UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

POGONA, LLC,
Patent Owner.

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

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

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Ex-1061	*Emergence of PCV13 Nonvaccine-Specific Streptococcus Pneumoniae Serotypes 6C and 23A, and Serogroups 15, 33, and 35 Isolated from Children in Kansas City, Missouri* (2011) ("IDSA Abstract")

I. INTRODUCTION

Merck Sharp & Dohme LLC ("Petitioner") seeks *inter partes* review of Claims 1–19 of U.S. Patent No. 11,058,757 ("the '757 Patent"), currently assigned to Patent Owner Pogona, LLC ("PO"). The claimed subject matter was neither novel nor nonobvious. But for clear examiner error, the claims would have been rejected as anticipated and/or obvious as demonstrated by the rejection of substantially similar claims in a continuation application by a different examiner.

To begin with, the challenged claims cover nothing more than well-known pneumococcal conjugate vaccine constructs including three "serotypes" selected from the group consisting of 23A, 23B, and 35B. The field had already identified these serotypes as candidates long before the patent's earliest filing date. Indeed, pneumococcal conjugate vaccines containing multiple serotypes were ubiquitous. The literature uniformly taught that selection of serotypes for a pneumococcal vaccine was driven by surveilling the prevalence and virulence of serotypes in the patient population and replacing or adding serotypes, including 23A, 23B, and 35B, as their clinical significance increased. That background made these serotypes anticipated and/or obvious choices for inclusion in vaccines using routine methods in the conventional conjugate vaccine field. This is clearly demonstrated by the art of record both here and in a related continuation application.

But during prosecution of the ’757 Patent, the examiner missed it. Allowance turned on a single examiner-initiated interview, with no prior-art rejection ever entered. Indeed, following that interview, the examiner stated that serotypes 23A, 23B, and 35B were “free of prior art,” and then amended the claims to recite only those three serotypes before allowing the claims. As discussed below, that premise—that serotypes 23A, 23B, and 35B were novel and without prior art—was demonstrably wrong. This is underscored by the fact that a different examiner later conducted a search in a related continuation application and located prior art teaching the very 23A, 23B, and 35B serotypes at issue here—art that, when applied, the examiner found anticipated or rendered obvious similar claims. That subsequent, straightforward search confirms that a minimally adequate search during the examination of the ’757 Patent would have uncovered the same references presented here and would have likewise barred allowance.

At bottom, the examiner’s allowance of the ’757 Patent rested on a demonstrably incorrect assertion that the three recited serotypes were “free of prior art,” coupled with a failure to conduct a sufficient search or engage with the art of record that would have revealed still more disclosures directly on point. Because the claims add only these routine serotype selections (without disclosure of any unique structure) to long-familiar conjugate vaccine constructs and methods, they were anticipated and/or obvious at the time.

Such material prosecution error also defeats any discretionary denial under 35 U.S.C. § 325(d) and the PTAB's precedential framework in *Advanced Bionics* and *Becton Dickinson*, premised on prior Office consideration because the Office's earlier consideration was substantively flawed in a manner material to patentability, and prior art references not discovered by the examiner were not before the PTO during prosecution.[1] The PTAB should therefore decline any invitation to discretionarily deny institution. *Inter partes* review should thus be instituted and Claims 1–19 should be found unpatentable and canceled.

II. GROUNDS FOR STANDING

Petitioner certifies that the '757 Patent is available for review, and Petitioner is not barred or estopped from requesting review.

III. PRECISE RELIEF REQUESTED

Petitioner requests review and cancellation of Claims 1–19 of the '757 Patent as unpatentable based on the following grounds, supported by a declaration from

[1] Discretionary denial under *Fintiv* factors is unwarranted because there is no case schedule in place and any trial is likely to occur years from now. Discretionary denial under 35 U.S.C. § 314(a) is unwarranted where, as here, the Petition presents compelling evidence of unpatentability and a streamlined record that will promote efficiency and consistency. Full discretionary denial arguments are reserved for discretionary denial briefing pursuant to USPTO guidance.

Dr. Dennis Kasper. Ex-1002 ¶¶1–297[2]; Ex-1003.

Ground	Summary
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
4	Claims 1–19 are Obvious Over Mekalanos in View of Porro and Siber (Ex-1007)

IV. BACKGROUND AND STATE OF THE ART

A. Pneumococcal Vaccines

A vaccine prevents infectious disease by priming the immune system prior to exposure to pathogens such as bacteria, viruses, or parasites. Ex-1002 ¶33 (citing Ex-1027). It does this by mimicking disease-causing pathogens, stimulating the immune system to attack the pathogen. *Id*. Specifically, the immune system builds antibodies that can identify and coordinate an immune response to kill the pathogen. Ex-1002 ¶34. These antibodies are then stored in long-term immunological memory to defend against future exposures. *Id*.

A common class of disease-causing agents are bacterial pathogens, such as

[2] Citations are to stamped pages, except for the '757 Patent (Ex-1001), Kasper Declaration (Ex-1002), Porro (Ex-1005), Mekalanos (Ex-1006), and Siber (Ex-1007), which reference original pages, column, line numbers, and/or paragraph numbers.

pneumococcus (or *S. Pneumoniae*), which causes pneumonia and meningitis among other diseases. Ex-1002 ¶¶35, 50 (citing Ex-1011, Ex-1026, Ex-1028, Ex-1029, Ex-1041, Ex-1048, Ex-1049). Pneumococcus is encapsulated by capsular polysaccharides, which are long polymers composed of repeating units of simple sugars that protect the bacteria from the immune system. Ex-1002 ¶¶36, 51 (citing Ex-1011, Ex-1012, Ex-1026, Ex-1028). When incorporated into a vaccine, these capsular polysaccharides induce antibody production through the stimulation of "B-cells," facilitating opsonophagocytosis (i.e., the engulfment or killing of the bacteria by the immune system). Ex-1002 ¶¶36, 51. Accordingly, capsular polysaccharides were attractive molecules for use as antigens in pneumococcal vaccines. Ex-1002 ¶¶36–37, 52.

Various strains of pneumococcus, often labeled as "serotypes" or "serogroups," are characterized by variations (differences in structure) in the capsular polysaccharides displayed on their surface. Ex-1002 ¶47 (citing Ex-1011, Ex-1028, Ex-1039). They are identified by number, and by March 2016, there were over ninety recognized serotypes of *S. pneumoniae*, including 23A, 23B, and 35B. Ex-1002 ¶51; Ex-1012. In general, antibodies are serotype-specific, recognizing the specific structure of a capsular polysaccharide serotype. Ex-1002 ¶47. Skilled artisans therefore understood that the particular serotypes to include in a vaccine were those known to be associated with disease and prevalent in the patient

population as determined through routine epidemiological studies. Ex-1002 ¶¶48–49. Commercial vaccines did, and still do, include multiple polysaccharides from different serotypes (i.e., "multivalent") to maximize disease coverage. Ex-1002 ¶47.

Commercial multivalent pneumococcal vaccines consisting of individually extracted capsular polysaccharides ("pneumococcal polysaccharide vaccines" or "PPVs") have been available in the United States since the 1970s. Ex-1002 ¶¶52–53 (citing Ex-1011). Indeed, a 14-valent (containing 14 serotypes) and then a 23-valent (containing 23 serotypes) PPV were approved in 1977 and 1983, respectively. Ex-1002 ¶53 (citing Ex-1028, Ex-1053, Ex-1054).

While PPVs were effective to immunize adults and older children, they were less immunogenic in younger children. Ex-1002 ¶38 (citing Ex-1028, Ex-1029, Ex-1030). To resolve this issue, researchers discovered that immunogenicity could be enhanced by attaching the polysaccharide to a protein through a process called conjugation, i.e., by coupling the capsular polysaccharide to a carrier protein. Ex-1002 ¶39–41, 54 (citing Ex-1011, Ex-1005, Ex-1006, Ex-1009, Ex-1028, Ex-1031, Ex-1033, Ex-1039). These enhanced vaccines are called pneumococcal conjugate vaccines ("PCVs"). *Id.* PCVs elicit a robust, long-term immune response, even in younger children.

The first commercial PCV (Prevnar 7®) was approved in the United States in 2000. Ex-1002 ¶54. Prevnar 7® contained *S. pneumoniae* serotypes 4, 6B, 9V, 14,

18C, 19F, and 23F, each conjugated to a CRM_{197} carrier protein. *Id*. In 2009, Synoflorix®, a 10-valent PCV containing 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), was approved. *Id*. 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 a CRM_{197} carrier protein was approved. *Id.* (citing Ex-1016).

