UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MERCK SHARP & DOHME CORP.
Petitioner

v.

WYETH LLC
Patent Owner

_____

Case IPR2016-_____
U.S. Patent No. 8,562,999

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PETITION FOR *INTER PARTES* REVIEW

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1021	Rappuoli and Pizza, "Toxin-Based Vaccines (Diphtheria, Tetanus, Pertussis)," *Handbook Exp. Pharmacol.* 133:201-224 (1999)
1022	Avery and Goebel, "Chemo-immunological studies on conjugated carbohydrate-proteins: II. Immunological specificity of synthetic sugar-protein antigens," *J. Exp. Med.* 50:533-550 (1929).
1023	Anderson *et al.*, "Priming and induction of *Haemophilus influenzae* type b capsular antibodies in early infancy by Dpo20, an oligosaccharide-protein conjugate vaccine," *J. Pediatr.* 111(5):644-650 (1987)
1024	Kniskern *et al.*, "*Haemophilus influenzae* type b conjugate vaccines" in *Vaccine Design: The Subunit and Adjuvant Approach* (1995)
1025	Mazmanian and Kasper, "The love–hate relationship between bacterial polysaccharides and the host immune system," *Nat. Rev. Immunol.* 6:849-858 (Nov. 2006)
1026	Vadheim *et al.*, "Safety evaluation of PRP-D *Haemophilus influenzae* type b conjugate vaccine in children immunized at 18 months of age and older: follow-up study of 30 000 children," *Pediatr. Infect. Dis. J.* 9(7):555-561 (1990)
1027	Kimmel, "Prevention of meningococcal disease," *Am. Fam. Physician* 72(10):2049-2056 (2005)
1028	Rüggeberg and Pollard, "Meningococcal vaccines," *Paediatr. Drugs* 6(4):251-66 (2004)
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1031	Lin et al., "The efficacy of a *Salmonella typhi* Vi conjugate vaccine in two-to-five-year-old children," *N. Engl. J. Med.* 344(17):1263-1269 (2001)

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1032	Paoletti *et al.*, "Neonatal mouse protection against infection with multiple group B streptococcal (GBS) serotypes by maternal immunization with a tetravalent GBS polysaccharide-tetanus toxoid conjugate vaccine," *Infect. Immun.* 62(8):3236-3243 (1994)
1033	Hausdorff *et al.*, "Multinational study of pneumococcal serotypes causing acute otitis media in children," *Pediatr. Infect. Dis. J.* 21(11):1008-1016 (2002)
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1038	Zhang *et al.*, "Mucosal immune responses to meningococcal conjugate polysaccharide vaccines in infants," *Pediatr. Infect. Dis. J.* 21(3):209-213 (2002)
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1040	Pujar *et al.*, "Base hydrolysis of phosphodiester bonds in pneumococcal polysaccharides," *Biopolymers* 75(1):71-84 (2004)
1041	Gudlavaletti *et al.*, "The *Neisseria meningitidis* Serogroup A Capsular Polysaccharide O-3 and O-4 Acetyltransferase," *J. Biol. Chem.* 279(41):42765-42773 (2004)
1042	Bentley *et al.*, "Genetic analysis of the capsular biosynthetic locus from all 90 pneumococcal serotypes," *PLOS Genet.* 2(3):262-269 (2006)

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1044	Redwan, "Cumulative updating of approved biopharmaceuticals," *Hum. Antibodies* 16(3-4):137-58 (2007)
1045	Akers *et al.*, "Formulation Development of Protein Dosage Forms," in *Pharm. Biotech.* 14 ("Development and Manufacture of Protein Pharmaceuticals"):47-128 (2002)
1046	Prefilled Syringes: Innovations That Meet the Growing Demand (2005), http://www.ondrugdelivery.com/publications/prefilled_syringes.pdf
1047	Woerder, "Pharmaceutical primary packaging materials made of tubular glass from the aspect of drug safety and product applications," *Eur. J. Parent. Pharma. Sci*. 9(4):123-128 (2004)
1048	BD Hypak catalog (2000)
1049	Cash, "Medical home builders tackle reimbursement, coding issues," *AAP News* 20:230 (2002)
1050	*Gazzetta Ufficiale della Repubblica Italiana*, Anno 141, Numero 132 (Supplemento ordinario Numero 90) (8 Giugno 2000) (Original Italian Publication)
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1065	Dixit and Kalonia, "Silicone Oil in Biopharmaceutical Containers: Applications and Recent Concerns" in *Concise Encyclopedia of High Performance Silicones* (2014)
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1072	[RESERVED]
1073	Rubin, "Pneumococcal Vaccine," *Pediatr. Clin. N. Am.* 47(2):269-285 (2000)
1074	Nieminen *et al.*, "Differences in product information of biopharmaceuticals in the EU and the USA: implications for product development," *Eur. J. Pharm. Biopharm*. 60:319-326 (2005) (published online April 6, 2005)
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1078	Tzeng *et al.*, "Translocation and Surface Expression of Lipidated Serogroup B Capsular Polysaccharide in *Neisseria meningitides*," *Infect. Immun.* 73(3):1491-1505 (2005)
1079	Cieslewicz *et al.*, "Structural and Genetic Diversity of Group B *Streptococcus* Capsular Polysaccharides," *Infect. Immun.* 73(5):3096-3103 (2005)

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner" or "Merck") hereby requests *inter partes* review of claims 1-6, 10-11, 14 and 17-20 of U.S. Patent No. 8,562,999 ("the '999 Patent") (Ex. 1001), assigned to Wyeth LLC ("Patent Owner" or "Wyeth"). There is a reasonable likelihood that Petitioner will prevail since the prior art renders all the challenged claims obvious under pre-AIA 35 U.S.C. § 103 by a preponderance of the evidence.

The '999 Patent is a formulation patent. Sole independent Claim 1 recites common vaccine ingredients provided in a standard container treated with the standard silicone oil lubricant (*i.e.*, a "siliconized" container). The claim also recites an inherent property of that formulation: it inhibits aggregation induced by the silicone oil. In the specification of the '999 Patent and during prosecution, Patent Owner emphasized that the aluminum salt of the claimed formulation – the most common vaccine "adjuvant" for boosting immunogenicity – also inhibits silicone induced aggregation.

There is no invention. The formulation ingredients of claim 1 are polysaccharide-protein conjugates (a sugar antigen joined to a protein), buffer (to stabilize pH), saline (to match the salt concentration of the body), and aluminum salt. These were common vaccine components as of the earliest possible priority date of April 26, 2006, as evidenced by the Chiron 2003 prior art reference (Ex.

1011). During prosecution, the Examiner recognized that the claimed formulation is old. The Examiner only allowed the claims after Patent Owner argued the nonobviousness of providing the old formulation of claim 1 in a siliconized container. Citing concerns of silicone-induced protein aggregation, Patent Owner stressed that the cited prior art did not disclose housing such formulations in siliconized containers.

Patent Owner's own Prevenar vaccine (described in the Prevenar 2005 prior art reference (Ex. 1017)) squarely contradicts its argument to the PTO. Prevenar was a polysaccharide-protein conjugate vaccine, containing aluminum phosphate adjuvant, and approved for use in pre-filled glass syringes; such syringes were known to be treated with the standard, best-characterized, and safe lubricant, silicone oil.

The formulation of Prevenar 2005 meets all of the limitations claimed in the single independent claim 1 of the '999 Patent, with the exception of buffer. Buffer is a standard component of many protein-based pharmaceuticals, including polysaccharide-protein conjugate vaccines. And Chiron 2003 expressly teaches the addition of histidine buffer to formulations of aluminum phosphate-adjuvanted conjugates (as in Prevenar 2005 and the '999 Patent) to enhance their stability. In view of Chiron 2003, a person of ordinary skill in the art ("POSITA") would have successfully optimized the Prevenar 2005 formulation with buffer.

The remaining limitations in the dependent claims of the '999 Patent are directed to obvious details that reflect routine optimization of claim 1's old formulation, and are taught by the prior art: (a) surfactant and its concentration range (claims 2 and 14); (b) bacterial antigens and particular polysaccharide-protein conjugates (claims 3-5, 17-18); (c) aluminum salt/adjuvant (claim 6, 10-11); and (d) particular containers (claims 19-20). Just as with single independent claim 1, all of the dependent claims would have been obvious to a POSITA.

Patent Owner may allege the addition of 6 other pneumococcal CRM_{197}-conjugates to Prevenar (as reflected by the 13 conjugates recited in claim 18) would not have been obvious, due to purported concerns that too much CRM_{197} protein lowers the immunogenicity of a vaccine. But none of the claims of the '999 Patent recite any particular level of immunogenicity; the only requirement is inhibition of silicone-induced aggregation. In any event, there was no definitive teaching that would have discouraged the natural progression of vaccine development from the 7-conjugate Prevenar to the 13-conjugate version recited in claim 18. Indeed, the Pena 2004 prior art reference (Ex. 1015) discloses the 7 specific conjugates of Prevenar, as well as expansion to the 13 conjugates of claim 18.

As discussed in this Petition and the accompanying Declarations of Devendra Kalonia, Ph.D. (a formulation expert specializing in protein-silicone oil

interactions, including silicone-induced protein aggregation in pharmaceuticals) (Ex. 1009) and Dennis L. Kasper, M.D. (a renowned researcher focusing on the development of human vaccines, including polysaccharide-protein conjugate vaccines) (Ex. 1007), each of the challenged claims would have been obvious over the prior art. Petitioner respectfully submits that the challenged claims should be found obvious and unpatentable.

II. MANDATORY NOTICES

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

The real parties-in-interest are: Petitioner Merck Sharp & Dohme Corp., and Merck & Co., Inc.

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

Petitioner is concurrently filing two additional Petitions for *inter partes* review of the '999 Patent on other grounds and/or addressing other patent claims. Petitioner is unaware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding.

C. Lead and Backup Counsel and Service Info (37 C.F.R. § 42.8(b)(3)-(4))

Lead counsel is Arlene L. Chow (Reg. No. 47,489), Hogan Lovells US LLP, 875 Third Avenue, New York, NY 10022, Phone: 212-918-3000, Fax: 212-918-3100, and Email: arlene.chow@hoganlovells.com. Back-up counsel is: Ernest Yakob, Ph.D. (Reg. No. 45,893), Hogan Lovells US LLP, 875 Third Avenue, New

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Petitioner consents to electronic service.

III. PAYMENT OF FEES (37 C.F.R. §§ 42.15(a), 42.103)

Petitioner submits the required fees with this Petition. Please charge any additional fees required during this proceeding to Deposit Account No. 50-1349.

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

Petitioner certifies that the '999 patent is available for *inter partes* review, and that Petitioner is not barred or estopped from requesting review on the grounds identified.

