coverage of a pneumococcal vaccine. *Id.* This is evidenced by the multiple references expressly identifying serotypes 23A, 23B, and/or 35B including for inclusion in PCVs. *Supra* §VI.B.2 (Technology Background) (citing, e.g., Ex-1018 (Dransfield), 6; Ex-1020 (Richter 2014), 1; Ex-1023 (Imöhl), 4; Ex-1019 (Domenech), 2; Ex-1017 (Wagenvoort), 1, 5; Ex-1024 (Flasche), 2, 4; Ex-1022 (Nierop), 2, 11; Ex-1021 (Blay), 10–12; Ex-1005 (Porro), 14:26–15:3; Ex-1010 (Gu), 1, 12; Ex-1006 (Mekalanos), 3:20–25; Ex-1009 (Matur), 10; Ex-1008 (Babb), 19).

231. Further, Siber teaches immunization schedules that involve, for example, administration of an initial dose, followed by a second dose (which Siber refers to as a “booster” dose) of the same or different conjugated pneumococcal vaccine four weeks after the initial dose in order to achieve “greater immunoprotective efficacy and coverage.” Ex-1007, 10:23–31. As I explained above, a POSITA would have understood that under some circumstances, such as conditions of greater immune deficiency or immune immaturity, multiple administrations of a vaccine may improve immunogenic protection. *Supra* §VI.D (Technology Background) (citing, e.g., Ex-1007 (Siber), 10:33–12:5; Ex-1011 (Plotkin), 14–15; Ex-1021 (Blay), 3; Ex-1056 (Sigurdardottir), 1). Moreover, in my opinion, a POSITA would have been motivated to use the administration methods taught by Siber (i.e., more than one dose of one (or more than one) conjugated pneumococcal vaccines) with the vaccine formulations described in Mekalanos because a POSITA would have recognized that both Siber and Mekalanos relate to pneumococcal-conjugate vaccines with similar antigens (i.e., capsular polysaccharides corresponding to serotypes of *S. pneumoniae*) with a similar general structure.

232. In my opinion, a POSITA would have had a reasonable expectation of success in using the administration methods taught by Siber with the vaccine formulations described in Mekalanos and Porro because a POSITA would have

understood that the Mekalanos and Porro conjugation methods would not result in any change to the amount of antigen necessary to induce an immune response. Moreover, as I have explained, determining the proper interval between doses in a vaccine schedule for a specific vaccine (or combination of vaccines) is a common exercise for a POSITA. A POSITA would have been able to determine the proper interval between doses of the vaccine formulations described in Mekalanos. *Supra* §VI.D (Technology Background) (citing, e.g., Ex-1007 (Siber), 10:33–12:5; Ex-1011 (Plotkin), 14–15; Ex-1021 (Blay), 3; Ex-1056 (Sigurdardottir), 1).

**2. Independent Claim 1**

**a. Element 1[pre]: A pharmaceutical composition comprising**

233. In my opinion, Mekalanos in view of Porro and Siber (“Mekalanos-Porro-Siber”) teaches Element 1[pre].

234. As I explained above, Mekalanos, Porro, and Siber each teach pharmaceutical pneumococcal vaccine compositions. *Supra*, e.g., §§VIII.A–C, IX.A.1.a., IX.B.1.a; Ex-1005, 1:8–9 (“glycoconjugate vaccines and formulations containing the same.”); Ex-1007, 8:1–9:10 (describing existing conjugated pneumococcal vaccines).

- b. Element 1[a]: a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides conjugated to a polypeptide,**

235. In my opinion, Mekalanos-Porro-Siber teaches Element 1[a].

236. Mekalanos teaches each limitation of Element 1[a] for the reasons described in Sections IX.B.1.b and IX.C.1.a. While Mekalanos alone meets Element 1[a], in my opinion, it would also have been obvious to include a plurality of at least two unique immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide conjugated to a polypeptide in view of Siber's teachings.

237. Specifically, Siber teaches that for its conjugate vaccines, "individual isolated antigens [i.e., polysaccharides] may be separately coupled to polypeptide carriers and then combined with one another after coupling." Ex-1007, 6:55–58. Siber also teaches that multiple vaccines known in the art included 7 to 11 serotypes individually conjugated to carrier proteins, meaning that they included "at least two immunogenic saccharide-polypeptide conjugates" in a pharmaceutical composition as recited in Claim 1 of the '757 Patent. Ex-1007, 8:1–9:10.