Based on the decades of experience and clinical data associated with PPVs and PCVs prior to March 2016, POSITAs understood that as new serotypes were identified, those serotypes should be included in updated vaccines. Ex-1002 ¶¶55–59 (citing Ex-1005, Ex-1011, Ex-1028). This was not a theoretical suggestion but a standard in the field, as evidenced by the commercialized vaccines highlighted above. Indeed, 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. Ex-1002 ¶57. The first, a 7-valent PCV7 (which included serotypes 4, 6B, 9V, 14, 18C, 19F, 23F), was then extended to 10-valent and 13-valent vaccine compositions as surveillance revealed additional important serotypes.

By March 2016, skilled artisans viewed PCVs, as a "golden standard" due to their success in improving quality of life in pediatric populations. *See* Ex-1005

(Porro), 1:22–29; Ex-1002 ¶¶42–43. Further, routine methods (epidemiological studies) of identifying specific serotypes for inclusion in vaccines were known. Ex-1002 ¶59 (citing, e.g., Ex-1005). Many methods of conjugating polysaccharide antigens to carrier proteins were also known, including classical methods such as CDAP and reductive amination, as well as other methods utilizing sortase linkers and alternative chemistries. Ex-1002 ¶¶43–46 (citing, e.g., Exs-1006–1007). Additionally, numerous carrier proteins derived from modified toxins, such as CRM_{197} were known and included in commercial PCVs. Ex-1002 ¶44 (citing, e.g., Ex-1007, Ex-1033, Ex-1034). Skilled artisans were also well versed in designing PCV compositions, selecting excipients and adjuvants, assessing immunogenicity, and determining appropriate dosages and methods of administration. Ex-1002 ¶¶43–46, 78–81. Thus, pneumococcal conjugate vaccines and their components were mature technologies well before 2016.

B. *S. Pneumoniae* Serotypes 23A, 23B, and 35B Were Known Vaccine Targets

Before March 2016, multiple epidemiological studies had identified *S. pneumoniae* serotypes 23A, 23B, and/or 35B to increase disease potential risk. Ex-1002 ¶¶60–63. 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, 6. Another study 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, 1.

Similarly, a 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, 4. Another 2015 study 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, 2. Likewise, a third 2015 study 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, 2, 5. Additionally, a 2008/2009 study 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. Ex-1024, 2, 4.

The prior art also proposed adding these serotypes to multivalent PCVs. Ex-1002 ¶¶64–72 (citing, e.g., Ex-1022, 2, 11 (listing **23A, 23B**, and **35B**, among

others, as particularly preferred serotypes of *S. pneumoniae* for production); Ex-1021, 10–12 (describing use of pneumococcal conjugate vaccines that include "*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), 23F (**23A, 23B**), and 33F (33C)"); Ex-1010, 12 ("[T]he Pn [pneumococcal] capsular polysaccharide is selected from the group consisting of Pn-serotype 2, 9N, 15A, 17F, 20, **23A, 23B** and **35B** capsular polysaccharides"); Ex-1005, 14:26–15:3; Ex-1006, 3:20–25; Ex-1009, 10). Thus, a POSITA would have anticipated serotypes 23A, 23B, and/or 35B for inclusion in conjugated vaccines and/or would have considered them obvious vaccine targets by March 2016. Ex-1002 ¶73.

V. THE '757 PATENT

A. Specification

The '757 Patent broadly describes pneumococcal saccharide-polypeptide conjugate vaccines, including known isolation, purification, carriers, and conjugation techniques used in commercial vaccines. Ex-1001, 15:40–17:20, 18:22–52, 22:44–26:43; Ex-1002 ¶¶82–83. The specification lists over thirty *S. pneumoniae* serotypes including, 23A, 23B, and 35B, but provides no testing of any specific serotype or any reason to prefer these three serotypes over any of the others listed. Ex-1001, 8:3–10; Ex-1002 ¶84.

B. Claims

Claim 1 does not recite any particular carrier protein or conjugation technique, and thus encompasses conventional pneumococcal conjugate vaccines, using ***any*** carrier and method. Ex-1001, Cl. 1; Ex-1002 ¶¶82, 85. The only purported distinction is the selection of serotypes 23A, 23B, and/or 35B, which were already disclosed in the prior art. Dependent Claims 12–14 recite additional serotypes that were also found in the prior art that the examiner failed to consider during prosecution. The remaining dependent claims recite routine excipients and carriers, as well as routine dosing and administration regimens. Ex-1002 ¶86.

C. Prosecution History

The claims of the '757 Patent were allowed with no prior art rejections. Instead, the claims were allowed based on a single examiner-initiated interview, during which "[t]he applicant agreed to the examiner's amendment." Ex-1004, 1244. In particular, the examiner allowed the claims by amending the Markush listing from the thirty-eight serotypes originally listed to just three—23A, 23B, and 35B—discussed during the interview, which he erroneously stated were "free of prior art." *Id*., 1239–40, 1244.

The examiner explained that he allowed the claims because the recited vaccines comprising capsular polysaccharide conjugates from *S. pneumoniae* serotypes 23A, 23B, and 35B were "novel and nonobvious." Ex-1004, 1241–42. But

even the references before him stated otherwise. References of record such as Matur (Ex-1009) and Babb (Ex-1008) disclosed *S. pneumoniae* serotypes **23A**, **23B**, and/or **35B**. *Infra* §IV.B; Ex-1002 ¶¶70–72. Additionally, due to the lack of a sufficient search, ***references never before the examiner***, including Nierop, Blay, Gu, ***Porro***, and ***Mekalanos***, disclosed conjugate vaccines including the claimed serotypes. *Id.*; §§IX.A–D.[3] Accordingly, the examiner materially erred in allowing the claims. Ex-1002 ¶¶87–93; *see also id.*, ¶¶64–73.

D. Priority Date

For purposes of this proceeding only, Petitioner applies March 31, 2016, as the earliest alleged priority date.

VI. LEVEL OF ORDINARY SKILL IN THE ART

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 with 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

[3] While a number of references disclosed pneumococcal conjugate vaccines comprising capsular polysaccharides from *S. pneumoniae* serotypes selected from a group consisting of 23A, 23B, and 35B as recited in Claim 1 of the '757 Patent, Porro (Ex-1005) and Mekalanos (Ex-1006) are included in the Grounds below.

protein (and analyzing the conjugates), and performing immunologic testing. Ex-1002 ¶¶17–20.

VII. CLAIM CONSTRUCTION

For the purposes of this Petition and pursuant to 37 C.F.R. § 42.104(b)(3), no express constructions are necessary to resolve the patentability issues presented. Ex-1002 ¶¶21–23. To the extent any term is disputed, the prior art discloses the elements under any possible construction.

Claims 1 and 12, however, are written in Markush format. As a result, if one embodiment of a group is anticipated or obvious, e.g., 23A (for Claim 1), PO is precluded from arguing that any other recited alternative, *e.g.*, 23B or 35B, is not obvious. *See, e.g.*, *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1298 (Fed. Cir. 2009) ("Element (a) is written in Markush form, such that the entire element is disclosed by the prior art if one alternative in the Markush group is in the prior art.").

VIII. BRIEF DESCRIPTION OF THE APPLIED PRIOR ART

A. Porro (Ex-1005)

Porro (WO2014/118201) is the WIPO publication of PCT International Application No. PCT/EP2014/051670 designated for the United States and published on August 7, 2014. Thus, Porro is prior art to the '757 Patent under 35 U.S.C. § 102(a)(1). Ex-1005, Cover. Notably, ***Porro was never in front of the***

examiner during prosecution of the '757 Patent despite its teachings of the claimed serotypes in pneumococcal conjugate vaccines, further evidencing material error for failing to conduct a sufficient search in this application, and as further evidenced by the fact that a different examiner in a related prosecution uncovered this reference, barring allowance of similar claims as explained in Ground 1. Ex-1015, 1426; *supra* §V.C; *infra* § IX.A.

Porro discloses improved conjugate vaccines using multivalent conjugate antigens that express multiple carbohydrate specificities (i.e., multiple polysaccharides linked to a single carrier protein) to reduce carrier protein requirements and lower immunogenic burden, enhancing safety. Ex-1005, 4:6–24; Ex-1002 ¶¶94–97. Its teachings include different serotypes in "broad-spectrum vaccines" based on "epidemiology and antibiotic resistance" data. Ex-1005, 66:28–67:9. Specifically, Porro identifies certain *S. Pneumoniae* serotypes as "preferred embodiments" for its multivalent molecular constructs, including serotypes ***23A*** and ***35B***. Ex-1005, 14:26–15:3. These are the very serotypes that the examiner erred in stating were "free of prior art." Ex-1004, 1239–44; *supra* §V.C.