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

Petitioner challenges claims 1-6, 10-11, 14 and 17-20 of the '999 Patent, and respectfully submits that the claims are unpatentable based on the following grounds:

Ground 1. Claims 1-6, 10-11, 14 and 17-20 are unpatentable as obvious under pre-AIA 35 U.S.C. § 103(a) over Prevenar 2005 (Ex. 1017[1]) in view of Chiron 2003 (Ex. 1011) and the general knowledge of a POSITA.

[1] Prevenar 2005 is also provided as Exhibit B of Ex. 1016 (an affidavit attesting to the publication date of Prevenar 2005 and related documents).

Ground 2. Claim 18 is unpatentable as obvious under pre-AIA 35 U.S.C. § 103(a) over Prevenar 2005 (Ex. 1017) in view of Chiron 2003 (Ex. 1011), Pena 2004 (Ex. 1015[2]) and the general knowledge of a POSITA.

The above prior art references (including publication information) are summarized in Section VI.D-F *infra*; claim construction is addressed in Section VIII *infra*; and a detailed explanation of the grounds for unpatentability is provided in Section IX *infra*.

VI. BACKGROUND

A. State of the Art of Polysaccharide-Protein Conjugate Vaccines as of the Earliest Possible Priority Date of the '999 Patent (April 26, 2006)

1. Polysaccharides in Bacterial Vaccines

A vaccine prevents infectious diseases by priming the immune system prior to exposure to disease-causing organisms (*i.e.*, pathogens), such as bacteria, viruses or parasites. Ex. 1007, ¶ 25. An important class of bacterial pathogens that typically cause disease in young children (with potentially severe outcomes, such as sepsis, pneumonia, and meningitis) includes pneumococcus, meningococcus, and group b *Streptococcus*. *Id.*, ¶ 26.

[2] Pena 2004 is a certified English translation of the original Spanish publication (Ex. 1014).

When the source of infection is encapsulated bacteria (*i.e.*, bacteria covered in a shell of polysaccharides (which are polymers of sugars)), the immune system often targets its response to the polysaccharides; this makes the polysaccharides attractive molecules for vaccines. *Id.*, ¶ 27. As of April 26, 2006, many polysaccharides had been used successfully as vaccines in adults and older children, for example against meningococcus and pneumococcus. *Id.*

2. Polysaccharide-Protein Conjugates in Bacterial Vaccines

Despite the successful use of bacterial polysaccharides to immunize adults and older children, polysaccharides were not very immunogenic in children under 2 years of age. Ex. 1007, ¶ 28. Successful immunization of that particularly susceptible age group took place with bacterial proteins, *e.g.*, tetanus and diphtheria toxoids (inactivated toxins). *Id.*

As far back as the 1920s, it had been shown that, by conjugating polysaccharides to "carrier proteins," one could greatly enhance the immune response to the polysaccharide. *Id.*, ¶ 29. Studies performed in the 1980's and 1990's showed that such conjugation resulted in vaccines that were better immunogens (than polysaccharides alone) in children under 2 years of age. *Id.* As of April 26, 2006, common carrier proteins for such polysaccharide-protein conjugates were tetanus and diphtheria toxoids, and CRM_{197} (a non-toxic mutant of diphtheria toxin). *Id.*

Through conjugation to carrier proteins, a robust antibody-mediated response against the polysaccharides can be achieved. *Id*., ¶ 30. The immune cells responsible for producing antibodies ("B cells") recognize the polysaccharide, but process both the polysaccharide and carrier protein (because they are conjugated). *Id*. Those B cells then produce antibodies specific to the polysaccharide, but with the robustness of a protein-mediated response. *Id*.

Polysaccharide-protein conjugate vaccines had been commercialized for nearly two decades before April 26, 2006. *Id*., ¶ 32. As of April 26, 2006, numerous conjugate vaccines had been approved, including vaccines against *Haemophilus influenzae* type b (ProHIBiT, Vaxem Hib, PedvaxHIB®, ActHIB®, HibTITER), pneumococcus (Prevnar®/Prevenar) and meningococcus (Menactra®, Meningitec, Menjugate®, NeisVac-C). *Id*. (citing Exs. 1026 (at 2[3]), 1051[4], 1053, 1058 (at 28, 38, 42), 1059, 1027 (at 5-6), 1028 (at 6)). Notably, of the above

[3] Except for citations to patents and patent publications (which refer to the originally-published column and line numbers) and citations to expert declarations (which refer to paragraph numbers), this Petition cites to the page numbers added by Petitioners at the bottom of each Exhibit (and designated "IPR PAGE __").

[4] Exs. 1051, 1053, and 1055 are certified translations from Italian to English of Exs. 1050, 1052, and 1054, respectively.

vaccines, half of them (Vaxem Hib, HibTITER, Prevnar®/Prevenar, Meningitec, Menjugate®) used CRM_{197} as the carrier protein. *Id*.

3. Multivalent Polysaccharide-Protein Conjugate Vaccines

Strains of a species of extracellular bacteria, called "serotypes" or "serogroups," are characterized by the particular polysaccharides displayed on their surface. Ex. 1007, ¶ 35. As of April 26, 2006, the field had already identified the most prevalent and/or virulent serotypes of extracellular bacteria affecting young children, such as meningococcus, and streptococcus (including pneumococcus). *Id*., ¶ 39. In general, antibodies are serotype-specific, recognizing the specific structure of a polysaccharide; antibodies against a polysaccharide from one serotype are generally not cross-protective against structurally-unrelated serotypes. *Id*., ¶ 35. Because of this lack of cross-protection, vaccines are frequently multivalent, *i.e.*, they include polysaccharides from more than one serotype. *Id*.

There is a natural progression in the development of multivalent vaccines. *Id*., ¶ 36. The earliest version utilizes the most prevalent polysaccharide serotypes. *Id*. Over time, later vaccine versions will incorporate additional clinically-relevant serotypes for broader protection. *Id*. For example, early meningococcal polysaccharide vaccines developed in the 1960's to the 1980's were initially monovalent and then tetravalent, with the same serotypes featured in later

tetravalent conjugate vaccines. *Id*., ¶¶ 37, 39 (citing Exs. 1027 (at 4-6), 1028 (at 4-7)).

An early pneumococcal polysaccharide vaccine (Pneumovax®) was licensed in 1977 and contained 14 serotypes. *Id*., ¶ 41 (citing Ex. 1062 (at 2)). That 14-valent Pneumovax® was replaced with a 23-valent version (Pneumovax® 23) in 1983. *Id*. (citing Ex. 1061 (at 4)). Because the pneumococcal polysaccharide vaccines were not immunogenic in young children, Patent Owner introduced a polysaccharide-protein conjugate vaccine (Prevnar® a/k/a Prevenar in some countries) in 2000. *Id*. (citing Ex. 1015 at 3). Prevnar®/Prevenar was a 7-valent vaccine, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated to the CRM_{197} carrier protein. *Id*., ¶ 42 (citing Ex. 1058 (at 42)). Pneumococcal conjugate vaccines progressed to a 9-valent (adding serotypes 1 and 5), 11-valent (adding serotypes 3 and 7F), and the 13-valent (adding serotypes 6A and 19A) versions. *Id*., ¶ 38 (citing Ex. 1015 (at 7)).

4. Containers for Conjugate Vaccines

Conjugate vaccines are merely one example of the many protein-based pharmaceutical formulations in common use as of April 26, 2006. Ex. 1009, ¶ ¶ 25 (citing Exs.1044, 1045 (at 11-17)). Because protein cannot survive the GI tract, such protein-based pharmaceuticals are generally administered to patients parenterally (usually by injection). *Id*., ¶ 26.

Historically, injectable formulations were housed in glass vials and sealed with rubber stoppers, with a syringe withdrawing the formulation through the stopper prior to injection. *Id*., ¶ 27. Beginning in the 1980's, the industry turned to single dose, pre-filled syringes for injection of the formulation into patients. *Id*., ¶ 28 (citing Ex. 1046 (at 9)). The clear advantages of pre-filled syringes: ease of use and convenience, accurate dosing, minimized overfilling of containers, less contamination than multi-dose vials, shorter needles, and product differentiation. *Id*., ¶¶ 29-31 (citing Ex. 1048 (at 2-3), 1049 (at 2)). By April 26, 2006, it was routine practice to provide protein-based vaccine formulations in pre-filled syringes, *e.g.*, vaccines by Chiron (*e.g.*, Vaxem Hib), GSK (*e.g.*, Twinrix®, Havrix®, Engerix-B®, Infanrix®, Pediarix®, Lymerix), Merck (*e.g.*, Recombivax HB®, Vaqta®), Sanofi Pasteur (HBVaxPro, Hexavac) and Wyeth/Pfizer (Prevenar). *Id*., ¶ 33 (citing Exs. 1051, 1053, 1058 (at 7, 10, 15, 22, 26, 33, 37), 1060, 1056 (at 16, 28, 39, 40), 1017).

5. Siliconization of Pharmaceutical Containers

As of April 26, 2006, it was standard industry practice to lubricate components of pharmaceutical containers (including but not limited to syringe barrels, plunger tips, and vial stoppers). Ex. 1009, ¶ 34. As noted in 2006 by scientists at Dow Corning (a leading supplier of medical grade silicone oil): "Most parenteral packaging components (e.g., needles, syringes, stoppers, vials, etc.)

require the use of some form of surface treatment or lubrication in order to improve their processability and functionality." *Id*. (quoting Ex. 1064 (at 2)). For syringes, lubrication of the barrel interior and plunger tips is required to help smooth plunger movement during delivery. *Id*., ¶ 35 (citing Exs. 1012 (at 4), 1065 (at 6)).

For decades, silicone oil has been the standard lubricant used in pharmaceutical containers. *Id*., ¶ 37 (citing Ex. 1012 (at 5)). In 1988, the "Task Force on Lubrication of Packaging Components" reported that "[e]ssentially all treatments utilized for the lubrication of parenteral components are based on the use of PDMS fluid (Silicone Oil)." *Id*., ¶ 38 (citing Ex. 1012 (at 8)). In a patent issued in 2003, Becton Dickinson (a leading supplier of medical syringes) described the ubiquitous use of silicone oil in syringes and vial stoppers: "Traditionally, the inside of the syringe tubular barrels, whether constructed of plastic or glass, and the outside of the stoppers have been lubricated with a silicone oil to reduce the friction between the two parts." *Id*. (quoting Ex. 1066 (at 1:22-25)). As of 2006, Dow Corning stressed the necessity of such lubrication, with siliconization as "the most common" form. *Id*. (quoting Ex. 1064 (at 2)). The '999 patent itself acknowledges the widespread use of silicone oil as a lubricant in pharmaceutical containers:

> Paradoxically, silicone oil is a necessary component of plastic syringes, as it serves to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel (i.e., silicone oil improves the syringeability of the formulation). Furthermore, the use of silicone oil is not limited to syringes, as it is used as a coating for glass vials to minimize protein adsorption, as a lubricant to prevent conglomeration of rubber stoppers during fil[l]ing procedures, as a lubricant critical to the processability/machinability of glass and elastomeric closures and as a lubricant to ease needle penetration of vial rubber stoppers.