238. For example, Siber teaches that "Wyeth reported a nonavalent conjugated pneumococcal vaccine, containing *capsular polysaccharides from pneumococcal serotypes* 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F, *each conjugated to*

*the non-toxic CRM197 variant of diphtheria toxin.*” Ex-1007, 8:30–35 (emphases added). Moreover, Siber teaches that “[t]wo tetravalent conjugated pneumococcal vaccines have also been generated and reported by Sanofi-Aventis, Swiftwater, Pa.,” the first containing “*capsular polysaccharides* of serotypes 6B, 14, 19F, and 23F *individually conjugated to diphtheria toxoid* (Aventis 4vPnD)” and the second containing “the same *polysaccharides conjugated to tetanus toxoid* (Aventis 4vPnT).” Ex-1007, 8:41–47 (emphases added). Siber further teaches that “GlaxoSmithKline has reported an eleven-valent conjugated pneumococcal vaccine, containing *capsular polysaccharides* from a different set of serotypes, namely 6B, 14, 19F, 23F, 1, 3, 4, 5, 7F, 9V, and 18C,” which “are *individually conjugated to protein D of H. influenzae* (GlaxoSmithKline, 11vPnC D).” Ex-1007, 8:48–53 (emphases added); *see also id.* at 8:54–59 (“GlaxoSmithKline has also reported a ten-valent conjugated pneumococcal vaccine, containing *capsular polysaccharides* from serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F,” which “are *individually conjugated to protein D of H. influenzae* (GlaxoSmithKline, 10vPnC D).” (emphases added)).

239. In my opinion, a POSITA would have been motivated to combine Siber’s teachings of combinations of individually isolated capsular polysaccharide antigens each conjugated to carrier proteins (i.e., “at least two unique immunogenic saccharide-polypeptide conjugates”) with the “immunogenic conjugates” taught by

Mekalanos, especially in view of Mekalanos's teaching that "[t]he immunogenic conjugates of the invention may be used in combination." Ex-1007, 6:55–58; Ex-1006, 25:30–31.

240. Additionally, Mekalanos explains that its invention is an incremental improvement on such well-known conventional vaccines, providing even more motivation to utilize the well-known configurations described in Siber. Ex-1006, 16:14–18. Indeed, as I have previously explained, a POSITA would have understood that antibodies against a polysaccharide from one serotype are generally not cross-protective against structurally unrelated serotypes. *Supra* §VI.A.2 (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 8, 39; Ex-1028 (Obaro), 2–3; Ex-1039 (Lesinski), 3–4). Accordingly, a POSITA would have understood that multiple (or plurality of) pneumococcus serotypes needed to be included in a vaccine to cover a meaningful percentage of disease caused by *S. pneumoniae*. *Supra* §VI.B.1 (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 8, 39; Ex-1028 (Obaro), 2–3; Ex-1005 (Porro), 2:5–16).

241. A POSITA would thus have had a reasonable expectation of success in including at least two immunogenic conjugates in the vaccine configuration taught by Mekalanos because such configurations (i.e., polyvalent/multivalent vaccines) had been in use since at least the early 1990s and were viewed as an “outstanding success.” Ex-1005, 1:22–30; Ex-1007, 1:41–49 (discussing how the introduction of

Prevnar® “reduced the incidence of invasive pneumococcal disease (IPD) in children nearly 94% (from 80 per 100,000 in 1998-1999 to 4.6 per 100,000 in 2003)”); *see also* §§VI.A–B (Technology Background).

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

242. In my opinion, Mekalanos-Porro-Siber teaches Element 1[b].

243. As explained in Sections IX.B–C, Mekalanos teaches that each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23B and 35B. While, in my opinion, Mekalanos alone teaches Element 1[b], it would also have been obvious to select serotypes 23A and 35B, as taught by Porro.

244. Porro teaches including serotypes **23A** and **35B** in a pneumococcal polysaccharide conjugated vaccine. For example, Porro states that “[n]ew emerging serotypes of *S. pneumoniae* according to the public available data on epidemiology and antibiotic resistance, are ... type **23A** ... and 35 (type **35B**) (Swanson D., IDSA meeting, Boston, 2011)” and “such antigen Ps [polysaccharide] might be likely included in a further up-dated broad-spectrum vaccine formulation prepared according to the molecular construct disclosed.” Ex-1005, 66:28–67:9 (citing Ex-1061 (IDSA Abstract)).