B. Mekalanos (Ex-1006)

Mekalanos (WO2017/011338) is the WIPO publication of PCT Application No. PCT/US2016/041608, which has an international filing date of July 8, 2016, and claims priority to a U.S. provisional application filed on July 10, 2015. Ex-1006,

Cover. Like Porro, ***Mekalanos was never in front of the examiner during prosecution*** of the '757 Patent despite its teachings of the claimed serotypes in pneumococcal conjugate vaccines, further evidencing material error for failing to conduct a sufficient search. Ex-1004; *supra* §V.C; *infra* §§ IX.B–C.

Mekalanos teaches "immunogenic polysaccharide-protein conjugates, a novel sortase-mediated method of making immunogenic polysaccharide-protein conjugates, and methods of administering immunogenic polysaccharide-protein conjugates." Ex-1006, 1:8–10; Ex-1002 ¶¶98–102. Mekalanos teaches that its vaccine compositions may comprise the *S. pneumoniae* polysaccharide serotypes recited in the claims of the '757 Patent, including, *inter alia*, serotypes **23B** and **35B**. Ex-1006, 3:14–26. These are the very serotypes that the examiner erroneously found were "free of prior art." Ex-1004, 1239–44; *supra* §V.C.

Mekalanos's Provisional Application No. 62/191,028 provides written description support for Mekalanos as the disclosures in the provisional are substantially the same as the published application. Ex-1013; Ex-1014; *see also Dynamic Drinkware, LLC v. Nat'l Graphics, Inc*., 800 F.3d 1375, 1380 (Fed. Cir. 2015). Consistent with the requirements of *Dynamic Drinkware*, Petitioner includes a chart (Ex-1040) showing that the disclosures in the provisional application support at least Claim 1 of Mekalanos. *Compare* Ex-1006, Cl. 1 *and* Ex-1013, 5.

Accordingly, Mekalanos was effectively filed before the earliest alleged priority date for the '757 Patent and is prior art to the '757 Patent under 35 U.S.C. § 102(a)(2).

C. Siber (Ex-1007)

Siber (U.S. Patent No. 8,808,707) issued on August 19, 2014. Ex-1007, Cover. Thus, Siber is prior art to the '757 Patent under 35 U.S.C. § 102(a)(1).

Siber concerns immunizing older adults with an "initial" conjugated pneumococcal polysaccharide vaccine followed by additional doses of conjugated or unconjugated vaccines. Ex-1007, Abstract; Ex-1002 ¶¶103–107. It discloses conjugated pneumococcal vaccines comprising polysaccharides from multiple *S. pneumonia* serotypes linked to different carrier polypeptides, including CRM_{197}, Aventis 4vPnD, Protein D of *H. influenzae,* and tetanus toxoid utilizing conventional conjugation methods. *Id.*

Siber teaches that then-available vaccines covered about 90% of pneumococcal blood isolates but could be modified to include additional or different serotypes as epidemiology shifts for specific populations. Ex-1007, 5:31–42. It further teaches that an initial dose followed by a booster (same or different, conjugated, or unconjugated) may yield "beneficial immunoprotective" effects. Ex-1007, 2:46–51, 10:23–11:14.

IX. DETAILED EXPLANATION OF GROUNDS

A. Ground 1: Claims 1, 3, and 12 Are Anticipated by Porro

Porro discloses the very pneumococcal serotypes and conjugate structures recited in the '757 Patent and thus anticipates at least Claims 1, 3, and 12. Ex-1002 ¶108. Critically, ***Porro was not before the examiner during prosecution*** of the '757 Patent. Porro's direct disclosures of the claimed serotypes and conjugate vaccine formats, would have been central to patentability and underscores the examiner's failure to conduct a sufficient search. *Supra* §§ I, V.C, VIII.A. The significance of this error is confirmed by the prosecution of the related Continuation Application No. 17/347,435 ("the '435 Application"), where a different examiner rejected similarly structured claims ***as anticipated by Porro***. *Id.*; Ex-1015, 1426–27. Specifically, the examiner rejected Claim 296 of the '435 Application (reproduced below) as anticipated by Porro:

> A pharmaceutical composition comprising
>
> ***at least 2 immunogenic saccharide-polypeptide conjugates each comprising individually a capsular polysaccharide***, fragment thereof, or combination thereof, conjugated to a polypeptide, wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype group,
>
> wherein a first serotype is selected from the group consisting of 6C, 15A, 16F, 20B, 24F, 31, and 34 and at least one additional serotype is selected from the group consisting of 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 20A, 22F, ***23A, 23B***, 24F, 31, 33F, 34, ***35B***, and 38,
>
> wherein the at least one additional serotype is not the first serotype.

Ex-1015, 179, 1426–27.

PO then repeatedly amended the claims in response to renewed Porro anticipation rejections. *See, e.g.*, Ex-1015, 1468, 1493–94, 1504-05, 1817–18, 1880–82. Ultimately, PO narrowed the independent claim to "consist of" a capsular polysaccharide conjugated to a polypeptide and added explicit fragment limitations, while maintaining overlapping serotype sets. The latest amendment is reproduced below:

> A pharmaceutical composition comprising
>
> a plurality of at least two immunogenic saccharide-polypeptide conjugates, each immunogenic saccharide-polypeptide conjugate ~~comprising individually~~ consisting of a capsular polysaccharide, fragment thereof, or combination thereof, conjugated to a polypeptide,
>
> wherein the capsular polysaccharide, fragment thereof, or combination thereof is from a unique Streptococcus pneumoniae serotype,
>
> wherein a first serotype comprises 16F, 20A, 20B, 24F, or 31, and at least one additional serotype comprises 1, 2, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15B, 15C, 16F, 17F, 18C, 19A, 19F, 20A, 20B, 22F, **23A**, **23B**, 23F, 24F, 31, 33F, 34, **35B**, or 38,
>
> wherein the at least one additional serotype is not the first serotype; and
>
> wherein the fragment of the capsular polysaccharide is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, a pentasaccharide, hexasaccharide, or an oligosaccharide.

Ex-1015, 1903. PO added limitations, which are not contained in the challenged claims of the '757 Patent, in an attempt to overcome Porro's anticipation rejection. While the amended claims remain rejected as obvious in view of Porro and other

references, the '435 Application examiner withdrew their anticipation rejection only in view of PO's narrowing amendments, which are not present in the challenged claims. Ex-1015, 1937–42.

PO's amendments—prompted specifically by Porro and not present here—confirm that the broader, originally presented continuation claims were anticipated. The same logic applies here. Claim 1 of the '757 Patent is not patentably distinct from the rejected continuation claims and is anticipated for the same reasons.

1. Independent Claim 1

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

Porro discloses the preamble. Ex-1002 ¶109. 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 [sic] conjugated to a polypeptide,

For the reasons below, Porro discloses Element 1[a]. Ex-1002 ¶¶110–16.

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

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

individually a capsular polysaccharide conjugated to a polypeptide. Ex-1002 ¶¶111–14.

Specifically, 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. Although Porro discloses "a minimum of three carbohydrate structures" covalently bound/conjugated to each "carrier protein," such constructs fall within Element 1[a], which states "each comprising individually a capsular polysaccharides [sic] conjugated to a polypeptide," meaning the term covers the structural elements recited plus additional elements. *In re Burke, Inc*., 991 F.2d 812 (Fed. Cir. 1993) ("comprising" is an open-ended term). *See* Ex-1015, 1426 ("Porro et al. disclose conjugated polypeptides to capsular polysaccharides").[4]

Porro further discloses that "the term carbohydrate structure is intended to comprise … polysaccharides (such as capsular polysaccharides)." Ex-1005, 12:19–22; Ex-1015, 1426.

Porro also discloses that in "preferred embodiments ... the helper-T dependent carrier protein ... is selected between the group of natural diphtheria mutant protein

[4] The examiner in the continuation '435 Application found Porro disclosed each of the claim limitations in Ground 1 and PO had to amend the claims to overcome that rejection. Accordingly, Petitioner provides citations to both Porro and the prosecution history of the '435 Application.