Id. (quoting Ex. 1001 (at 2:31-42)).

Notably, there were no suitable alternatives to silicone oil for lubricating the glass barrel interiors of pre-filled syringes. As explained in a 2002 treatise on "Development and Manufacture of Protein Pharmaceuticals":

> Proteins are packaged not only in glass vials, but also in glass cartridges and, potentially, in glass syringes. Normally, glass vials are not siliconized, but **glass cartridges and syringes must be siliconized** in order for the rubber-tip plunger rod to be moved easily through the lumen of the glass barrel. Studies must be done to assure that there is little or no interaction between the silicone on the glass and the protein or other formulation ingredients.

Id., ¶ 39 (quoting Ex. 1045 (at 46-47) (emphasis added)).

A 2004 paper describing glass pharmaceutical containers made the same observation:

> Similarly, the **siliconisation** of pen cylinders and disposable syringes **is a requirement that must be met** to ensure that the rubber-tipped plunger can slide smoothly along the walls of the syringe throughout the product's shelf life. Available options for certain containers of this type include treatment with a silicon emulsion that is baked, or treatment with a high-viscosity silicon oil.

Ex. 1047 at 3 (emphasis added).

6. Aggregation of Proteins

Proteins include hydrophilic and hydrophobic regions. Ex. 1009, ¶ 43. Generally, hydrophilic portions of a protein stay at the protein surface (to be close to water/buffer) whereas hydrophobic residues stay in the core of a protein (to avoid water/buffer). *Id*. Proteins tend to "adsorb," *i.e.*, accumulate at surfaces and interfaces (such as solid/liquid, liquid/liquid and air/liquid interfaces). *Id.*, ¶ 44. When a protein adsorbs to a hydrophobic interface, the protein may unfold so that the protein's own hydrophobic regions can bind to the interface. *Id*. With their newly exposed hydrophobic regions, the proteins in turn can bind to each other and aggregate, in order to minimize exposure of their hydrophobic regions to water/buffer. *Id*.

Pharmaceutical formulators consider visible protein aggregates to be undesirable. *Id*., ¶ 45. Protein aggregates signal potential quality control issues with regulatory agencies (and patients and doctors). *Id*. And aggregates may flag

the possibility of a different response compared to the non-aggregated protein, *e.g.*, decreased/increased potency or toxicity. *Id*.

7. Silicone-Induced Aggregation

The extreme hydrophobicity of silicone oil makes it a desired lubricant. Ex. 1009, ¶ 46. But the hydrophobicity of silicone oil may cause the protein to unfold so that the protein's own hydrophobic regions can bind to the silicone oil, with protein aggregation as a result. *Id*., ¶ 47 (citing Ex. 1065 (at 10)).

As of April 2006, it was widely acknowledged that the silicone oil lubricant in protein-based pharmaceutical formulations could lead to protein aggregation. *Id*., ¶ 48. In the "Background of the Invention" section, the '999 Patent describes aggregation and precipitation caused by silicone oil:

> It has been suggested in the art, that silicone oil, which induces protein secondary and tertiary conformational changes, might be responsible for the aggregation/precipitation seen in certain protein pharmaceutical preparations (Jones et al., 2005). For example, several reports in the 1980s implicated the release of silicone oil from disposable plastic syringes as the causative agent in the aggregation of human insulin (citations omitted). Chantelau et al. (1986) observed that after three or more withdrawals from a ten-dose preparation of insulin (using a siliconized disposable syringe), the vial would begin clouding due [to] silicone oil contamination, thereby resulting in aggregation and deactivation of the insulin.

Id. (citing Ex. 1001 (at 2:17-24)). During prosecution of the '999 patent, the Patent Owner stressed that: "It was known at the time of the invention that silicone oil causes aggregation/precipitation." *Id*. (citing Ex. 1002 (at 291)).

8. Protein Drives Aggregation in Conjugate Vaccines

Proteins and polysaccharide-protein conjugates undergo aggregation by similar mechanisms. Ex. 1009, ¶ 50. In both instances, it is the protein component that drives aggregation. *Id*. Any exposed hydrophobic portions at the protein surface – due to exposure to silicone oil and in an effort to reduce exposure to water – will seek other hydrophobic surfaces presented by other proteins, leading to aggregation. *Id*. In contrast, polysaccharides are hydrophilic and have a favorable interaction with water; they are not inclined to aggregate. *Id*.

9. Use of Surfactants to Inhibit Aggregation

As of April 26, 2006, there were known ways of preventing and minimizing interface-induced protein aggregation. Ex. 1009, ¶ 51. Surfactants (also known as surface active molecules or detergents) were widely-used in licensed products to address this specific issue, with polysorbates (commercially sold as Tween®) as the most commonly-used surfactants. *Id*. (citing Ex. 1067 (at 2), 1045 (at 74)). As of April 26, 2006, surfactants had been included in many licensed protein-based formulations (*e.g.*, Tubersol®, Actimmune®, RhoGAM®, Neupogen®, Activase®, Koate®-HP, Kogenate®) and vaccines (Vaxem Hib, Havrix®, Twinrix®, Pentacel®).

Id., ¶ 52 (citing Exs. 1068 (at 3), 1051, 1053, 1058 (at 8, 24), 1063). Since polysaccharides do not compromise surfactant's inhibition of silicone-induced protein aggregation, as of April 26, 2006, surfactants were included in at least one licensed polysaccharide-protein conjugate vaccines, Vaxem Hib. *Id*. (citing Exs. 1051, 1053). A formulator would have had every incentive to rely on this same solution to a known problem again:

> In the pharmaceutical industry, a major concern is ease of approval from the regulating body controlling licensing of drug products. An attraction of nonionic surfactants for use in producing, purifying, and stabilizing drugs is that many have already been approved for use internationally in medicinal products. Table I is a list of a few of the approved surfactants. The acceptance is based largely on the general low toxicity and low reactivity with ionic species exhibited by these excipients (13).

Id., ¶ 53 (quoting Ex. 1068 (at 2)).

10. Use of Aluminum Adjuvants in Conjugate Vaccines

As of April 26, 2006, it was well known in the art that aluminum salt adjuvants boosted immunogenicity by adsorbing protein-based antigens. Ex. 1007, ¶ 53; Ex. 1009, ¶54. Patent Owner's prior art 7-valent Prevnar®/Prevenar (with pneumococcal polysaccharides conjugated to CRM_{197} protein) included aluminum phosphate adjuvant. Ex. 1007, ¶ 54 (citing Ex. 1058 (at 42)). And, as of April 26, 2006, many other licensed conjugate vaccines, such as Vaxem Hib, PedvaxHIB®,

Meningitec, and Menjugate®, included an aluminum salt adjuvant. *Id.*, ¶ 53 (citing Exs. 1051, 1053, 1058 (at 28, 42), 1038 (at 2)). In fact, aluminum salts, such as aluminum phosphate and aluminum hydroxide, were the most commonly used adjuvants for enhancing immunogenicity of human vaccines. *Id.*

11. Use of Buffers in Protein-Based Formulations

As of April 26, 2006, buffers were common components of protein-based formulations, including conjugate vaccines. Ex. 1009, ¶ 57. Buffers are combinations of a weak acid and its salt (or alternatively, a weak base and its salt) used in appropriate concentrations to resist a change in solution pH. *Id.* A change in pH can adversely affect a protein's stability and physical properties (*e.g.*, solubility or structure). *Id.* For injectable protein-based formulations, there are a limited number of standard biocompatible buffers, including histidine and succinate. *Id.*, (citing 1045 (at 21-22)). The accepted pH range for buffers in pharmaceuticals is constrained by physiological acceptability and is relatively narrow, typically pH 5.5 to 7.5. *Id.* As part of routine optimization a POSITA would select from such buffers and the associated, suitable pH range. *Id.*

B. <u>The '999 Patent</u>

The '999 Patent claims formulations that inhibit protein aggregation caused by the silicone oil lubricant present in pharmaceutical containers. Single independent claim 1 recites a "polysaccharide-protein conjugate" formulation in a

siliconized container, which includes at least a buffer and aluminum salt, and which inhibits silicone-induced aggregation:

> 1. A formulation comprising
>
> (i) a pH buffered saline solution,
>
> wherein the buffer has a pKa of about 3.5 to about 7.5,
>
> (ii) an aluminum salt and
>
> (iii) one or more polysaccharide-protein conjugates,
>
> wherein the formulation is comprised in a siliconized container means and inhibits aggregation induced by the siliconized container means.

Ex. 1001.

According to the '999 Patent, aggregation is undesirable for several reasons. Aesthetics are important, and changes in physical appearance "may cause a patient or consumer to lose confidence in the product." *Id*. at 1:33-36. Aggregation can also affect vaccine efficacy, as "any breakdown of the immunogenic composition to an inactive or otherwise undesired form (e.g., an aggregate) lowers the total concentration of the product." *Id*. at 1:41-46.

As acknowledged by Patent Owner in the Background of the Invention, silicone oil had been identified as a potential cause of aggregation in protein-based pharmaceutical formulations since the 1980's. *Id*. at 2:17-31. Given the widespread use of silicone oil in pharmaceutical containers (despite the known potential for silicone-induced aggregation), *id*. at 2:31-42, the inventors felt that "[t]here is therefore an ongoing need in the art for formulations which enhance

stability and inhibit precipitation of immunogenic compositions." *Id*. at 2:47-49. During prosecution of the European counterpart to the '999 Patent, Patent Owner stressed the importance of such formulations in pre-filled syringes which were known to be siliconized. Ex. 1075 at 5 (arguing that prior art did not teach formulations stabilized "against aggregation/precipitation when filled in siliconized means, **which is very desirable in the context of prefilled syringes for example**") (underlining in original, bold added).

To that end, the inventors purported to be the first to recognize that surfactants inhibit silicone-induced aggregation:

> [T]he present invention relates to the unexpected and surprising results that formulating an immunogenic composition with a surfactant such as Tween™80 significantly enhances the stability and inhibits precipitation of an immunogenic composition.

Ex. 1001 at 10:35-39.

The '999 Patent also suggests that adsorption of antigens onto aluminum phosphate adjuvant inhibits silicone-induced aggregation. In Example 3, the inventors formulated 13vPnC in siliconized syringes "with and without 0.25 mg/mL aluminum phosphate as an adjuvant." *Id*. at 23:36-49. The inventors reported that "in the absence of $AlPO_4$, the 13vPnC particulates were readily observable, whereas, in the presence of $AlPO_4$, the 13vPnC particulates were significantly diminished and more difficult to detect." *Id*. at 23:49-52. Contrasting

aluminum-adsorbed conjugates and "free" (non-adsorbed) conjugates, they noted that (1) "the free protein-polysaccharide in solution, in conjunction with silicone, is responsible for the formation of the particulates," whereas (2) a 7-valent aluminum-adjuvanted vaccine formulation (shown to be 100% bound to aluminum) "exhibited no particulate formation." *Id*. at 26:10-17.