245. A POSITA would have been specifically motivated to select serotypes 23A and 35B because Porro teaches that these serotypes are “preferred” for its multivalent vaccine. *See, e.g.,* Ex-1005, 14:26–15:3 (“According to *preferred embodiments* of the antigenic multivalent molecular construct of the invention the carried carbohydrate structures are selected among, but not limited to, *Ps of Streptococcus pneumoniae* (type 1, 2, 3, 4, 5, 6A, 6B, 6C, 6D, 7F, 8, 9N, 9V, 10A, 11A, 11B, 11C, 11F, 12F, 14, 15A, 15B, 15C, 17F, 18C, 19A, 19F, 20, 22F, **23A**, 23F, 33F, **35B**.” (emphases added). Further, in my opinion, a POSITA would also have understood that each of the claimed serotypes—23A, 23B, and 35B—were well known as potential targets for conjugated vaccines by 2016 and, therefore, would have been motivated to select them from the finite lists of options taught by Mekalanos and Porro. *Supra* §VI.B.2 (Technology Background) (citing, e.g., Ex-1018 (Dransfield), 6; Ex-1020 (Richter 2014), 1; Ex-1023 (Imöhl), 4; Ex-1019 (Domenech), 2; Ex-1017 (Wagenvoort), 1, 5; Ex-1024 (Flasche), 2, 4; Ex-1022 (Nierop), 2, 11; Ex-1021 (Blay), 10–12; Ex-1005 (Porro), 14:26–15:3; Ex-1010 (Gu), 1, 12; Ex-1006 (Mekalanos), 3:20–25; Ex-1009 (Matur), 10; Ex-1008 (Babb), 19).

246. A POSITA would have been further motivated to include 23A, 23B, and/or 35B in the vaccine formulations taught by Mekalanos (using sortase-mediated conjugation) or Siber (using conventional CDAP conjugation) in order to achieve

increased coverage over emerging serotypes. *Supra* §VI.B.1 (Technology Background) (citing, e.g., Ex-1011 (Plotkin), 10-11, 46; Ex-1012 (Nahm), 9; Ex-1026 (Bentley), 1-2; Ex-1028 (Obaro), 2-3; Ex-1005 (Porro), 2:5-16, 66:28-67:9; Ex-1057(Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract); Ex-1052 (Bertaud), 10; Ex-1034 (Emini), 19; Ex-1021 (Blay), 12). As explained by Siber, “[i]n principle, a polysaccharide vaccine could be modified so as to include additional and/or different combinations of serotype specific polysaccharides.” Ex-1007, 5:36-37. Siber further teaches that “[m]odification and/or addition of polysaccharides may be desirable for example, as infectious serotypes may shift over time, and/or various serotypes may be particularly relevant for specific populations.” Ex-1007, 5:37-42.

247. As I have explained above, a POSITA would have understood that serotypes in commercial vaccines must be replaced or changed over time to optimize protection of the population and would have known to look to recently published sero-epidemiological studies to identify relevant serotypes. *Supra* §VI.B.1 (Technology Background) (citing, e.g., Ex-1005 (Porro), 66:28-67:9; Ex-1057(Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract)).

248. In my opinion, a POSITA would have had a reasonable expectation of success in including 23A, 23B, and/or 35B in the vaccine formulations taught by

Mekalanos (using sortase-mediated conjugation) because Mekalanos teaches that “[t]he methods of making immunogenic compositions described herein may be used with *any* antigenic polysaccharide capable of being covalently linked by a free carboxyl group, e.g., *any* capsular polymer.” Ex-1006, 17:30–34; *see also supra* §VI.B.2. Further, Mekalanos specifically identifies and claims compositions with serotypes 23B and/or 35B that elicit “a T-cell dependent immune response.” Ex-1006, 3:14–26, 4:23–25, Cls. 37, 54. Mekalanos also specifically lists and claims 23B and 35B as serotypes to include in its immunogenic conjugates. *See, e.g.,* Ex-1006, 3:16–26, Cl. 37. Based on these teachings, a POSITA would have had a reasonable expectation of success in including 23A, 23B, and/or 35B in the pharmaceutical vaccine compositions taught by Mekalanos.

249. A POSITA would also have had a reasonable expectation of success in including 23A, 23B, and/or 35B in the vaccine formulations taught by Siber (i.e., including conjugates prepared using CDAP or reductive amination conjugation technology) because these conjugation methods were the industry standard for polysaccharide conjugate vaccines, and were used successfully in multiple pneumococcal polysaccharide conjugate vaccines. *Supra* §VI.A.1 (Technology Background) (citing, e.g., Ex-1007 (Siber), 7:55–67; Ex-1035 (Caulfield), 8–9; Ex-1036 (Anderson 1994)).