CRM_{197} ... tetanus toxoid, [and others]." Ex-1005, 13:4–19. These are the same polypeptides/carrier proteins used for conjugation that are disclosed by the '757 Patent. Ex-1001, 17:31–50 ("[a] polypeptide ... can be a carrier protein" such as "CRM_{197}, tetanus toxoid, a cholera toxoid," among others); Ex-1015, 1427 ("Porro et al. disclose that examples of carrier proteins which may be used in the present invention are diphtheria toxoid, tetanus toxoid, CRM197, pneumococcal surface protein (see claims 4, 7 8) meeting the limitation of claims.").

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

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" for *S. pneumoniae*. Ex-1005, 25:6–11; Ex-1002 ¶¶115–16. Indeed, the examiner in the continuation '435 Application found this limitation met by Porro. Ex-1015, 1426–27.

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.

Porro discloses combining serotypes 23A and 35B in a conjugated vaccine. Ex-1002 ¶¶117–19. For example, Porro teaches 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**)" and "such antigen

P[olysaccharide]s 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. Indeed, Porro discloses that these serotypes are "preferred." *Id.*, 14:26–15:3; Ex-1015, 1426 ("Porro et al. disclose[s] … capsular polysaccharides selected among 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, 19F, 20, 22F, ***23A***, 23F, 33F and ***35B*** of *Streptococcus pneumoniae*).

Accordingly, Claim 1 of the '757 Patent is anticipated by Porro for ***exactly*** the same reasons that the '435 Application examiner found the claims in the '435 Application to be anticipated by Porro, further highlighting the material error on the part of the '757 Patent examiner for not conducting appropriate searches to identify and apply Porro. Moreover, this limitation is anticipated even though Porro does not list 23B. As described above, because this element is written in Markush format, if one embodiment of a group is anticipated (with respect to Porro, 23A and 35B), PO cannot argue that 23B is not anticipated. *Supra* §VII; *Fresenius*, 582 F.3d at 1298; Ex-1002 ¶119.

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_{197}, tetanus toxoid, a diphtheria toxoid, cholera toxoid, pertussis toxoid, inactivated or mutant pneumococcal pneumolysin, pneumococcal surface protein A, pneumococcal adhesion protein A, pneumococcal lipoprotein PsaA, C5a peptidase group A or group B *Streptococcus*, a non-typable *H. influenzae* P4 protein, a non-typable *H. influenzae* P6 protein, *M. catarrhalis* uspA, keyhole limpet haemocyanin (KLH), OMPC from *N. meningitidis*, a purified protein derivative of tuberculin (PPD), protein D from *H. influenzae*, PspA, any fragment thereof, or any combination thereof.

Porro discloses Claim 3. Ex-1002 ¶¶120–21. Porro, for example, discloses CRM_{197}. Ex-1005, 2:5–11, 13:4–9, 13:20–22. Ex-1015, 1427 ("Porro et al. disclose[s] … 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.

Porro discloses Claim 12. Ex-1002 ¶¶122–23. 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, P[olysaccharide]s 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 (emphasis added); Ex-1015, 1426. Serotype 20 comprises serotypes 20A and 20B. *See, e.g.*, Ex-1001, 1:38; Ex-1002 ¶178. Moreover, this limitation is anticipated even though Porro does not list 16F and 34. As described above, because this element is written in Markush format, if one embodiment of a group is anticipated (with respect to Porro, 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 20A, 20B, 22F, 23A and 35B), PO cannot argue that 16F and 34 are not anticipated. *Supra* §VII; *Fresenius*, 582 F.3d at 1298; Ex-1002 ¶119.

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

Mekalanos discloses a novel method of conjugating capsular polysaccharide antigens to carrier proteins to make immunogenic conjugates and applies this method to pneumococcal conjugate vaccines and their use. Ex-1006, Title, 2:1–9; Ex-1002 ¶125. As described above, the '757 Patent claims are not limited to any particular conjugation method, and Mekalanos's sortase-mediated method is thus encompassed by the claims. Ex-1002 ¶127. Addressing the production challenges inherent in conventional pneumococcal conjugation, namely that "one single conjugation method may not be appropriate for all serotypes," Mekalanos discloses a unifying conjugation chemistry that obviates the need for "differing chemical

linkages specialized to produce each combination" of the polysaccharide-polypeptide conjugate. Ex-1006, 11:5–10, 14:28, 16:14–18; Ex-1002 ¶126.

The examiner never considered Mekalanos during prosecution of the '757 Patent. That was material error. Mekalanos specifically identifies and uses *S. Pneumoniae* serotypes in its conjugate vaccine constructs—the very subject matter the examiner deemed "appear[ing] to be free of prior art" with respect to serotypes such as 23A, 23B, and 35B. Ex-1006, 3:16–26; Ex-1004, 1244. A reasonable search no different from what should have uncovered Porro would have surfaced Mekalanos and its direct teachings on pneumococcal serotype conjugates and the claimed conjugation architecture. As detailed below, those disclosures anticipate Claims 1–5, 8–9, 11–12, 15, and 18–19. The allowance of these claims without considering Mekalanos reflects a failure to perform and review nothing more than a cursory prior art search and led to the erroneous conclusion that the claimed pneumococcal serotype conjugate compositions were novel when, in fact, they are squarely taught by Mekalanos. Ex-1002 ¶¶124–27.

1. Independent Claim 1

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

Mekalanos discloses the preamble. Ex-1002 ¶¶128–29.

Mekalanos discloses "pharmaceutical compositions" comprising "immunogenetic compositions containing a polysaccharide-sortase conjugate" and

"a pharmaceutically acceptable excipient." Ex-1006, Abstract, 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 [sic] conjugated to a polypeptide,

Mekalanos discloses Element 1[a]. Ex-1002 ¶¶130–42.

(1) Immunogenic saccharide-polypeptide conjugates

Mekalanos discloses two main embodiments, both of which comprise immunogenic saccharide-polypeptide conjugates. Ex-1002 ¶¶130–33. In the first embodiment, the "***immunogenic*** conjugates … include a ***polysaccharide antigen conjugated*** to a sortase ***carrier protein*** capable of stimulating an immune response." Ex-1006, 16:32–33. In this first 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)."). In the second embodiment, the "immunogenic conjugates ... include a ***polysaccharide antigen*** conjugated to a ***carrier protein*** capable of stimulating an immune response." Ex-1006, 16:33–35. The non-sortase carrier proteins of the second embodiment include "CRM 197," "tetanus toxoid," and "cholera toxin B." Ex-1006, 20:22–41. These 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 "CRM_{197}, tetanus toxoid, a cholera toxoid," among others). Mekalanos thus discloses immunogenic saccharide-polypeptide conjugates.

(2) Each comprising individually a capsular polysaccharides [sic] conjugated to a polypeptide

Mekalanos discloses that the pharmaceutical composition comprises "capsular" polysaccharides. Ex-1002 ¶¶134–36. Specifically, 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; *see also id.*, Cl. 37. As described above, each of these capsular polysaccharides is conjugated to a polypeptide. Ex-1006, 16:32–35, 23:13–15. The '757 Patent is not limited by conjugation method. Mekalanos thus discloses immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharide conjugated to a polypeptide. Ex-1002 ¶¶135–36.

(3) A plurality of at least two … conjugates

Mekalanos expressly discloses pharmaceutical compositions comprising multiple saccharide–polypeptide conjugates. It states that the "***immunogenic conjugates*** of the invention may be ***used in combination***," including in pediatric immunizations, and describes immunogenic conjugate formulations that "desirably include[] ***at least one*** carrier protein [and] ***at least one*** antigen of interest." Ex-1006,

25:29–40. The plural use of "conjugates" means a plurality of at least two, or more simply put, more than one. Ex-1002 ¶¶137–39. Mekalanos further claims compositions that "comprise ***a second antigen of interest***," thereby identifying combinations involving more than one antigen and more than one carrier protein within a single composition. Ex-1006, Cl. 44; Ex-1002 ¶¶140–42. The disclosure that the conjugates are "used in combination," coupled with the express teaching that there are multiple "antigens of interest" in addition to the claim set referencing a "second antigen of interest," describes the very arrangement that Claim 1 of the '757 Patent requires: a composition comprising "at least two" immunogenic saccharide–polypeptide conjugates, each individually formed by conjugating a capsular polysaccharide to a protein carrier. Ex-1002 ¶¶137–42.