Example 4 of the '999 Patent also purports to show that aluminum phosphate decreases silicone-induced aggregation, using antigenicity losses as a surrogate for aggregation. In particular, for two low-silicone syringes (with 0.04 mg silicone/barrel and 0.056 mg silicone/barrel), the aluminum-adjuvanted formulations exhibited less antigenicity loss than the formulation without the aluminum adjuvant. *Id*. at 29:14-26.

In addition to surfactant and aluminum salt, the '999 Patent discloses and claims other common formulation ingredients (such as bacterial antigens, including specifically-identified proteins and polysaccharide-protein conjugates) without describing how they are inventive or contribute to inhibition of silicone-induced aggregation. Ex. 1009, ¶ 72 (citing Ex. 1001 (at 6:10 - 7:10)). Similarly, the '999 Patent does not allege anything inventive as to buffer (type, concentration and pH). *Id*., ¶ 73. To the contrary, the '999 Patent states that "[t]he preparation of these pharmaceutically acceptable compositions, from the above-described components, having appropriate pH isotonicity, stability and other conventional characteristics

is within the skill of the art." Ex. 1001 at 16:12-15. Example 2 demonstrates that choice of buffer had no effect on the ability of surfactant to inhibit silicone-induced aggregation.[5] Ex. 1009, ¶ 73. The inventors studied the:

> storage stability of the SCP/Tween™80 (0.025%) formulation . . . at 25° C. and 37° C. for eight weeks and six weeks, respectively (data not shown) . . . in either succinate buffer or phosphate buffer as follows: succinate buffer (5 mM, pH 6.0) or phosphate buffer (15 mM, pH 7.4), 0.9% NaCl and 0.025% Tween™80.

Ex. 1001 at 23:17-23. The formulations were stable in both succinate and phosphate buffer: "It was observed in this study, that the SCP/Tween™80 formulations (in either buffer) were completely stable at 25° C. and 37° C. for the entire stability study (i.e., up to eight weeks and six weeks, respectively)." *Id*. at 23:25-29.

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[5] The only other comparison of buffers is provided in Example 5, where the '999 Patent measures protein adsorption to aluminum phosphate, when the composition is formulated in succinate buffer, pH 6.0 vs. phosphate buffer, pH 7.0. Ex. 1001 at 29:34 - 30:13. There is no discussion in the '999 Patent regarding the significance, if any, of this comparison. Ex. 1009, ¶ 74. Given that pH affects adsorption to aluminum phosphate, the data does not establish any benefit of succinate buffer over other buffers typically used at pH 6.0 (such as histidine buffer). *Id*.

With respect to surfactants and aluminum salts, the '999 Patent discloses specific embodiments, but does not provide any data (or even suggest) that there are optimal surfactants and aluminum salts with respect to inhibition of silicone-induced aggregation. Ex. 1009, ¶ 75. Indeed, the '999 Patent claims a laundry list of suitable surfactants (claim 14), aluminum salts generally (claim 1), and each of the commonly used salts (claim 10). Ex. 1001.

C. Prosecution History of the '999 Patent

The '999 Patent is the last in a family of three non-provisional applications, all claiming priority back to Provisional Application No. 60/795,261, filed April 26, 2006. Claim 1 of the '999 Patent, as originally filed, recited:

> A formulation which inhibits silicone induced aggregation of a polysaccharide-protein conjugate comprised in a siliconized container means, the formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) an aluminum salt and (iii) one or more polysaccharide-protein conjugates.

Ex. 1002 at 103. The Examiner found this formulation anticipated by the prior art, namely U.S. Publication No. 2006/0228380 to Hausdorff et al. ("Hausdorff") and U.S. Publication No. 2006/0134142 to Kasper et al. ("Kasper"). *Id*. at 138-140.

Patent Owner did not dispute the fact that Kasper and Hausdorff taught every limitation of the claimed formulation, but, instead, alleged that those

references did not disclose formulations in siliconized container means. *Id*. at 237-238. The Examiner maintained the anticipation rejections, noting that both prior art formulations were filled into and administered via syringes, thereby meeting the siliconized container means requirement. *Id*. at 249-250. The Examiner also rejected all of the pending claims, for obviousness-type double patenting, over the claims of Patent Owner's U.S. Patent No. 7,935,787 (Ex. 1004. *Id*. at 252-253.

In response to the Examiner's prior art-based rejections, Patent Owner argued that "the use of a siliconized container means is a mere possibility, not a necessity." *Id*. at 291. Patent Owner further argued it was not obvious to try a siliconized container, because it was known at the time of the invention that silicone oil causes aggregation, but the claimed formulations "showed unexpected stability." *Id*. at 291-292. In light of this argument, the Examiner withdrew the prior art-based rejections. *Id*. at 303.

With respect to the obviousness-type double patenting rejection, Patent Owner argued that "recitation of the formulation inhibiting silicone induced aggregation" overcame the rejection. *Id*. at 293-294. In response, the Examiner maintained the rejection, noting that the '787 Patent claims include a siliconized container limitation and that recitation of an inherent property did not distinguish the claimed formulation over structurally identical prior art formulations:

> Accordingly, the instantly claimed formulation is structurally identical to the formulation claims of '787, as such any property of the formulation "inhibits aggregation induced by the siliconized container means" is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the results applicant discloses and/or claims (inhibits aggregation induced by the siliconized container means) are necessarily present.

Id. at 305. Patent Owner did not further dispute the Examiner's double patenting rejection; instead, Patent Owner filed a Terminal Disclaimer over the '787 Patent. *Id*. at 318. The claims of the '999 Patent were then allowed. *Id*. at 334.

D. Prevenar 2005

Grounds 1 and 2 of this Petition rely on a "Summary of Product Characteristics" of Patent Owner's 7-valent Prevenar vaccine ("Prevenar 2005"), published on the website of the European Medicines Agency ("EMEA" or "EMA") as of January 25, 2005. Ex. 1017. Prevenar 2005 is an archived copy that is currently accessible via the "Internet Archive" website (https://archive.org/ a/k/a "Wayback Machine"), and the authenticity of Prevenar 2005 is evidenced by the affidavit of Christopher Butler, dated November 28, 2016. Ex. 1016; *see, e.g.*, *Creston Elecs., Inc. v. Intuitive Building Controls, Inc.*, IPR2015-01460, Paper 14 (PTAB Jan. 14, 20116) at 12-15 (Internet Archive's affidavit of authenticity is sufficient to authenticate documents as prior art).

Prevenar 2005 is part of the EMEA's European Public Assessment Report ("EPAR") for Prevenar, and was publicly accessible via a link on the EMEA's webpage devoted to the Prevenar EPAR.[6,7] Because Prevenar 2005 was published as of January 25, 2005, which is more than one year before the earliest possible priority date of the '999 Patent (April 26, 2006), Prevenar 2005 is prior art under pre-AIA § 102(b).

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[6] Archived copies of the contemporaneous Prevenar EPAR webpage are also accessible via the Internet Archive. Ex. 1016 at 4-8. Although the frame linking to the Prevenar 2005 SPC (Ex. 1016 at 7) was archived January 24, 2005 (one day prior to the date that the Prevenar 2005 SPC was archived), the Prevenar SPC did not change during that time. Ex. 1077 (printout of the EU Community Register entry for Prevenar, establishing that no Prevenar marketing decisions were rendered between January 24, 2005 and January 25, 2005).

[7] Moreover, it had been expressly reported in the literature prior to April 26, 2006 that the EMEA SPCs – including specifically the Prevenar SPC – were publicly accessible via the EMEA's website. *See* Nieminen *et al.*, "Differences in product information of biopharmaceuticals in the EU and the USA: implications for product development," *Eur. J. Pharm. Biopharm*. 60:319-326 (2005) (published online April 6, 2005) ("Nieminen 2005") (Ex. 1074).

Prevenar 2005 discloses both the composition and container of Patent Owner's Prevenar vaccine, which was licensed in the European Union on February 2, 2001. An approved form of the vaccine was a "0.5 ml suspension for injection in pre-filled syringe (Type I glass)." Ex. 1017 at 16 (§ 6.5). Such pre-filled syringes were known to be siliconized. Ex. 1009, ¶ 108. As explained *supra* at Section VI.A.5, no suitable alternatives existed at the time for lubricating glass syringe barrels to allow for smooth plunger movement. Notably, in Prevenar 2005, the components in contact with the glass barrel interior or formulation – *i.e.*, the plunger stopper and the tip cap – were made of standard butyl rubber, which reinforces that the glass barrel interiors were lubricated with silicone oil. *Id*. (citing Ex. 1076 at 7).

Prevenar 2005 includes every formulation ingredient of the single independent claim 1 of the '999 Patent, other than a buffer. Ex. 1009, ¶ 109. Prevenar 2005 features 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein"; these are the same polysaccharide-protein conjugates recited in dependent claim 17 of the '999 Patent. Ex. 1017 at 11 (§ 2). The polysaccharide-protein conjugates of Prevenar 2005 were "adsorbed on aluminium phosphate (0.5 mg)." *Id*. And the excipients included "[s]odium chloride." *Id*. at 16 (§ 6.1).

Prevenar 2005 indicates that particulates should not be visible in the pre-filled syringe: "The vaccine should be well shaken to obtain a homogeneous white suspension and be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise." *Id*. (§ 6.6). An absence of particulates means that there is no visible protein aggregation, including that induced by silicone oil. Ex. 1009, ¶ 110.

E. Chiron 2003

Grounds 1 and 2 of this Petition also rely on Chiron's International Patent Publication No. WO 03/009869 ("Chiron 2003"). Ex. 1011. Because Chiron 2003 was published on February 6, 2003, more than one year prior to the earliest possible priority date of the '999 Patent (April 26, 2006), it is prior art under pre-AIA § 102(b). Chiron 2003 is directed to aluminum-adjuvanted vaccine formulations (just like the '999 Patent); Chiron 2003 teaches that histidine buffer provides enhanced pH- and antigen-stability, as well as enhanced antigen adsorption to aluminum phosphate. *See, e.g., id*. at 1:27 - 2:3, 5:17-20. Chiron 2003 discloses saccharide-protein conjugate antigens, preferably with a CRM_{197} carrier protein. *Id*. at 2:5, 3:20-23. The teachings of Chiron 2003 are preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus and meningococcus species. *Id*. at 6:32-35.

In addition to the core aluminum salt (adjuvant) and histidine (buffer) components, *see, e.g.*, *id*. at 2:1, 5:15-16, Chiron 2003 teaches the inclusion of a sodium salt (such as sodium chloride), a surfactant (such as polysorbate/Tween® 80), and other adjuvants (in addition to the aluminum salt). *Id*. at 5:28, 6:14-15; 7:27. The polysaccharide-protein conjugate formulations of Examples 7-9 each include one or more meningococcal oligosaccharide-CRM_{197} conjugates, aluminum salt (either aluminum hydroxide or aluminum phosphate), pH buffered saline solution (sodium chloride, with histidine and/or phosphate buffer), and 0.005% polysorbate/Tween® 80 surfactant. *Id*. at 14:3-15:9.