**3. Dependent Claims 2-19**

- a. Claim 2: The pharmaceutical composition of claim 1, wherein at least one polypeptide comprises a mixture of polypeptides.**

250. In my opinion, Mekalanos-Porro-Siber teaches Claim 2 for the reasons described in Section IX.B.2.a. Specifically, Mekalanos teaches that “a mixture of carrier proteins can be conjugated to the antigenic [polysaccharide] PS in a single reaction or multiple sequential reactions.” Ex-1006, 17:19–20.

- b. Claim 3: The pharmaceutical composition of claim 1, wherein at least one polypeptide of the plurality comprises CRM<sub>197</sub>, 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.**

251. In my opinion, Mekalanos-Porro-Siber teaches Claim 3 for the reasons described in Sections IX.A.2.a and IX.B.2.b. Moreover, as explained above, the polypeptides recited in Claim 3 are common carrier proteins used in pneumococcal conjugate vaccines. *See Supra* §§VI.A.1 (Technology Background) (citing, e.g., Ex-1007 (Siber), 6:63–7:53; Ex-1033 (Kniskern), 5–6; Ex-1034 (Emini), 21), VI.B (Technology Background) (citing, e.g., Ex-1005 (Porro), 2:5–16, 32:5–16; Ex-1011

(Plotkin), 11–12, 46, 508; Ex-1009 (Matur), 3, 10; Ex-1006 (Mekalanos), 30:1–14; Ex-1016 (PDR 2011 Prevnar 13®)). Indeed, CRM197, “a non-toxic variant (i.e., toxoid) of diphtheria toxin” taught in each Mekalanos, Porro, and Siber, had been used in multiple commercial and developmental polysaccharide-polypeptide conjugate vaccines for decades. *Supra* §§VI.A.1 (Technology Background) (citing, e.g., Ex-1007 (Siber), 1:41–43, 6:63–7:53; Ex-1033 (Kniskern), 5-6), Ex-1034 (Emini, 21); B (Technology Background) (citing, e.g., Ex-1005 (Porro), 2:5–16, 13:20-22, 32:5–16; Ex-1011 (Plotkin), 11, 46, 508; Ex-1006 (Mekalanos), 30:1–14, 20:23–24; Ex-1016 (PDR 2011 Prevnar 13®)).

252. Based on this knowledge, a POSITA would have been motivated with a reasonable expectation of success to use the recited carrier proteins in any of the formulations described in Mekalanos, Porro, and/or Siber because each recites one or more of these carrier proteins as potential proteins to be used in vaccines.

- c. **Claim 4: The pharmaceutical composition of claim 1, 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.**

253. In my opinion, Mekalanos-Porro-Siber teaches Claim 4 for the reasons described in Section IX.B.2.c. The excipients recited in Claim 4 are common excipients used in pneumococcal polysaccharide conjugate vaccine formulations.

254. Additionally, a POSITA would have understood that adjuvants are commonly used to “enhance the immunogenicity of the formulation,” as taught by each of Mekalanos, Porro, and Siber. Ex-1005, 26:10–12; Ex-1006, 26:21–23; Ex-1007, 17:32–36.

- d. Claim 5: The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an intramuscularly injectable composition, intradermally injectable composition, subcutaneously injectable composition, or an intranasally administrable composition.**

255. In my opinion, Mekalanos-Porro-Siber teaches Claim 5 for the reasons described in Section IX.B2.d.

256. The administration methods recited in Claim 5 (i.e., intramuscular injection, intradermal injection, subcutaneous injection, or intranasal administration) include the most common methods of administering vaccines. Indeed, each of Mekalanos, Porro, and Siber teach that their vaccine compositions may be administered by one or more of these methods.; Ex-1005, 31:24–29; Ex-1006, 26:15–19; Ex-1007, 13:55–14:4.

- e. Claim 6: The pharmaceutical composition of claim 1, wherein at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response.**

257. In my opinion, Mekalanos-Porro-Siber teaches Claim 6 for the reasons described in Section IX.C.2.a.

258. In the Mekalanos-Porro-Siber combination, the immunogenic saccharide-polypeptide conjugates prepared using the CDAP method, as taught by Siber, using an *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B, as taught by Mekalanos and Porro, would elicit an opsonophagocytic response, as taught by Mekalanos. *Supra* §§VI.C (Technology Background) (citing, e.g., Ex-1049 (Burton), 1; Ex-1011 (Plotkin), 13; Ex-1055 (Mantis), 36); IX.C.2.a.