Indeed, Mekalanos discloses that its "at least one" antigen of interest includes "at least two" since Mekalanos specifically discloses the use of "two" antigens of interest and "two" is included in "at least one." Ex-1002 ¶¶140–42; *see also Enzo Biochem Inc. v. Applera Corp.*, 780 F.3d 1149, 1154–56 (Fed. Cir. 2015) (finding limitation reciting "at least one component" indicates multiple components). Mekalanos's discussion of conventional pneumococcal conjugate vaccines reinforces that understanding. Mekalanos explains that its conjugation chemistry improves on standard polysaccharide–carrier protein conjugates, not by altering the basic multi-conjugate architecture of such vaccines but by enabling a uniform

conjugation approach across multiple serotypes. Ex-1002 ¶139; Ex-1006, 14:30–32, 16:14–18. It identifies the challenge posed by the 90+ pneumococcal serotypes—each with distinct capsular polysaccharides—and addresses the need to produce multi-serotype conjugate formulations agnostic to the chemistries for each pairing. *Id*. In doing so, Mekalanos points to Prevnar 13® as a mixture of 13 distinct conjugate vaccines, each comprising a serotype-specific pneumococcal polysaccharide individually conjugated to CRM_{197} and notes the well-known multi-valent pneumococcal conjugate paradigm in which polysaccharides from multiple serotypes are each linked to a protein carrier. Ex-1006, 31:12–14. This confirms that when Mekalanos describes immunogenic conjugates "used in combination" and recites multiple "antigens of interest," it means multivalent conjugate vaccines comprised of a plurality of distinct saccharide–protein conjugates. Ex-1002 ¶¶137–42.

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.

Mekalanos discloses Element 1[b]. Ex-1002 ¶¶143–49.

Mekalanos discloses that each of the capsular polysaccharides is from a *Streptococcus pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B. Specifically, 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, 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, 3:16–26; *see also id.*, Cl. 37.

This limitation is anticipated even though Mekalanos does not list 23A. As stated above, because this element is written in Markush format, if one embodiment of a group is anticipated (with respect to Mekalanos, 23B and 35B), PO cannot argue that 23A is not anticipated. *Supra* §VII; *Fresenius*, 582 F.3d at 1298.

This limitation is also anticipated despite Mekalanos listing 84 other serotypes because a POSITA would have had "no difficulty in understanding or following [Mekalanos's] teachings" to include 23B and 35B. *See, e.g.*, *In re Parameswar Sivaramakrishnan*, 673 F.2d 1383, 1384–85 (C.C.P.A. 1982) (finding prior art disclosure of a list of 70 salts anticipated claims reciting a single salt included in that list because "there is no suggestion in the record that one of ordinary skill would have had any difficulty in understanding or following the prior art's teachings concerning their combination"); Ex-1002 ¶¶145–46. In particular, Mekalanos 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…" Ex-1006, 17:30–34. And Mekalanos specifically lists and claims 23B and 35B as serotypes to be included in its immunogenic conjugates. Ex-1006, 3:16–26, Cl. 37. Additionally, the '757 Patent itself does not provide any reason for why the serotypes 23A, 23B, and 35B would have been selected from its list of over 39 serotypes listed in its specification. Ex-1001, Figs. 11A–11F, Table 1. This is because selecting an appropriate subset of serotypes from a larger list is within the level of skill in the art. Ex-1002 ¶¶147–49.

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.

Mekalanos discloses Claim 2. Ex-1002 ¶¶150–52.

As explained in Section IX.B.1.b, Mekalanos discloses that the carrier protein is a polypeptide. Ex-1006, 2:13–15, 20:40–41. Mekalanos also discloses that at least one polypeptide comprises a mixture of polypeptides. Specifically, Mekalanos discloses that "a mixture of carrier proteins can be conjugated to the antigenic P[olysaccharide] in a single reaction or multiple sequential reactions." Ex-1006, 17:19–20.

b. Claim 3:

Mekalanos discloses Claim 3. Ex-1002 ¶¶153–56.

Mekalanos discloses that at least one polypeptide of the plurality comprises CRM_{197}, tetanus toxoid, diphtheria toxoid, cholera toxoid, pneumolysin, KLH, any fragment thereof, or any combination thereof. Specifically, 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***," Ex-1006, 20:22–33. 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. Once again, Mekalanos specifically claims such examples. Ex-1006, Cls. 28 ("***pneumolysin***"), 31 ("***diphtheria toxoid***"), 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.

Mekalanos discloses Claim 4. Ex-1002 ¶¶157–59.

Mekalanos discloses that the pharmaceutical composition further comprises an adjuvant, an emulsifier, a salt, or a combination thereof. Specifically, Mekalanos

discloses that "[t]he immunogenic conjugate formulation desirably includes … a pharmaceutically acceptable carrier or excipient (e.g., aluminum phosphate, sodium chloride, or sterile water)." Ex-1006, 25:38–40. Aluminum phosphate and sodium chloride are salts. Ex-1002 ¶158. Mekalanos further 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.*, 31:23–27 ("The [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 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.

Mekalanos discloses Claim 5. Ex-1002 ¶¶160–61.

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.*, 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.

Mekalanos discloses Claim 8. Ex-1002 ¶¶162–67.

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. Specifically, Mekalanos discloses that "[t]he novel [polysaccharide]-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, 16:22–26. Mekalanos also 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.

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.

Mekalanos discloses Claim 9. Ex-1002 ¶¶168–70.

Mekalanos discloses that a toxin activity of at least one of the polypeptides of the plurality is at least partly mitigated. As 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; *see also id.*, Cl. 33 (Mekalanos claiming "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.

Mekalanos discloses Claim 11. Ex-1002 ¶¶171–73.

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

Mekalanos discloses Claim 12. Ex-1002 ¶¶174–78.

Mekalanos discloses that the pharmaceutical composition further comprises at least one additional immunogenic saccharide-polypeptide conjugate comprising a capsular polysaccharide. Specifically, as described above (Section IX.B.1), Mekalanos expressly discloses pharmaceutical compositions comprising multiple saccharide–polypeptide conjugates. *Supra* §IX.B.1.b.3.

Moreover, Mekalanos discloses 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. Specifically, Mekalanos 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, 41A, 41F, 42, 43, 44, 45, 46, 47A, 47F, or 48." Ex-1006, 3:20–26, Cls. 37 and 45. Serotype 20 comprises serotypes 20A and 20B. *See, e.g.*, Ex-1001, 1:38; Ex-1002 ¶178.

Although Mekalanos does not list 6C, it still anticipates Claim 12. As described above (Section VII), Claim 12 is written in Markush format and if one embodiment of a group is anticipated, PO cannot argue that any other embodiment of the claim is not anticipated. *Fresenius*, 582 F.3d at 1298.

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

Mekalanos discloses Claim 15. Ex-1002 ¶179.

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.

Mekalanos discloses Claim 18. Ex-1002 ¶180.

Mekalanos discloses that the subject is a human. 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.

Mekalanos discloses Claim 19. Ex-1002 ¶¶181–84.

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. Specifically, 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. 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. For example, 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, 31:26–29.

Moreover, Mekalanos discloses that its invention is an incremental improvement on conventional vaccines, which themselves are mixtures of immunogenic conjugates, comprising an adjuvant. Ex-1006, 16:14–18, 14:30–32, 31:12–14 (disclosing Prevnar 13® as an "***alum absorbed*** mixture of 13 different

conventional conjugate [polysaccharide] vaccines coupled to CRM197"); Ex-1002 ¶184.

C. Ground 3: Claims 1–12, 15, and 18–19 Are Obvious Over Mekalanos

Petitioner incorporates by reference the analysis and evidentiary support set forth in the Mekalanos anticipation ground (Ground 2) for all limitations of independent Claim 1 and the challenged dependent claims. As shown below, Mekalanos teaches the same immunogenic saccharide-polypeptide conjugates including serotypes selected from a group consisting of 23A, 23B, and 35B with a reasonable expectation of success.

Petitioner also relies on the anticipation analysis for dependent Claims 2–5, 8–9, 11–12, 15, and 18–19. For the reasons described below, Claims 6–7 and 10 are also invalid as obvious in view of Mekalanos. Ex-1002 ¶185.

1. Independent Claim 1

a. Element 1[a]:

Mekalanos teaches Element 1[a]. Ex-1002 ¶¶186–90.