Chiron 2003 explains that aluminum salts are the "most common" adjuvants used in human vaccines, with aluminum hydroxide and aluminum phosphate preferred. *Id*. at 1:9-12, 4:19-21. However, if the antigen is a saccharide (as in a polysaccharide-protein conjugate), there are concerns that aluminum hydroxide will hydrolyze (and degrade) the saccharide. *Id*. at 1:22-24. Thus, in Example 2, Chiron 2003 focuses on the adsorption of a MenC-CRM_{197} conjugate vaccine to aluminum phosphate (not aluminum hydroxide). *Id*. at 12:1-15.

Chiron 2003 expressly teaches that histidine buffer enhances the stability of aluminum-adjuvanted vaccines. In Example 2, histidine proved to be "a useful additive" for enhancing the adsorption of a MenC-CRM_{197} conjugate to aluminum phosphate. *Id*. at 12:14-15. The combination of histidine and aluminum phosphate

"is particularly advantageous for acidic antigens," which includes the majority of bacterial polysaccharides, as well as CRM_{197} carrier protein. *Id*. at 5:3-4; Ex. 1007, ¶ 55. Since histidine "is inherently biocompatible, it is safe, and thus advantageous as [a] component in vaccines." *Id*. at 5:6-7.

Chiron 2003 also discloses that "[t]he pH of the composition is preferably between 6 and 7 (e.g. betwee[n] 6.3 and 7.0)." *Id*. at 6:7. Nevertheless, for the stable, histidine-buffered polysaccharide-protein conjugate formulation of Example 8, the pH was 7.15±0.05, slightly outside the preferred range of pH 6-7. *Id*. at 15:6. Similarly, for the histidine-buffered polysaccharide-protein conjugate formulation of Example 7, the pH was 7.2±0.05. *Id*. at 14:6-9.

F. Pena 2004

Ground 2 of this Petition presents an additional prior art reference, a translation of Pena *et al.*, "Present and future of the pneumonia vaccination," *Pediatrika* 24(4):147-155 (2004) ("Pena 2004"). Ex. 1015. Because Pena 2004 was published in April 2004,[8] more than one year prior to the earliest possible priority date of the '999 Patent (April 26, 2006), it is prior art under pre-AIA § 102(b). Pena 2004 is a review by Patent Owner regarding pneumococcal

[8] Petitioner notes that the original Spanish version of Pena 2004 was cataloged by the National Library of Medicine on July 7, 2004, more than one year before April 26, 2006. Ex. 1014 at 10.

vaccines. Pena 2004 describes the 7-valent Prevnar®/Prevenar: "The 7-valent pneumococcal conjugate vaccine contains the purified saccharides of the capsular antigens of seven serotypes of *Streptococcus pneumoniae* (4, 6B, 9V, 14, 18C, 19F and 23F) conjugated individually with a protein, a nontoxic mutant of the diphtheria toxin, CRM_{197}, and forming [*sic:* forms] glycoconjugates." *Id*. at 3. Pena 2004 also discloses efforts to increase the serotype coverage provided in the 7-valent Prevnar®/Prevenar vaccine: "There are other pneumococcal conjugates that have not yet been marketed and that are in advanced phases of study," including "[t]he 9-serotype vaccine (adds 1 and 5) . . . [t]he 11-serotype vaccine (adds 3 and 7F) . . . [and t]he 13-serotype vaccine (add 6A and 19A)." *Id*. at 7.

A study cited in Pena 2004 describes – in its title – the 9-valent version as having all its polysaccharide serotypes conjugated to CRM_{197}, just like the 7-valent Prevnar®/Prevenar. *Id.* at 8 (citing paper entitled "Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM_{197} . . ."). It was also reported that Patent Owner was developing 9- and 11-valent conjugate vaccines using only CRM_{197} as a carrier protein. *See, e.g.*, Ex. 1035 at 4; Ex. 1036 at 5. And, in around 2003, when Patent Owner applied for a facility license to produce the 13-valent conjugate vaccine, the Ireland EPA noted that CRM_{197} would be the only carrier protein for the 7-, 9- and 13-valent versions:

> The Strep-Pnemo vaccine (Prevenar) will be imported from Wyeth USA in the form of bulk carrier protein (CRM) and purified serotypes. [. . .] Prevenar can be manufactured as 7, 9 or 13 valent Pnemo Conjugate vaccine.

Ex. 1037 at 4. Pena 2004 does not suggest that any other carrier proteins were being considered or used. Ex. 1007, ¶ 45.

VII. LEVEL OF ORDINARY SKILL IN THE ART

The claims of the '999 Patent recite protein-based formulations that inhibit aggregation caused by the silicone in siliconized containers, and which also include general components of bacterial vaccines. Ex. 1009, ¶ 80. Therefore, a POSITA of the '999 Patent (as of April 26, 2006) would have had a Ph.D. degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least 2 years of work experience formulating protein-based compositions, and would have had familiarity or experience with the general components of bacterial vaccines. *Id*. Alternatively, a POSITA would have had a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least 4 years of work experience formulating protein-based compositions, and would have had familiarity or experience with the general components of bacterial vaccines. *Id*.

VIII. CLAIM CONSTRUCTION

Petitioner submits that three claim terms require construction. Because the '999 Patent has not expired and will not expire before a final written decision is

entered in this proceeding, each claim term below is construed based on "its broadest reasonable construction in light of the specification of the patent in which it appears."[9] 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

The terms – "polysaccharide" and "container means" – are explicitly defined in the specification of the '999 Patent. "In such cases, the inventor's lexicography governs." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005); *Sony Mobile Commc'ns (USA) Inc. v. B.E. Tech., L.L.C.*, IPR2014-00029, Paper No. 31 (April 6, 2015) at 8-9 (construing claim terms in accordance with explicit definitions provided in patent). The third term at issue – "the formulation . . . inhibits aggregation induced by the siliconized container means" – covers any formulation that inhibits silicone-induced aggregation, without identifying which ingredient(s) provide that inhibitory property.

A. "polysaccharide"

The term "polysaccharide" appears in independent claim 1, as well as dependent claims 3, 4, 5, 17 and 18. The '999 Patent specifically defines the term "polysaccharide" broadly:

[9] Petitioner reserves the right to argue for different claim constructions in district courts, where a different claim construction standard applies.

> As defined hereinafter, the term "polysaccharide" is meant to include any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a "saccharide", an "oligosaccharide", a "polysaccharide", a "liposaccharide", a "lipo-oligosaccharide (LOS)", a "lipopolysaccharide (LPS)", a "glycosylate", a "glycoconjugate" and the like.

Ex. 1001 at 16:32-38. With this definition, the term "polysaccharide" is not limited to polysaccharide found on bacteria in nature, but also includes "any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts." *Id.* at 16:33-35. For example, "polysaccharide" includes any polysaccharide, including bacterial polysaccharides that have been shortened, and even much shorter oligosaccharides. Ex. 1007, ¶ 51. This is consistent with common practice at the time of the invention: prior to protein conjugation, polysaccharides were broken into smaller units. *Id.*, ¶ 50. This maintained solubility of the conjugates, and prevented extensive cross-linking of polysaccharides which would hinder purification of the conjugate. *Id.*

The '999 Patent makes clear that acceptable forms of bacterial polysaccharides for conjugation to proteins include "oligosaccharides," as well as other "saccharides":

> Polysaccharides are prepared by standard techniques known to those skilled in the art. . . . [S]treptococcal polysaccharides (**e.g., one or**

> **more polysaccharides (or oligosaccharides)** from a (3-hemolytic Streptococcus such [as] group A Streptococcus, group B Streptococcus, group C Streptococcus and group G Streptococcus) and **meningococcal saccharides** (e.g., an N. meningitidis lipo-oligosaccharide (LOS) or lipo-polysaccharide (LPS)) are prepared from clinically relevant serotypes or serogroups, using general techniques and methods known to one of skill in the art. The purified polysaccharides are then chemically activated (e.g., via reductive amination) to make the saccharides capable of reacting with the carrier protein.

Ex. 1001 at 17:19-37 (emphasis added).

Given that explicit and unambiguous definition, Petitioner submits that the broadest reasonable construction of the term "polysaccharide" is:

> any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a saccharide, an oligosaccharide, a polysaccharide, a liposaccharide, a lipo-oligosaccharide (LOS), a lipopolysaccharide (LPS), a glycosylate, a glycoconjugate and the like.

Ex. 1007, ¶ 52; Ex. 1009, ¶ 89.

B. "container means"

The term "container means" appears in independent claim 1, as well as dependent claims 19 and 20. The specification of the '999 Patent specifically defines "container means":

> As defined herein, a "container means" of the present invention includes any composition of matter which is used to "contain", "hold", "mix", "blend", "dispense", "inject", "transfer", "nebulize", etc. an immunogenic composition during research, processing, development, formulation, manufacture, storage and/or administration. For example, a container means of the present invention includes, but is not limited to, general laboratory glassware, flasks, beakers, graduated cylinders, fermentors, bioreactors, tubings, pipes, bags, jars, vials, vial closures (e.g., a rubber stopper, a screw on cap), ampoules, syringes, syringe stoppers, syringe plungers, rubber closures, plastic closures, glass closures, and the like. A container means of the present invention is not limited by material of manufacture, and includes materials such as glass, metals (e.g., steel, stainless steel, aluminum, etc.) and polymers (e.g., thermoplastics, elastomers, thermoplastic-elastomers).

Ex. 1001 at 13:40-56. The above definition expressly includes, "vials, vial closures (e.g., a rubber stopper, a screw on cap), ampoules, syringes, syringe stoppers, [and] syringe plungers." *Id.* at 13:49-51. And the Examples report data in relation to a similarly broad range of "container means." *See, e.g., id.* at 24:49 - 25:18 (Table 3) (syringes, stoppers, vials, and tip caps), 27:24-48 (Table 6) (glass and plastic syringes, plungers, stoppers, and tip caps).

Given the express and unambiguous definition of the term "container means" in the specification, Petitioner submits that the broadest reasonable construction is:

> any composition of matter which is used to contain, hold, mix, blend, dispense, inject, transfer, and/or nebulize, an immunogenic composition during research, processing, development, formulation, manufacture, storage and/or administration, including but not limited to general laboratory glassware, flasks, beakers, graduated cylinders, fermentors, bioreactors, tubings, pipes, bags, jars, vials, vial closures (e.g., a rubber stopper, a screw on cap), ampoules, syringes, syringe stoppers, syringe plungers, rubber closures, plastic closures, and glass closures.

Ex. 1009, ¶ 93.