**f. Claim 7: The pharmaceutical composition of claim 1, 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.**

259. In my opinion, Mekalanos-Porro-Siber teaches Claim 7 for the reasons described in Section IX.C.2.b.

260. In addition, Siber teaches that “[g]enerally it is expected that each dose will comprise 0.1-100 µg of polysaccharide.” Ex-1007, 15:6–21. In my opinion, this is a broad range for the amount of polysaccharide or conjugate that should be included in the vaccine. And this range encompasses the claimed concentration. Siber also provides examples of administering between 34 (16+18) and 154 (80+74) µg of conjugate. Ex-1007, 20:45–60 (Example 1, Table 2). As I have explained above, 0.001% of a typical 0.5 ml formulation is 5 µg, above which is within in the range disclosed by Siber. *Supra* §IX.C.2.b.

261. In my opinion, given the broad range of doses taught by Mekalanos and Siber, a POSITA would have been motivated with a reasonable expectation of success to administer a pharmaceutical composition “wherein the immunogenic saccharide-polypeptide conjugates are collectively present in an amount of at least 0.001%, by weight.” *Supra* §§VI.D, IX.D.1.

- g. Claim 8: The pharmaceutical composition of claim 1, 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.**

262. In my opinion, Mekalanos-Porro-Siber teaches Claim 8 for the reasons described in Section IX.B.2.e.

- h. Claim 9: The pharmaceutical composition of claim 1, wherein a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated.**

263. In my opinion, Mekalanos-Porro-Siber teaches Claim 9 for the reasons described in Sections IX.B.2.f and IX.D.3.b.

- i. Claim 10: The pharmaceutical composition of claim 1, 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.**

264. In my opinion, Mekalanos-Porro-Siber teaches Claim 10 for the reasons described in Section IX.C.2.c. and IX.D.3.f.

265. Moreover, Siber teaches that Prevnar® included 2-4 µg of each polysaccharide. Ex-1007, 20:45–57. Accordingly, a POSITA would have understood this to be about 4-8 µg of each conjugate in a typical 0.5 ml dose. Ex-1007, 20:45–57.

266. A POSITA would therefore have been further motivated with a reasonable expectation of success to include at least 0.001% by weight of “each of the immunogenic saccharide-polypeptide conjugates” for the vaccine formulations disclosed in Mekalanos because vaccines like Prevnar® had successfully included about 8 µg of at least one conjugate for decades.

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

267. In my opinion, Mekalanos-Porro-Siber teaches Claim 11.

268. As explained in Section IX.B.2.g, Mekalanos teaches administering a first composition and a second composition because Mekalanos teaches that “[a]dministering may involve a single administration of an immunogenic conjugate or administering an immunogenic conjugate in multiple doses.” Ex-1006, 6:11–13.

269. Siber also teaches administering a first composition and a second composition of a pneumococcal polysaccharide conjugate vaccine. Specifically, Siber teaches that its “invention encompasses the finding that an initial

immunization dose with conjugate vaccine followed by at least one additional immunization dose with either conjugate or unconjugated polysaccharide vaccine gives a beneficial immunoprotective effect.” Ex-1007, 2:46–51; *see also id.* at Abstract (“initial immunization may be followed by additional immunization doses comprising conjugated pneumococcal polysaccharide vaccine”), 3:11–14 (“methods of administering additional dose(s) of pneumococcal vaccine to an older subject in order to extend immunoprotection against *S. pneumoniae* infection”), 9:12–15 (“vaccine administration may involve delivery of only a single dose, or alternatively may involve an initial dose followed by one or several additional immunization doses, adequately spaced”).

270. A POSITA would have been motivated to utilize the administration methods taught by Siber with the formulations taught by Mekalanos because a person of skill in the art would have understood that multiple administrations of a vaccine—for example, an initial dose and a second dose—may improve immunogenicity in populations with weaker immune systems. *Supra* §VI.D (Technology Background) (citing, e.g., Ex-1007 (Siber), 10:33–12:5; Ex-1011 (Plotkin), 14–15; Ex-1021 (Blay), 3; Ex-1056 (Sigurdardottir), 1).