Mekalanos teaches ***a plurality of at least two*** unique immunogenic saccharide-polypeptide conjugates, ***each comprising*** individually a capsular polysaccharide conjugated to a polypeptide. Specifically, Mekalanos teaches that its pharmaceutical composition comprises immunogenic conjugates (plural) "used in combination." Ex-1006, 25:29–31 ("Immunogenic Conjugate Compositions:

antigenic [polysaccharide]-carrier protein … The ***immunogenic conjugates*** of the invention may be ***used in combination***, for example, in pediatric immunizations."). Mekalanos further teaches that its "immunogenic conjugate compositions" include more than one antigen of interest and more than one carrier protein. Ex-1006, 25:29–40 ("The immunogenic conjugate formulation desirably includes ***at least one*** carrier protein, ***at least one*** antigen of interest."); Ex-1002 ¶138 (explaining that "at least one antigen of interest" includes two or more such antigens). And Mekalanos expressly claims inclusion of a second antigen of interest. Ex-1006, Cl. 44 (limiting Claim 1's "immunogenic composition comprising a polysaccharide-sortase conjugate" to "further comprise[] a second antigen of interest").

A POSITA would have understood and been motivated to implement those antigens of interest as capsular polysaccharides in a multivalent pneumococcal conjugate vaccine because, as Mekalanos teaches, "[Polysaccharide] derived from capsules are the primary antigenic components involved in protective immunity against encapsulated bacterial pathogens such as … *Streptococcus pneumoniae*." Ex-1006, 12:24–26; Ex-1002 ¶¶186–90. Multivalent PCVs comprising multiple capsular polysaccharides—each antigen conjugated to a carrier protein—were widely viewed as the standard of care. Ex-1002 ¶¶ 42, 54, 187 (citing e.g., Ex-1005, Ex-1006, Ex-1009, Ex-1011, Ex-1016, Ex-1026, Ex-1028).

A POSITA would also have been motivated to conjugate each capsular polysaccharide to a polypeptide because conjugation was known to enhance B-cell help, drive isotype switching, and produce protective anti-[polysaccharide] IgG with high affinity—precisely the attributes Mekalanos identifies for its "immunogenic conjugates." Ex-1006, 12:37–41; Ex-1002 ¶188.

Accordingly, a POSITA would also have understood that including at least two unique capsular polysaccharide–polypeptide conjugates in a single pharmaceutical composition would have been a predictable variation of Mekalanos with a reasonable expectation of success, given decades of successful multivalent PCVs in which multiple capsular polysaccharides are each conjugated to protein carriers. Ex-1002 ¶¶187–90 (including pneumococcal conjugate vaccines such as Prevnar®).

b. Element 1[b]:

Mekalanos teaches Element 1[b]. Ex-1002 ¶¶191–97.

As explained in the previous section, Mekalanos teaches that the pharmaceutical composition includes "at least two immunogenic saccharide-polypeptide conjugates, each comprising individually a capsular polysaccharides [sic]" conjugated to a polypeptide. Ex-1002 ¶191. Specifically, Mekalanos teaches that "[t]he polysaccharide of the immunogenic composition may include a ***Streptococcus pneumoniae polysaccharide***," which "may be a ***capsular type*** …

23B…***35B***….," which the '757 Patent claims and the examiner found were "free of prior art." Ex-1006, 3:16–26.

Additionally, Mekalanos specifically claims the pharmaceutical compositions claimed in the Markush group recited in the '757 Patent. For example, Claim 37 of Mekalanos recites: "The immunogenic composition of claim 34, ***wherein said Streptococcus pneumoniae polysaccharide is capsular type*** 1, 2, 3… ***23B,*** … ***35B*** ...." Ex-1006, Cl. 37. Moreover, Claim 44 recites "[t]he ***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. A POSITA would thus have understood that Claim 37's teaching that the "***Streptococcus pneumoniae polysaccharide is capsular type*** … ***23B, … 35B***" applies to Claim 44's "second antigen of interest." Ex-1002 ¶¶192–94.

A POSITA would have also understood that the particular serotypes were chosen based on prevalence because that was how the serotypes were selected in prior art vaccines. Ex-1002 ¶¶ 148, 195. For example, Bentley, which is cited in Mekalanos, taught that "polyvalent polysaccharide vaccines have been developed in which [pneumococcal capsular 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." Ex-1006, 14:30–32, 24:21–23 (citing Ex-1026 (Bentley), 1–2).

A POSITA would therefore have been motivated to select or modify these serotypes based on disease prevalence in the treatment population. Ex-1002 ¶196.

A POSITA would also have understood that each of the claimed serotypes—23A, 23B, and 35B—were known as potential targets for conjugated vaccines by 2016 and, therefore, would have found it obvious to select them from the finite lists of options taught by Mekalanos. Ex-1002 ¶¶195–97 (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 (Imohl), 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"). Moreover, multiple references taught inclusion of these serotypes in pneumococcal conjugate vaccines. Ex-1002 ¶¶64–70, 196–97 (citing Ex-1005, Exs-1009–1010, Exs-1021–1022).

Additionally, as described above, it was well known in the art and specifically taught by references cited in Mekalanos that serotypes in commercial vaccines were selected by prevalence in the population. Ex-1006, 14:30–32, 24:21–23 (citing Ex-1026 (Bentley), 1–2). Importantly, neither the '757 Patent itself, nor the examiner who amended the claim, provided any reason for why the serotypes 23A, 23B, and 35B would have been selected from its list of over 39 serotypes that it mentions in the specification. Ex-1001, Figs. 11A–11F, Table 1; Ex-1004, 1240–44.

A POSITA would have had a reasonable expectation of success in conjugating the recited serotypes to a carrier protein in a pharmaceutical composition because the '757 Patent is not limited by conjugation method, and 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; Ex-1002 ¶¶193–94. Further, Mekalanos specifically lists and claims 23B and 35B as serotypes to be included in its immunogenic conjugates. 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 in Mekalanos. Ex-1002 ¶¶ 194, 197.

2. Dependent Claims 6–7 and 10

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

Mekalanos teaches Claim 6. Ex-1002 ¶¶74–77, 199–207.

Mekalanos teaches that at least one of the immunogenic saccharide-polypeptide conjugates elicits an opsonophagocytic response. Dr. Kasper explains that 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). Ex-1002 ¶199. 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. *Id.*

Mekalanos teaches that an opsonophagocytic response is expected for an effectively conjugated immunogenic saccharide-polypeptide conjugate. Ex-1002 ¶200–201. Specifically, Mekalanos teaches that "[p]rotective antibodies have high affinity for their [polysaccharide] antigens, and typically are of the Immunoglobulin G (lgG) subclass, a long-lived antibody with complement fixing and ***opsonic effector activity***." Ex-1006, 12:39–41. A POSITA would have understood that "opsonic effector activity" is a prerequisite to achieving "opsonophagocytic response." Ex-1002 ¶201.

Additionally, Mekalanos teaches testing immunogenic saccharide-polypeptide conjugates created from 23 serotypes for an opsonophagocytic response in Example 4. Ex-1006, 30:3–20. Specifically, Mekalanos teaches that "[t]he functionality of the antibody responses induced with immunogenic conjugates can be assessed … by measuring the ability of the anti-[polysaccharide] antibody to opsonize encapsulated *S. pneumococcus* and lead to bacterial killing after phagocytosis by macrophages." Ex-1006, 31:16–19. Mekalanos further 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.

A POSITA would have been motivated to test the pharmaceutical composition taught by Mekalanos, which comprises a plurality of polysaccharide-polypeptide conjugates including serotypes 23B and/or 35B, for an opsonophagocytic response by, for example, measuring serum levels in a human subject following administration of the pharmaceutical composition, as taught by Mekalanos, because this is the most common way to determine if a desired therapeutic response has been elicited. Ex-1002 ¶205. A POSITA would have reasonably expected to successfully elicit an opsonophagocytic response using the recited pharmaceutical composition based on Mekalanos's teachings because as long as the critical epitopes are maintained through the conjugation process, the opsonophagocytic response should

be preserved. Ex-1002 ¶206. Indeed, 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." Ex-1006, 17:30–34; Ex-1002 ¶207. 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, Cls. 37, 54; Ex-1002 ¶207. Therefore, a POSITA would have been motivated to incorporate the claimed serotypes in a vaccine composition with a reasonable expectation of success in achieving the "opsonophagocytic response" recited in Claim 6. *Id.*

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.

Mekalanos teaches Claim 7. Ex-1002 ¶¶81, 208–15.

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. By March 2016, a POSITA would have understood the typical dose for a pneumococcal conjugate vaccine was 0.5 ml. Ex-1002 ¶209. Indeed, in its "exemplary schedules" for dosing for polysaccharide-protein conjugate vaccines, Mekalanos teaches administration of 0.5 ml doses. Ex-1006, 26:31–40.