C. "the formulation . . . inhibits aggregation induced by the siliconized container means"

The single independent claim 1 is open-ended and recites "[a] formulation comprising" at least three ingredients (pH buffered saline solution, aluminum salt and a polysaccharide-protein conjugate), "wherein the formulation is comprised in a siliconized container means and inhibits aggregation induced by the siliconized container means." Petitioner submits that the phrase "the formulation . . . inhibits aggregation induced by the siliconized container means" recites a property of the formulation as a whole, without attributing inhibitory effect to any specific ingredient recited in the claim. Ex. 1009, ¶ 95.

Patent Owner may attempt to argue that independent claim 1 requires that the specifically-recited ingredients of the formulation (*e.g.*, aluminum salt) inhibit silicone-induced aggregation. Such a construction, however, ignores the plain

language of the claim, and is also inconsistent with the specification, which expressly teaches that the invention includes the use of surfactants to inhibit silicone-induced aggregation. *Id.*, ¶ 96.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Claims 1-6, 10-11, 14 and 17-20 Would Have Been Obvious over Prevenar 2005 in View of Chiron 2003 and the General Knowledge of a POSITA

The claims of the '999 Patent are directed to polysaccharide-protein conjugate formulations in siliconized containers, wherein the formulations inhibit silicone-induced aggregation. The formulation of sole independent claim 1 recites nothing more than broad categories of staple vaccine components: polysaccharide-protein conjugates, saline, buffer and aluminum adjuvant. And, as recognized during prosecution, inhibition of silicone-induced aggregation recited in claim 1 is an inherent property of that old formulation containing the components of claim 1. The single supposed point of nonobviousness of the claims of the '999 Patent is the use of siliconized containers for polysaccharide-protein conjugate vaccines, despite purported concerns about silicone-induced aggregation. However, Patent Owner's own Prevenar vaccine (described in the Prevenar 2005 prior art reference (Ex. 1017)) demonstrates that Patent Owner itself was already using pre-filled syringes, known to be siliconzed, for such vaccines. According to the data presented in the '999 Patent, that aluminum phosphate-adjuvanted formulation inherently inhibits

silicone-induced aggregation. *See, e.g., Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (finding obviousness where the prior art did not recognize the claimed formulation property, but the challenged patent itself defined the limitation at issue as a property that is necessarily present). Indeed, Prevenar 2005 discloses that the vaccine is expected to be free of visible particulates. Ex. 1017 at 14.

The formulation of Prevenar 2005 includes the staple vaccine ingredients of claim 1, with the exception of buffer. But buffer is a standard component of many protein-based pharmaceuticals, including polysaccharide-protein conjugate vaccines (*e.g.*, Vaxem Hib and ProHIBiT). And based on Chiron 2003 (Ex. 1011) – a prior art reference that (like Prevenar 2005) discloses aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulations – a POSITA would have successfully optimized the Prevenar 2005 formulation with histidine buffer to enhance pH- and antigen-stability and improve adsorption of the antigens to the aluminum phosphate adjuvant. The remaining limitations in the dependent claims of the '999 Patent are directed to obvious details that reflect only routine optimization of claim 1's old formulation (and are taught by the prior art), and do not impact obviousness in view of Prevenar 2005 and Chiron 2003.

1. Claim 1

a. "A formulation comprising"

Prevenar 2005 discloses a formulation for a "Pneumococcal saccharide conjugated vaccine, adsorbed" to aluminum phosphate adjuvant. Ex. 1017 at 11. Chiron 2003 is directed to aluminum-adjuvanted vaccine formulations (including polysaccharide-protein conjugate vaccines) with histidine buffer, which results in enhanced pH- and antigen-stability. Ex. 1011 at 1:27 - 2:3, 5:17-20, 11:30 - 12:15 (Example 2), 14:3 - 17:4 (Examples 7-9). Chiron 2003 is preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcal infection. *Id*. at 6:32-35.

b. "(i) a pH buffered saline solution,"

A "saline solution" includes a salt, usually sodium chloride. Ex. 1009, ¶ 124. Prevenar 2005 discloses use of "[s]odium chloride." Ex. 1017 at 16 (§ 6.1). Chiron 2003 discloses that "[t]he composition may also comprise a sodium salt e.g. sodium phosphate or sodium chloride." Ex. 1011 at 5:28; *see, e.g.*, *id*. at 14:3 - 17:4 (Examples 7-9 with 9 mg/mL sodium chloride).

Buffer (used to resist change in pH) is a standard component of many protein-based pharmaceuticals, including polysaccharide-protein conjugate vaccines (*e.g.*, Vaxem Hib and ProHIBiT). Ex. 1009, ¶ 128 (citing Ex. 1011 (at 1:6-7)). Acknowledging this, Chiron 2003 teaches a preference for histidine buffer. *Id*. at 1:6-7 ("As well as containing antigenic substances, vaccines contain

substances such as diluents, excipients, preservatives, stabilisers and buffers."), 5:15 ("histidine preferably acts as a buffer."), 5:6-7 ("[histidine] is inherently biocompatible, it is safe, and thus advantageous as an [sic] component in vaccines"), 11:30 - 12:15 and 14:3 - 17:4 (Examples 2 and 7-9 with histidine buffer).

It would have been obvious to use the histidine buffer of Chiron 2003 for the aluminum phosphate-adjuvanted polysaccharide-protein conjugates of Prevenar 2005. Ex. 1009, ¶ 127. Chiron 2003 teaches that histidine improves the stability of aluminum-adjuvanted vaccines:

> **The invention is based on the surprising discovery that the amino acid histidine enhances the stability of vaccines which include aluminium salt adjuvants.** This has been found both for saccharide antigens and for protein antigens. The invention thus provides a composition comprising an antigen, an aluminium salt and histidine. The invention also provides a process for producing this composition, comprising the step of admixing an antigen, an aluminium salt and histidine.

Ex. 1011 at 1:31- 2:3 (emphasis added). Specifically, histidine provides pH- and antigen-stability to formulations without a buffer (such as Prevenar 2005):

> The histidine preferably acts as a buffer. Histidine buffers are well known to the skilled person. Accordingly, the histidine may be ionised within the composition of the invention. **The composition preferably has enhanced pH stability and/or reduced antigen**

> **hydrolysis when compared to an equivalent composition** in which histidine buffer system is either replaced with a sodium phosphate buffer system or **in which no buffer system is included.** Reduced hydrolysis may be a consequence of enhanced pH stability.

Id. at 5:15-20 (emphasis added); *see also id*. at 15:1-6 (a preferred formulation with "Histidine buffer" and "Sodium chloride" demonstrated pH- and antigen-stability for at least 1 month). And histidine improves the adsorption of antigens to the aluminum phosphate adjuvant of Prevenar 2005. *Id*. at 12:14-15. Chiron 2003 teaches that "[t]he use of histidine in combination with an aluminium phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." *Id*. at 5:3-4. As the CRM_{197} protein of Prevenar 2005, as well as many of the polysaccharides in Prevenar 2005, are acidic antigens, they benefit from histidine buffer. *Id*. at 12:2-3; Ex. 1007, ¶ 55.

c. "wherein the buffer has a pKa of about 3.5 to about 7.5,"

Given that histidine buffer is recited in dependent claim 8 of the '999 Patent, it is inherently within the scope of this claim limitation. Ex. 1009, ¶ 131. The histidine buffer disclosed in Chiron 2003 is an amino acid, and the pKa with respect to the side group proton is approximately 6.0. *Id*. (citing Ex. 1045 at 22).

d. "(ii) an aluminum salt"

Prevenar 2005 incorporates "aluminium phosphate."[10] Ex. 1017 at 11. Chiron 2003 "provides a composition comprising an antigen, an aluminium salt and histidine." Ex. 1011 at 2:1; *see, e.g.*, *id*. at 11:30 - 12:15 and 14:3 - 17:4 (Examples 2 and 7-9 with aluminum salt).

e. "and (iii) one or more polysaccharide-protein conjugates,"

Prevenar 2005 discloses 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein." Ex. 1017 at 11. Likewise, Chiron 2003 teaches that conjugation of a saccharide antigen to a carrier protein is preferred. Ex. 1011 at 3:20-21 ("Where a saccharide or carbohydrate antigen is used, it is preferably conjugated to a carrier protein in order to enhance immunogenicity [e.g. refs. 61 to 70]."). Chiron 2003 expressly discloses "a saccharide antigen from *Streptococcus pneumoniae* [*i.e.*, pneumococcus]," and that "[t]he composition may comprise one or more of these bacterial . . . antigens." *Id*. at 2:15, 3:14. Indeed, reference 23 of Chiron 2003 discloses the 7 pneumococcal CRM_{197}-conjugates of Prevenar 2005. Ex. 1073 at 14.

[10] "Aluminium" is an alternate name for "aluminum," used primarily in Europe. There is no difference between "aluminium" and "aluminum." Ex. 1009, ¶ 132.

f. "wherein the formulation is comprised in a siliconized container means"

An approved formulation of Prevenar 2005 is provided in a "pre-filled syringe (Type I glass)," which was known to be siliconized. Ex. 1009, ¶ 136 (citing Ex. 1017 at 14, Ex. 1076 at 7).

g. "and inhibits aggregation induced by the siliconized container means."

The aluminum phosphate-adjuvanted formulation of Prevenar 2005 (as modified further in view of Chiron 2003) inherently inhibits silicone-induced aggregation in siliconized containers.[11] Ex. 1009, ¶ 137. As recognized during prosecution, inhibition of silicone-induced aggregation is an inherent property of

[11] Even if Patent Owner was the first to appreciate this inherent property, it is well-established that reciting the inherent property in a claim does not confer patentability to otherwise old subject matter. *See, e.g.*, *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) ("In sum, '[t]he discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition.'") (internal citations omitted); *In re Spada*, 911 F.2d 705, 708-09 (Fed. Cir. 1990) ("When the claimed compositions are not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.").

the old formulation of claim 1. *See supra* at Section VI.C. Patent Owner also stressed in the specification of the '999 Patent and during prosecution that adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation. *See supra* at Sections VI.B-C. Both Prevenar 2005 and Chiron 2003 teach adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant. Each Prevenar 2005 conjugate is "adsorbed on aluminium phosphate (0.5 mg)." Ex. 1017 at 11. For Chiron 2003, "[a]ntigen is preferably adsorbed to the aluminium salt." Ex. 1011 at 4:5.

Patent Owner may stress that the data of the '999 Patent (associating aluminum phosphate adjuvant with silicone-induced aggregation) was obtained for formulations with succinate buffer, whereas the combination of Prevenar 2005 and Chiron 2003 yields a formulation with a different buffer – histidine. Such an argument is squarely contradicted by the numerous dependent claims (8, 12, 13, 15, 16) that specifically recite histidine buffer. Ex. 1009, ¶ 141.

h. A POSITA Would Have Had a Reasonable Expectation of Success in Combining Prevenar 2005 and Chiron 2003

It would have been obvious to combine Prevenar 2005 and Chiron 2003 to arrive at the claimed formulation, and a POSITA would have had a reasonable expectation of success in doing so. Ex. 1009, ¶ 142. Because inhibition of

silicone-induced aggregation is an inherent property of the claimed formulation, claim 1 would have been obvious.