271. A POSITA would also have been able to utilize the administration methods taught by Siber with the formulations taught by Mekalanos with a reasonable expectation of success because both relate to pneumococcal-conjugate

vaccines. *Supra* §IX.D.1. A POSITA would have understood that merely changing the conjugation method and specific serotypes from *S. pneumonia* would not require changes to the administration method.

- k. **Claim 12: The pharmaceutical composition of claim 1, 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.**

272. In my opinion, Mekalanos-Porro-Siber teaches Claim 12.

273. As explained in Section IX.B.2.h, Mekalanos teaches that the pharmaceutical composition further comprises at least one additional immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide. Ex-1006, 3:14–21, 4:1–2, Cl. 45 (limiting Claim 1’s “immunogenic composition comprising a polysaccharide-sortase conjugate” to “further comprise[] a third antigen of interest”). Mekalanos also teaches that the capsular polysaccharide is from a unique *Streptococcus pneumoniae* serotype selected from the group consisting of 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34. Ex-1006, 3:20–26, Cl. 37.

274. Porro teaches that “[a]ccording to *preferred* embodiments of the antigenic multivalent molecular construct of the invention the carried carbohydrate structures are selected among, but not limited to, Ps [polysaccharides] of

*Streptococcus pneumoniae* [type 1, 2, 3, 4, 5, 6A, 6B, **6C**, 6D, 7F, **8**, **9N**, 9V, **10A**, **11A**, 11B, 11C, 11F, **12F**, 14, **15A**, **15B**, **15C**, 17F, 18C, 19A, 19F, **20**, **22F**, 23A, 23F, 33F, 35B.” Ex-1005, 14:26-15:3 (emphases added).

275. As explained in Sections VI.B.1–2, IX.A.1.c, IX.B.1.c, and IX.C.1b a POSITA would have understood that the selection of various serotypes would have been based on “available data on epidemiology and antibiotic resistance,” as taught by Porro for example. Ex-1005, 66:28–67:9 (citing Ex-1057(Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract)). And a POSITA would have been motivated to select any of the serotypes in the Markush group of Claim 12 because each is included in the finite lists taught by Mekalanos and/or Porro. *Supra* §§IX.A.2.b, IX.B.2.h.

276. A POSITA would have had a reasonable expectation of success in including the recited serotypes in Mekalanos and Porro in the vaccine formulations taught by Mekalanos (using sortase-mediated conjugation) because Mekalanos teaches that “[t]he methods of making immunogenic compositions described herein may be used with **any** antigenic polysaccharide capable of being covalently linked by a free carboxyl group, e.g., **any** capsular polymer.” Ex-1006, 17:30–34. Further, Mekalanos specifically identifies and claims compositions with serotypes 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34 that elicit “a T-cell dependent immune response.” Ex-1006 3:14–26, Cls. 37, 54. And Porro identifies

overlapping serotypes as well as 6C. Ex-1005, 14:26–15:3. Based on these teachings, a POSITA would have had a reasonable expectation of success in additionally including 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, or 34 in the pharmaceutical vaccine compositions taught by Mekalanos.

277. A POSITA would have had a reasonable expectation of success in including 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and/or 34 in the vaccine formulations taught by Siber (using CDAP conjugation technology) because CDAP is one of the most widely used conjugation method for polysaccharide conjugate vaccines that had been successfully used in pneumococcal conjugate vaccines comprising *S. pneumoniae* capsular polysaccharides. *Supra* §VI.A.1 (Technology Background) (citing, e.g., Ex-1007 (Siber), 7:55–67; Ex-1035 (Caulfield), 8–9; Ex-1036 (Anderson 1994)).

278. In the Mekalanos-Porro-Siber combination, each of the capsular polysaccharides in the conjugates prepared using the CDAP method, as taught by Siber, would be from a *Streptococcus pneumoniae* serotype selected from the Markush group of Claim 12, as taught by Mekalanos and Porro.

- I. **Claim 13: The pharmaceutical composition of claim 1, wherein the plurality of unique immunogenic saccharide-polypeptide conjugate comprises individually capsular polysaccharides from a *Streptococcus pneumoniae* serotype comprising 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.**

279. In my opinion, Mekalanos-Porro-Siber teaches Claim 13 for the reasons described in the Section IX.D.3.k, namely, because Mekalanos and Porro together teach all of the serotypes recited in Claim 13.