Mekalanos further 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. A POSITA would have understood this teaching to mean that the 0.5 ml dose may include 4 to 1000 μg of total immunogenic conjugate. Ex-1002 ¶211.

As explained by Dr. Kasper, 0.001%, by weight of a 0.5 ml dose is about 5 μg, which falls well within the range of 4 to 1000 μg of total conjugate described above. Ex-1002 ¶212. Further, Mekalanos 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. Based on this teaching, 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. Ex-1002 ¶¶214–15; *see Merck Serono S.A. v. Hopewell Pharma Ventures, Inc*., 159 F.4th 10, 17, 29 (Fed. Cir. 2025) (finding "dosing optimization was a result-effective variable" and affirming obviousness finding).

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.

Mekalanos teaches Claim 10 for the reasons described in Section IX.C.2.b. Ex-1002 ¶¶81, 216–19. Additionally, as explained by Dr. Kasper, with respect to Claim 10 (each immunogenic saccharide-polypeptide conjugate), 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 described above. Ex-1002 ¶217.

D. Ground 4: Claims 1–19 Are Obvious Over Mekalanos in View of Porro and Siber

Ground 4 further demonstrates that the examiner erred in finding the serotypes claimed in the '757 Patent "free of prior art." As described above, neither Porro nor Mekalanos were ever considered by the examiner even though they clearly disclosed the recited serotypes. If the examiner had these two references, he would have combined them with Siber (which he did consider) to find the claims obvious. Ex-1002 ¶¶220–21.

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.

A POSITA would have been motivated to combine Mekalanos, Porro, and Siber because they all relate to similarly structured pneumococcal conjugate vaccines and methods of administering them. Ex-1002 ¶¶222–32; Ex-1005,

Abstract; Ex-1006, Abstract; Ex-1007, Abstract. Specifically, while Siber relates to methods of administering pneumococcal polysaccharide conjugate vaccines made by conventional conjugation methods (such as CDAP and reductive amination) that had been available for decades, Mekalanos and Porro both sought to improve upon those classical conjugation methods through alternative conjugation chemistry. Ex-1007, 2:52–54, 7:55–67; Ex-1005, 1:6–14, 4:20–5:20; Ex-1006, 11:5–10, 14:28–36. All three teach conjugation methods that fall within the claims of the '757 Patent, which are not limited to any particular conjugation method. Ex-1002 ¶223

All three references teach inclusion of additional or different serotypes of *S. pneumoniae* in their respective pneumococcal polysaccharide conjugate vaccines to provide protection across a broader population as infections and serotypes may shift over time or become prevalent in specific populations. Ex-1002 ¶¶224–30; Ex-1007, 5:36–43; Ex-1005, 1:6–14, 4:20–5:20; Ex-1006, 11:5–10, 14:28–36. Moreover, Mekalanos and Porro teach inclusion of the same serotypes recited in Claims 1 and 12–14 of the '757 Patent. Ex-1002 ¶¶226–27; Ex-1005, 14:26–15:3; Ex-1006, 3:14–26, 16:14–18; Ex-1007, 5:36–43.

A POSITA would have also understood that both 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-1002 ¶228; Ex-1007, 3:23–36, 6:35–36. Accordingly, a POSITA would have been

motivated with a reasonable expectation of success to utilize 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. Ex-1002 ¶¶229–30.

For the same reasons (i.e., structural similarities), a POSITA would have been motivated to utilize the dosage and administration schedules disclosed in Siber (e.g., multiple administrations one month apart), with the vaccine formulations described in Mekalanos and/or Porro. Ex-1002 ¶231. A POSITA would have had a reasonable expectation of success in doing so because a POSITA would not have expected replacing the conventional conjugation methods with those used in Mekalanos and Porro to change the amount of antigen necessary to induce an immune response. *Id.* ¶232. Moreover, a POSITA would have been able to determine the proper doses and interval between doses for a given vaccine formulation, including those taught by Mekalanos and Porro. *Id*.

2. Independent Claim 1

a. Element 1[pre]:

Mekalanos in view of Porro and Siber ("Mekalanos-Porro-Siber") teaches Element 1[pre]. Ex-1002 ¶¶233–34. Mekalanos, Porro, and Siber each teach pharmaceutical pneumococcal vaccine compositions. *Supra* §§ 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]:

Mekalanos-Porro-Siber teaches Element 1[a]. Ex-1002 ¶¶235–41.

Mekalanos teaches each limitation of Element 1[a] for the reasons described in Sections IX.B.1.b and IX.C.1.a. Ex-1002 ¶236. While Mekalanos alone meets Element 1[a], 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.

Siber specifically teaches that "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 additionally teaches multiple vaccines that were known in the art, which included 7 to 11 serotypes individually conjugated to carrier proteins (i.e., at least two immunogenic saccharide-polypeptide conjugates) in a pharmaceutical composition. Ex-1002 ¶¶237–38; Ex-1007, 8:30–35 (Wyeth), 8:41–47 (Sanofi-Aventis), 8:54–59 (GlaxoSmithKline).

A POSITA would have been motivated to combine the conjugate configurations taught in Siber (i.e., "at least two unique immunogenic saccharide-polypeptide conjugates") with the "immunogenic conjugates" taught by Mekalanos because Mekalanos explains that its invention is an incremental improvement on such well-known conventional vaccines. Ex-1006, 16:14–18; Ex-1002 ¶¶239–40. A POSITA would have a reasonable expectation of success in doing so because such configurations had been in use since the early 1990s and were viewed as an "outstanding success." Ex-1002 ¶241; 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* §IX.D.1.

c. Element 1[b]:

Mekalanos-Porro-Siber teaches Element 1[b]. Ex-1002 ¶¶242–49.

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

Porro teaches combining serotypes ***23A*** and ***35B*** in a conjugated vaccine. For example, Porro teaches 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***)" and "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. Indeed, Porro teaches that these serotypes are "preferred" for its multi-valent vaccine, which would have motivated a POSITA to select them. 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, ***[polysaccharides] of Streptococcus pneumoniae*** (type 1, 2, 3 … ***23A***, … , ***35B***"); Ex-1002 ¶245. Further, as described above, a POSITA would also have understood that each of the claimed serotypes—23A, 23B, and 35B—were known as potential targets for conjugated vaccines by 2016 and, therefore, would have found it obvious to select them from the finite lists of options taught by Mekalanos and Porro. *See* §§IV.B, IX.A.1.c., IX.B.1.c, IX.C.1.b; Ex-1002 ¶245.

A POSITA would have therefore been 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) to achieve expanded coverage over emerging serotypes or to protect specific populations. Ex-1002 ¶¶246–47; Section IX.D.1.

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; Ex-1002 ¶248. 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, Cls. 37, 54. Mekalanos also specifically lists and claims 23B and 35B as serotypes to include in its immunogenic conjugates. 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.

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 such methods were widely used in polysaccharide conjugate vaccines for decades with success. Ex-1002 ¶248.

3. Dependent Claims 2–19

Petitioner incorporates by reference the analysis and evidentiary support set forth in Grounds 1–3 for dependent Claims 2–12, 15, and 18–19. Additional arguments are provided for Claims 3–7 and 9–17 below. Ex-1002 ¶¶250–91.

a. Claim 3:

Mekalanos-Porro-Siber teaches Claim 3 for the reasons described in Sections IX.A.2.a, IX.B.2.b. Ex-1002 ¶251. Additionally, Mekalanos, Porro, and Siber each recite one or more of the common carrier proteins recited in Claim 3. Ex-1002 ¶¶251–52. For example, Mekalanos, Porro, and Siber all teach CRM_{197}. Ex-1005, 2:9–10, 13:20–22; Ex-1006, 20:23–24; Ex-1007, 1:41–43, 7:30–31.

b. Claim 4:

Mekalanos-Porro-Siber teaches Claim 4 for the reasons described in Section IX.B.2.c. Ex-1002 ¶253. The excipients recited in Claim 4 are common excipients used in vaccine formulations. *Id*. Adjuvants, for example, are commonly used in pneumococcal vaccines 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; Ex-1002 ¶¶253–54.

c. Claim 5:

Mekalanos-Porro-Siber teaches Claim 5 for the reasons described in Section IX.B.2.d. Ex-1002 ¶255. The administration methods recited in Claim 5 include the

most common methods of administering vaccines. Ex-1002 ¶256. Mekalanos, Porro, and Siber each 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; Ex-1002 ¶256.

d. Claim 6:

Mekalanos-Porro-Siber teaches Claim 6 for the reasons described in Section IX.C.2.a. Ex-1002 ¶257.