Prevenar 2005 teaches a formulation containing pneumococcal polysaccharide-CRM_{197} conjugates adsorbed to aluminum phosphate salt, and sodium chloride, in pre-filled glass syringes (known to be siliconized). Ex. 1017 at 11, 16. As discussed *supra*, the Prevenar 2005 formulation inherently inhibits silicone-induced aggregation. The only limitation missing from Prevenar 2005 is buffer, but as discussed *supra*, Chiron 2003 provides explicit motivation to add histidine buffer to the Prevenar 2005 formulation. Ex. 1009, ¶ 143.

A POSITA would also have had a reasonable expectation of success in incorporating the histidine buffer of Chiron 2003 in the Prevenar 2005 formulation. *Id*., ¶ 144. Buffer was a common component of vaccines, and Chiron 2003 teaches that histidine buffer confers pH- and antigen-stability to a pneumococcal conjugate formulation with aluminum phosphate adjuvant (as in Prevenar 2005). *Id*. Based on Chiron 2003, a POSITA would have successfully optimized the Prevenar 2005 formulation with buffer to arrive at claim 1. *Id*.

2. Claim 2

a. "The formulation of claim 1, wherein the formulation further comprises polysorbate 80,"

Not only does Chiron disclose that surfactant advantageously minimizes adsorption of proteins to containers (Ex. 1011 at 6:14-15), it was well-known that

the surfactants of Chiron 2003 inhibit silicone-induced aggregation. Ex. 1009, ¶ 146 (citing Ex. 1013). A formulator would have been incentivized to optimize the formulation of Prevenar 2005 using surfactant, especially in the context of addressing silicone-induced aggregation. *Id.*, ¶ 145. Chiron 2003 identifies surfactants, such as polysorbate/Tween® 80, as components of the disclosed polysaccharide-protein conjugate formulations. *See, e.g.,* Ex. 1011 at 6:14-15, 14:3 - 17:4 (Examples 7-9 with 0.005% Tween® 80 a/k/a polysorbate 80). It was also well-established that surfactants were safe and standard components of pharmaceutical products. *Id.*, ¶ 147. Surfactants had been included in numerous protein-based pharmaceuticals, including polysaccharide-protein conjugate vaccines (such as Vaxem Hib, and the vaccines disclosed in Chiron 2003), other protein-based vaccines (such as Havrix®, Twinrix®, and Pentacel®), and other non-vaccine protein-based formulations (such as Tubersol®, Actimmune®, RhoGAM®, Neupogen®, Activase®, Koate®-HP and Kogenate®). *Id*. at ¶ 147 (citing Exs. 1051, 1053, 1058 (at 8, 24), 1063, 1068 (at 3), 1013).

b. "and wherein the final concentration of the polysorbate 80 in the formulation is at least 0.001% to 10% polysorbate 80 weight/volume of the formulation."

Chiron 2003 teaches polysorbate 80 in the claimed concentration range. Ex. 1009, ¶ 148. Chiron 2003 does not specify whether the 0.005% Tween®/polysorbate 80 is measured on a weight/volume basis; but, unless

otherwise specified, POSITAs assume that disclosure of a percent concentration is referring to weight/volume. *Id*., ¶ 149. Regardless of whether the concentration is weight/volume, weight/weight or volume/volume, 0.005% Tween® 80 is in the claimed weight/volume range. *Id*. The density of buffer or Tween® will not vary so much from water so as to have Tween® fall outside of the broadly claimed concentration range. *Id*. At minimum, recitation of 0.005% Tween® 80 in Chiron 2003 would have made it obvious to include 0.005% Tween® 80 on a weight/volume basis. *Id*.

3. Claim 3

a. "The formulation of claim 1, wherein the polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides."

Prevenar 2005 discloses 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein." Ex. 1017 at 11. The teachings of Chiron 2003 are preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus (*i.e.*, *Streptococcus pneumonia*). Ex. 1011 at 6:32-35. And, Chiron 2003 discloses "a saccharide antigen from *Streptococcus pneumoniae*" (preferably conjugated to CRM_{197} carrier protein), and that "[t]he composition may comprise one or more of these bacterial . . . antigens." *Id*. at 2:15, 3:14. Indeed, reference

23 of Chiron 2003 discloses the 7 pneumococcal CRM_{197}-conjugates of Prevenar 2005. Ex. 1073 at 14.

4. Claim 4

a. "The formulation of claim 1, wherein the formulation further comprises one or more meningococcal polysaccharides, one or more meningococcal antigenic proteins, or a combination thereof."

It would have been obvious to use meningococcal polysaccharide and/or protein antigens in the formulation of Prevenar 2005, which explicitly discloses "concomitant administration of Prevenar and $CRM_{[197]}$ conjugate meningococcal C vaccines." Ex. 1017 at 11. There is nothing inventive about incorporating meningococcal antigens in a vaccine; such antigens were well-known in the art long before April 26, 2006, and are expressly disclosed in Chiron 2003. Ex. 1007, ¶¶ 32, 34, 37, 39; Ex. 1009, ¶ 154. The teachings of Chiron 2003 are preferably directed to the "prevention and/or treatment of bacterial meningitis," with meningococcal antigens (both saccharide and protein) particularly preferred where "[t]he composition may comprise one or more of these bacterial . . . antigens." Ex. 1011 at 6:32-35; 2:5-7. Chiron 2003 discloses that the vaccine antigen can include "a protein antigen from *N.meningitidis* serogroup B. . . a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y." *Id.* at 2:9-14; *see also id.* at Examples 1, 3, 4 and 6 (meningococcal proteins) and Examples 2 and 7-9 (meningococcal oligosaccharide-protein conjugates).

A limitation directed to additional meningococcal polysaccharides and/or proteins does not impact the obviousness inquiry. Ex. 1009, ¶ 155. As discussed above with respect to claim 1, the aluminum phosphate-adjuvanted formulation of Prevenar 2005 (as modified further in view of Chiron 2003) inherently inhibits silicone-induced aggregation in siliconized containers. *Id*. Inhibition of silicone-induced aggregation is an inherent property of the old formulation. *Id*. The data presented in the '999 Patent suggests that adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation. *Id*. And both Prevenar 2005 and Chiron 2003 teach adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant. *Id*.

5. Claim 5

a. "The formulation of claim 1, wherein the formulation further comprises one or more streptococcal polysaccharides, one or more streptococcal antigenic proteins, or a combination thereof."

Pneumococcus (*i.e., Streptococcus pneumoniae*) is a species of the *Streptococcus* genus. Prevenar 2005 discloses 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein." Ex. 1017 at 9. There is nothing inventive about incorporating streptococcal antigens in a vaccine; such antigens were well-known in the art long before April 26, 2006, and are expressly disclosed in Chiron 2003. Ex. 1007, ¶¶ 32-34, 40, 42-46; Ex. 1009, ¶ 157. As discussed above with respect

to claim 3, Chiron 2003 is preferably directed to, *inter alia*, disease caused by pneumococcus, a streptococcal species (*i.e.*, *Streptococcus pneumoniae*). Chiron 2003 also discloses that the vaccine antigen can include "an antigen from *Streptococcus agalactiae* (group B streptococcus)," and "an antigen from *Streptococcus pyogenes* (group A streptococcus)" and that "[t]he composition may comprise one or more of these bacterial . . . antigens." Ex. 1011 at 2:30-31, 3:14.

A limitation directed to additional streptococcal polysaccharides and/or proteins does not impact the obviousness inquiry. Ex. 1009, ¶ 158. As discussed above with respect to claim 1, the aluminum phosphate-adjuvanted formulation of Prevenar 2005 (as modified further in view of Chiron 2003) inherently inhibits silicone-induced aggregation in siliconized containers. *Id*. Inhibition of silicone-induced aggregation is an inherent property of the old formulation. *Id*. The data presented in the '999 Patent suggests that adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation. *Id*. And both Prevenar 2005 and Chiron 2003 teach adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant. *Id*.

6. Claim 6

a. "The formulation of claim 1, wherein the formulation further comprises an adjuvant."

Prevenar 2005 discloses that each of the pneumococcal conjugates is "adsorbed on aluminium phosphate (0.5 mg)," a known adjuvant. Ex. 1017 at 11.

Similarly, Chiron 2003 is directed to aluminum-adjuvanted vaccines formulations, and explains that "[t]he vaccine may include an adjuvant in addition to the aluminium salt." Ex. 1011 at 1:27 - 2:3, 7:27.

7. Claim 10

a. "The formulation of claim 1, wherein the aluminum salt is aluminum hydroxide, aluminum phosphate or aluminum sulfate."

The formulation of Prevenar 2005 incorporates "aluminium phosphate (0.5 mg)." Ex. 1017 at 11. Chiron 2003 discloses that "[t]he aluminium salt is preferably an **aluminium hydroxide** (e.g. aluminium oxyhydroxide) or an **aluminium phosphate** (e.g. aluminium hydroxyphosphate or orthophosphate), but any other suitable salt may also be used (e.g. **sulphate**)." Ex. 1011 at 4:19-21 (emphasis added); *see also id*. at 11:30 - 12:15 and 14:3 - 17:4 (Examples 2 and 7-9 with "Aluminium oxyhydroxide" or "Aluminium hydroxyphosphate").

8. Claim 11

a. "The formulation of claim 10, wherein the aluminum salt is aluminum phosphate."

The formulation of Prevenar 2005 incorporates "aluminium phosphate (0.5 mg)." Ex. 1017 at 11. Chiron 2003 uses "aluminum hydroxyphosphate" (a specific aluminum phosphate) with polysaccharide-protein conjugates. *See* Ex. 1011 at 11:30 - 12:15 and 14:10 - 17:4 (Examples 2, 8 and 9), 4:19-21 (identifying aluminium hydroxyphosphate as a particular aluminium phosphate).

9. Claim 14

a. "The formulation claim 1, wherein the formulation further comprises a surfactant selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 85, nonylphenoxypolyethoxethanol, octylphenoxypolyethoxethanol, oxtoxynol 40, nonoxynol-9, triethanolamine, triethanolamine polypeptide oleate, polyoxyethylene-660 hydroxystearate, polyoxyethylene-35ricinoleate, soy lecithin and a poloxamer."