280. Mekalanos teaches that the plurality of unique immunogenic saccharide-polypeptide conjugate comprises individually capsular polysaccharides from a *Streptococcus pneumoniae* serotype comprising 9N, 15A, 15C, 16F, 23B, and 35B. Ex-1006, 3:20–26. And Porro teaches that its preferred embodiments include conjugates comprising capsular polysaccharides from the *Streptococcus pneumoniae* serotypes 6C, 9N, 15A, 15C, 23A, and 35B. Ex-1005, 14:26–15:3. As also explained in the Section IX.D.3.k, a POSITA would have understood that the selection of various serotypes would have been based on “available data on epidemiology and antibiotic resistance,” as taught by Porro. Ex-1005, 66:28–67:9.

281. Additionally, a POSITA would have understood that all of the claimed serotypes—6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B—were known as potential targets for vaccines for *Streptococcus pneumoniae* by 2016 and, therefore, would have found it obvious to select them from the finite lists of options taught by

Mekalanos and Porro. *See* Ex-1008 (Babb), 18:6–12 (“[T]he vaccines may comprise any one of more of *S. pneumoniae* serotypes ... **6C**, ... **9N**, ... **15A**, ... **15C**, ... **16F**, ... **23A**, **23B**, ... **35B**.”)); *see also* §VI.B.2 (Technology Background) (citing, e.g., Ex-1018 (Dransfield), 6; Ex-1020 (Richter 2014), 1; Ex-1023 (Imöhl), 4; Ex-1019 (Domenech), 2; Ex-1017 (Wagenvoort), 1, 5; Ex-1024 (Flasche), 2, 4; Ex-1022 (Nierop), 2, 11; Ex-1021 (Blay), 10–12; Ex-1005 (Porro), 14:26–15:3; Ex-1057 (Satzke); Ex-1058 (Richter 2009); Ex-1059 (Yao); Ex-1060 (Calix); Ex-1061 (IDSA Abstract)); Ex-1010 (Gu), 1, 12; Ex-1006 (Mekalanos), 3:20–25; Ex-1009 (Matur), 10; Ex-1008 (Babb), 19).

282. A POSITA would have had a reasonable expectation of success in including the recited serotypes in Mekalanos and Porro in the vaccine formulations taught by Mekalanos (using sortase-mediated conjugation) because Mekalanos teaches that “[t]he methods of making immunogenic compositions described herein may be used with **any** antigenic polysaccharide capable of being covalently linked by a free carboxyl group, e.g., **any** capsular polymer.” Ex-1006, 17:30-34. Mekalanos also describes examples generating “sortase-mediated immunogenic conjugates” comprising 23 types of capsular polysaccharides of *S. pneumoniae*. Ex-1006, 30–31. A POSITA would have understood the same methods could be utilized to conjugate carrier proteins to the recited serotypes.

283. Based on these teachings a POSITA would have had a reasonable expectation of success in additionally including 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B in the pharmaceutical vaccine compositions taught by Mekalanos.

- m. **Claim 14: The pharmaceutical composition of claim 1, wherein the plurality of unique immunogenic saccharide-polypeptide conjugate comprises individually capsular polysaccharides from a *Streptococcus pneumoniae* serotype consisting of 6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B.**

284. In my opinion, Mekalanos-Porro-Siber teaches Claim 14 for the reasons described in the previous section (Section IX.D.3.1).

- n. **Claim 15: The method of claim 11, wherein the pharmaceutical composition is administered intramuscularly.**

285. In my opinion, Mekalanos-Porro-Siber teaches Claim 15 for the reasons described in Section IX.B.2.i.

286. Additionally, Siber and Porro each teach intramuscular administration as a vaccine administration option. Ex-1005, 31:24–26; Ex-1007, 13:55–63.

- o. **Claim 16: The method of claim 11, 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.**

287. In my opinion, Mekalanos-Porro-Siber teaches Claim 16.

288. Mekalanos teaches administering the first composition before or after administering a second composition comprising an immunogenic saccharide-polypeptide conjugate. Specifically, Mekalanos teaches that “[a]dministering may involve a single administration of an immunogenic conjugate or administering an immunogenic conjugate in multiple doses.” Ex-1006, 6:11–13. Mekalanos also teaches that “a second administration is designed to boost production of antibodies in a subject to reduce the likelihood of infection by an infectious agent.” Ex-1006, 6:13–14. While Mekalanos does not describe a specific dosing schedule, it teaches that “[t]he frequency and quantity of the dosage of immunogenic conjugate depends on the specific activity of the immunogenic conjugate and ***can be readily determined by routine experimentation.***” Ex-1006, 6:14–16 (emphasis added).