In the Mekalanos-Porro-Siber combination, the immunogenic saccharide-polypeptide conjugates prepared using the CDAP method, as taught by Siber, using an *S. pneumoniae* serotype selected from a group consisting of 23A, 23B, and 35B, as taught by Mekalanos and Porro, would also elicit an opsonophagocytic response, as taught by Mekalanos. Ex-1002 ¶258.

e. Claim 7:

Mekalanos-Porro-Siber teaches Claim 7 for the reasons described in Section IX.C.2.b. Ex-1002 ¶259. Additionally, Siber teaches broad ranges for the amount of polysaccharide or conjugate that should be included in the vaccine, which encompass the claimed concentration. Ex-1002 ¶260; Ex-1007, 15:6–21 ("Generally it is expected that each dose will comprise 0.1–100 μg of polysaccharide."). Siber also provides examples of administering between 34 and 154 μg of conjugate. Ex-1002 ¶260; Ex-1007, 20:45–60 (Example 1, Table 2). As described above,

0.001% of a typical 0.5 ml formulation is 5 μg, which means claims directed to "at least 0.001%" are squarely in the range of conjugate disclosed by Siber. Ex-1002 ¶260.

Given the wide 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." Ex-1002 ¶261; Section IX.D.1.

f. Claim 9:

Mekalanos-Porro-Siber teaches Claim 9 for the reasons described in Section IX.B.2.f. Ex-1002 ¶¶263. As described above, Mekalanos, Porro, and Siber each teach $CRM_{197,}$ which is a "toxoid" that has had its toxicity "at least partially mitigated," as recited in Claim 9. Ex-1005, 2:9–10, 13:20–22; Ex-1006, 20:23–24; Ex-1007, 1:41–43, 7:30–31.

g. Claim 10:

Mekalanos-Porro-Siber teaches Claim 10 for the reasons described in Section IX.C.2.c and IX.D.3.e. Ex-1002 ¶264. Additionally, Siber also teaches that Prevnar® included 2–4 μg of each polysaccharide. Ex-1007, 20:45–57. A POSITA would have understood this to be about 4–8 μg of each conjugate in a typical 0.5 ml dose. Ex-1002 ¶¶265–66; Ex-1007, 20:45–57. 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 Prevnar® had successfully included about 8 μg of at least one conjugate for decades. *Id.*; *supra* § IX.D.1.

h. Claim 11:

Mekalanos-Porro-Siber teaches Claim 11 for the reasons described in Section IX.B.2.g. Siber also teaches administering a first composition and a second composition of a pneumococcal polysaccharide conjugate vaccine. Ex-1002 ¶¶267–69. 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.*, Abstract ("initial immunization may be followed by additional immunization doses comprising conjugated pneumococcal polysaccharide vaccine"); 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"). And while Claim 11 does not recite any efficacy limitations, Siber would have motivated a POSITA to administer a second composition in order to extend immune-protection. Ex-1002 ¶¶269–71; *Id.*, 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").

A POSITA would have been motivated to use the administration methods taught by Siber with the formulations taught by Mekalanos, with a reasonable expectation of success for the reasons described in Section IX.D.1. Ex-1002 ¶¶270–71.

i. Claim 12:

Mekalanos-Porro-Siber teaches Claim 12. Ex-1002 ¶¶272–78.

As explained in Section IX.B.2.h, Mekalanos teaches vaccines comprising capsular polysaccharides selected from *S. pneumoniae* serotype selected from the group consisting of 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 20A, 20B, 22F, and 34. Ex-1006, 3:14–26, 4:1–2, Cls. 37 and 45. As explained in Section IX.A.2.b, Porro teaches vaccines comprising capsular polysaccharides selected from *S. pneumoniae* serotype selected from the group consisting of 6C, 8, 9N, 10A, 11A, 12F. 15A, 15B, 15C, 20, 22F. Ex-1005, 14:26–15:3. As explained in Section IX.B.2.h, 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; Ex-1002 ¶275. 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. Ex-1002 ¶275.

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; Ex-1002 ¶276. 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.

A POSITA would also 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 methods for polysaccharide conjugate vaccines that had been successfully used in pneumococcal

conjugate vaccines comprising *S. pneumoniae* capsular polysaccharides. Ex-1002 ¶277.

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. Ex-1002 ¶278.

j. 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.

Mekalanos-Porro-Siber teaches Claim 13 for the reasons described in the previous section. Mekalanos and Porro together disclose all the serotypes recited in Claim 13. Ex-1002 ¶¶279–83. Mekalanos teaches that the plurality of unique immunogenic saccharide-polypeptide conjugate comprises individually capsular polysaccharides from a *S. pneumoniae* serotype comprising 9N, 15A, 15C, 16F, 23B, and 35B. Ex-1006, 3:20–26. Porro teaches preferred embodiments comprising capsular polysaccharides conjugates from the *S. pneumoniae* serotypes 6C, 9N, 15A, 15C, 23A, and 35B. Ex-1005, 14:26–15:3. As also explained in the previous section, a POSITA would have understood, consistent with Porro's express teachings, that

the selection of various serotypes would have been based on "available data on epidemiology and antibiotic resistance." Ex-1005, 66:28–67:9; Ex-1002 ¶280.

A POSITA would also have understood that all of the claimed serotypes—6C, 9N, 15A, 15C, 16F, 23A, 23B, and 35B—were known by 2016 as potential *S. pneumoniae* vaccine targets, and thus, would have found it obvious to select them from the finite serotype sets disclosed in Mekalanos and Porro. Ex-1002 ¶¶281 (citing, e.g., 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***.")).

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; Ex-1002 ¶282. Mekalanos also describes examples generating "sortase-mediated immunogenic conjugates" comprising 23 types of capsular polysaccharides of *S. pneumoniae*. Ex-1006, 30–31; Ex-1002 ¶282. A POSITA would have understood the same methods could be utilized to conjugate carrier proteins to the recited serotypes. Ex-1002 ¶282. 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. Ex-1002 ¶283; *supra* §IX.D.1.

k. 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.

Mekalanos-Porro-Siber teaches Claim 14 for the reasons described in the previous section and Section IX.D.2.i–j. Ex-1002 ¶284.

l. Claim 15:

Mekalanos-Porro-Siber teaches Claim 15 for the reasons described in Section IX.B.2.i. Ex-1002 ¶285. Siber and Porro also teach intramuscular administration. Ex-1002 ¶286; Ex-1005, 31:24–26; Ex-1007, 13:55–63.

m. 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.

Mekalanos-Porro-Siber teaches Claim 16. Ex-1002 ¶¶78–80, 287–91.

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. Mekalanos 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. 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. Ex-1002 ¶289. 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*.

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.*, 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. Moreover, 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.

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 … or longer." Ex-1007, 11:4–13.

n. 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.

Mekalanos-Porro-Siber teaches Claim 17. Ex-1002 ¶¶292–94.

Mekalanos teaches Claim 17 for the reasons described in the previous section and Sections IX.B.1 and IX.C.1, 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.*, 3:14–26), conjugated to a polypeptide (*id.*, 18:10–13).

Siber also teaches Claim 17 for the reasons described in the previous section and in Section IX.D.1, 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." Ex-1007, 10:51–11:1; Ex-1002 ¶294.

X. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Parties-in-Interest: Petitioner identifies the following real parties-in-interest: Petitioner Merck Sharp & Dohme LLC.

Related Matters: PO has asserted the '757 Patent against Petitioner in *Pogona, LLC v. Merck Sharp & Dohme LLC*, No. 2:25-cv-15294-BRM-JBC (D.N.J.).

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XI. FEE AUTHORIZATION

The PTO is authorized to charge any fees due during this proceeding to Deposit Account No. LA500639.

XII. CONCLUSION

Petitioner requests institution of IPR for Claims 1–19 of the '757 Patent based on each of the grounds in this Petition.

Dated: January 26, 2026

Respectfully Submitted,

/s/ Ben Haber
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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), Petitioner certifies that this petition includes 13,830 words, as measured by Microsoft Word, exclusive of the table of contents, mandatory notices under § 42.8, certificates of service, word count, and exhibits.

CERTIFICATE OF SERVICE (37 C.F.R. §42.6(e)(1))

The undersigned hereby certifies that the above document was served on January 26, 2026, by filing this document through the Patent Trial and Appeal Board P-TACTS System, as well as delivering a copy via express mail upon the following attorneys of record for the Patent Owner:

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