289. It would have been obvious to administer the first composition four weeks before or four weeks after the second composition because monthly administration (i.e., every four weeks) is a common dosing frequency for intramuscular injections. *Supra* §VI.D (Technology Background) (citing, e.g., Ex-1007 (Siber), 10:33–12:5; Ex-1011 (Plotkin), 14–15; Ex-1021 (Blay), 3; Ex-1056 (Sigurdardottir), 1). Additionally, the recited “four weeks” is one of a finite number of dosing frequency options so it at least would have been obvious to a POSITA to try, as taught by Siber. *Id.*

290. Siber teaches multiple administrations of a pneumococcal polysaccharide conjugate vaccine. Specifically, Siber teaches that “an initial immunization dose with conjugate vaccine followed by at least one additional immunization dose with either conjugate or unconjugated polysaccharide vaccine gives a beneficial immunoprotective effect.” Ex-1007, 2:46–51; *see also id.* at 10:23–27. Siber further teaches that “a first dose of pneumococcal conjugate vaccine administered according to the invention may be considered a ‘priming’ dose” and “a subsequent dose may be considered a ‘boosting’ dose.” Ex-1007, 10:32–37. In my opinion, a POSITA would understand that Siber uses the term “boosting” broadly to encompass a second administration with an antigen distinct from the first. Indeed, Siber teaches that a boosting dose may comprise “at least one of the conjugate(s) of the previously received priming dose” and “one or more additional conjugate(s) which were not contained in the priming dose”; or “at least some of the conjugate(s) of the previously received priming dose” and “one or more additional polysaccharide(s) which were not contained in the priming dose”; or “polysaccharide(s) which were not contained in the priming dose” and “conjugate(s) which were contained within the priming dose.” Ex-1007, 10:51–11:1.

291. Additionally, Siber teaches a four-week interval between administering the first and second compositions. Specifically, Siber teaches that “[i]n immunization schedules of the present invention, once a first vaccine dose has been

administered, there is a first interval before administration of a subsequent dose,” which “is generally at least about two weeks, **one month**, six weeks, two months, three months, six months, nine months, 12 months, or longer.” Ex-1007, 11:4–13.

- p. **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.**

292. In my opinion, Mekalanos-Porro-Siber teaches Claim 17 for the reasons described in Sections IX.B.1.b and IX.C.1.a and the previous section.

293. Mekalanos additionally teaches Claim 17 for the reasons described in the previous section (Section IX.D.3.o) and IX.B.1.b and IX.C.1.a, namely because Mekalanos teaches “immunogenic compositions” (plural) “containing a polysaccharide-protein conjugate” (Ex-1006, Abstract), wherein each polysaccharide is a capsular polysaccharide from a serotype of *Streptococcus pneumoniae* (*id.* at 3:14–26), conjugated to a polypeptide (*id.* at 18:10–13).

294. Siber also teaches Claim 17 for the reasons described in the previous section (Section IX.D.3.o), namely, because Siber teaches that the second composition may comprise “at least one of the conjugate(s) of the previously received priming dose” (i.e., first composition) and “one or more additional conjugate(s) which were not contained in the priming dose”; or “at least some of the conjugate(s) of the previously received priming dose” and “one or more additional

polysaccharide(s) which were not contained in the priming dose”; or “polysaccharide(s) which were not contained in the priming dose” and “conjugate(s) which were contained within the priming dose.” Ex-1007, 10:51–11:1.

**q. Claim 18: The method of claim 11 wherein the subject is a human.**

295. In my opinion, Mekalanos-Porro-Siber teaches Claim 18 for the reasons described in Section IX.B.2.j.

**r. 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.**

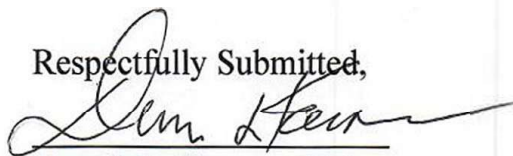
296. In my opinion, Mekalanos-Porro-Siber teaches Claim 19 for the reasons described in Section IX.B.2.k.

**X. CONCLUSION**

297. For the reasons above, it is my opinion that Claims 1-19 of the '757 Patent are anticipated or obvious based on each of the grounds specified in my Declaration.

U.S. Patent No. 11,058,757  
Declaration of Dennis L. Kasper, M.D.

Respectfully Submitted,

A handwritten signature in black ink, appearing to read "Dennis L. Kasper", written over a horizontal line.

Dennis L. Kasper, M.D.

January 26, 2026