As discussed with respect to claim 2, not only does Chiron disclose that surfactant advantageously minimizes adsorption of proteins to containers (Ex. 1011 at 6:14-15), it was well-known that the surfactants of Chiron 2003 inhibit silicone-induced aggregation. Ex. 1009, ¶ 166 (citing Ex. 1013). A formulator would have been incentivized to optimize the formulation of Prevenar 2005 using surfactant, especially in the context of addressing silicone-induced aggregation. Ex. 1009, at ¶ 165. Chiron 2003 identifies surfactants, such as polysorbate/Tween® 80, as components of the disclosed polysaccharide-protein conjugate formulations. *See, e.g.,* Ex. 1011 at 6:14-15, 14:3 - 17:4 (Examples 7-9 with 0.005% Tween® 80 a/k/a polysorbate 80). It was also well-established that surfactants were safe and standard components of pharmaceutical products. *Id.*, ¶ 167. Surfactants had been included in numerous protein-based pharmaceuticals, including polysaccharide-protein conjugate vaccines (such as Vaxem Hib, and the vaccines disclosed in Chiron 2003), other protein-based vaccines (such as Havrix®,

Twinrix®, and Pentacel®), and other non-vaccine protein-based formulations (such as Tubersol®, Actimmune®, RhoGAM®, Neupogen®, Activase®, Koate®-HP, and Kogenate®). *Id*. (citing Exs. 1051, 1053, 1058 (at 8, 24), 1063, 1068 (at 3), 1013).

10. Claim 17

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises [7 conjugates, each with a different *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F) conjugated to a CRM_{197} polypeptide]"[12]

Prevenar 2005 discloses 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein." Ex. 1017 at 9. The teachings of Chiron 2003 are preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus (*i.e.*, *Streptococcus pneumonia*). Ex. 1011 at 6:32-35. And, Chiron 2003 discloses "a saccharide antigen from *Streptococcus pneumoniae*" (preferably conjugated to CRM_{197} carrier protein), and that "[t]he composition may comprise one or more of these bacterial . . . antigens." *Id*. at 2:15, 3:14. Indeed, reference 23 of Chiron 2003 discloses the 7 pneumococcal CRM_{197}-conjugates of Prevenar 2005. Ex. 1073 at 14.

[12] The complete claims 17 and 18 are recited in the "Claim Listing Appendix" of this Petition.

11. Claim 18

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises [13 conjugates, each with a different *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A) conjugated to a CRM_{197} polypeptide]"

Claim 18 incorporates the 7 conjugates recited in claim 17 (and taught by Prevenar 2005 and Chiron 2003). That Claim 18 recites six additional conjugates does not impact the obviousness analysis, especially when the 13 claimed pneumococcal serotypes were well known in the art. Ex. 1007, ¶ 44 (citing Exs. 1033 (at 7), 1015 (at 7)). There is a natural progression in the development of multivalent vaccines. *Id*., ¶ 45. The earliest version of multivalent vaccines utilizes the most prevalent polysaccharide serotypes. *Id.*, ¶ 36. Over time, later versions of the vaccines will incorporate additional clinically-relevant serotypes for broader protection. *Id*. In the case of pneumococcal CRM_{197}-conjugated vaccines, the 7-valent vaccine was expanded to a 9-valent vaccine. *Id*., ¶¶ 38, 45 (citing Exs. 1015 (at 7, 10), 1034 (at 2), 1035 (at 4), 1036 (at 5), 1037 (at 4)). The literature subsequently disclosed a further progression to an 11-valent vaccine, again conjugated solely to CRM_{197}. *Id*., ¶¶ 38, 45 (citing Exs. 1015 (at 7, 10), 1035 (at 4), 1036 (at 5)**.** A POSITA would have understood that a further step in the natural progression included the 13 serotypes of claim 18 (which were well-known), conjugated only to CRM_{197}. *Id*., ¶¶ 45-46.

A limitation directed to additional pneumococcal polysaccharide-protein conjugates does not impact the obviousness inquiry. Ex. 1009, ¶ 172. As discussed above with respect to claim 1, the aluminum phosphate-adjuvanted formulation of Prevenar 2005 (as modified further in view of Chiron 2003) inherently inhibits silicone-induced aggregation in siliconized containers. *Id.* Inhibition of silicone-induced aggregation is an inherent property of the old formulation. *Id*. The data presented in the '999 Patent suggests that adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation. *Id*. And both Prevenar 2005 and Chiron 2003 teach adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant. *Id*.

Patent Owner may argue that its 13-valent conjugate vaccine was nonobvious, because each of the 13 polysaccharides is conjugated to the same carrier protein (CRM_{197}), despite alleged concerns that too much carrier protein could diminish immunogenicity. But, claim 18 does not recite any particular level of required immunogenicity or amount of CRM_{197}; per sole independent claim 1, the focal point is inhibition of silicone-induced aggregation.[13] Ex. 1007, ¶ 48, Ex.

[13] *See In re Gleave*, 560 F.3d at 1336 (irrelevant whether prior art taught composition with antisense activity "because the simple fact is that Gleave's composition claims do not require antisense activity either"); *Boehringer Ingelheim*

1009, ¶ 173. In any event, there was no definitive teaching of "immune interference" that would have discouraged the natural progression of conjugate vaccine development, from the 7-conjugate Prevenar to a 13-conjugate version, as recited in claim 18. Ex. 1007, ¶ 49.

12. Claim 19

a. "The formulation of claim 1, wherein the siliconized container means is selected from the group consisting of a vial, a syringe, a flask, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen."

An approved form of the Prevenar 2005 vaccine was provided in a "pre-filled syringe (Type I glass)," which was known in the art to be siliconized. Ex. 1009, ¶ 175 (citing Exs. 1017 (at 14), 1076 (at 7)).

Int'l GmbH v. AbbVie Biotech. Ltd., IPR2016-00408, Paper No. 9 (July 7, 2016) at 14 ("Patent Owner's argument concerning the facial inferiority of a 20 mg weekly dose as compared to a 40 or 80 mg dose is based on an incorrect interpretation of the claims. We determined, based on the record before us, that the claims do not require a particular level of efficacy.").

13. Claim 20

a. "The formulation of claim 19, wherein siliconized container means is a syringe."

An approved form of the Prevenar 2005 vaccine provided in a "pre-filled syringe (Type I glass)," which was known in the art to be siliconized. Ex. 1009, ¶ 175 (citing Exs. 1017 (at 14), 1076 (at 7)).

B. Claim 18 Would Have Been Obvious over Prevenar 2005 in view of Chiron 2003, Pena 2004 and the General Knowledge of a POSITA

1. Claim 18

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises [13 conjugates, each with a different *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A) conjugated to a CRM_{197} polypeptide]"

As discussed above with respect to Ground 1 of this Petition, Prevenar 2005 discloses 7 pneumococcal polysaccharide-protein conjugates adsorbed to aluminum phosphate adjuvant (in a saline solution), which are provided in siliconized pre-filled glass syringes. Incorporating the histidine buffer of Chiron 2003 in the Prevenar 2005 formulation yields the formulation of claim 1, which inherently inhibits silicone-induced aggregation. The six additional conjugates recited in claim 18 do not impact the obviousness analysis, as they reflect nothing more than the natural progression of Patent Owner's prior art 7-valent vaccine.

Ground 2 provides an additional basis for finding claim 18 unpatentable. To the extent Patent Owner argues that the conjugates recited in claim 18 were not part of the general knowledge of one of ordinary skill in the art, Petitioner adds the Pena 2004 (Ex. 1015) reference to the obviousness analysis of Ground 1. Pena 2004 discloses a 13-valent pneumococcal conjugate vaccine with the same serotypes recited in claim 18. Ex. 1015 at 178. A POSITA would also have understood that those conjugates each were conjugated to CRM_{197}, based on the published progression from 7-valent Prevnar®, to 9- and 11-valent iterations; each version contained CRM_{197} as the sole carrier protein. Ex. 1007, ¶¶ 45-46.

Patent Owner may argue that its 13-valent conjugate vaccine was nonobvious, because each of the 13 polysaccharides is conjugated to the same carrier protein (CRM_{197}), despite alleged concerns that too much carrier protein could diminish immunogenicity. But, claim 18 does not recite any particular level of required immunogenicity or amount of CRM_{197}; per sole independent claim 1, the focal point is inhibition of silicone-induced aggregation. *Id.*, ¶ 48, Ex. 1009, ¶ 180; *see In re Gleave*, 560 F.3d at 1336; *Boehringer*, IPR2016-00408, Paper No. 9 at 14. In any event, there was no definitive teaching of "immune interference" that would have discouraged the natural progression of conjugate vaccine development, from a 7-valent formulation to a 13-valent version, as recited in claim 18. Ex. 1007, ¶ 49.

C. Secondary Considerations

To the extent Patent Owner argues that secondary considerations support a finding of non-obviousness with respect to the challenged claims, Petitioner reserves the right to address any such arguments in Petitioner's Reply. However, any secondary considerations that Patent Owner may allege will not overcome the strong evidence of obviousness based on prior art.

By way of example, there is no nexus between any alleged commercial success of Patent Owner's purported commercial embodiment (Prevnar 13®) and the old, non-specific formulation claims of the '999 Patent. The claims are not directed to any level of immunogenicity or protection against disease, and they omit critical vaccine parameters, such as amounts of polysaccharide, CRM_{197} and adjuvant. As for the required amounts of the two claimed formulation ingredients that purportedly inhibit silicone-induced aggregation, surfactant and aluminum salt, the claims are either overly broad (*e.g.*, 0.001 to 10% polysorbate 80 in dependent claim 2) or entirely silent (with respect to aluminum salt). Even when an ingredient amount is disclosed, *e.g.*, the overly broad range of polysorbate 80 in dependent claim 2, it is not combined with any specific type or amount of conjugate(s), buffer, saline solution or aluminum salt.

X. CONCLUSION

Petitioner respectfully submits that it has established a reasonable likelihood that it will prevail as to the obviousness of claims 1-6, 10-11, 14 and 17-20 of the '999 Patent. Petitioner respectfully requests that this Petition be granted, *inter partes* review be instituted, and claims 1-6, 10-11, 14 and 17-20 of the '999 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: December 1, 2016

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CLAIM LISTING APPENDIX

1. A formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) an aluminum salt and (iii) one or more polysaccharide-protein conjugates, wherein the formulation is comprised in a siliconized container means and inhibits aggregation induced by the siliconized container means.

2. The formulation of claim 1, wherein the formulation further comprises polysorbate 80, and wherein the final concentration of the polysorbate 80 in the formulation is at least 0.001% to 10% polysorbate 80 weight/volume of the formulation.

3. The formulation of claim 1, wherein the polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides.

4. The formulation of claim 1, wherein the formulation further comprises one or more meningococcal polysaccharides, one or more meningococcal antigenic proteins, or a combination thereof.

5. The formulation of claim 1, wherein the formulation further comprises one or more streptococcal polysaccharides, one or more streptococcal antigenic proteins, or a combination thereof.

6. The formulation of claim 1, wherein the formulation further comprises an adjuvant.

10. The formulation of claim 1, wherein the aluminum salt is aluminum hydroxide, aluminum phosphate or aluminum sulfate.

11. The formulation of claim 10, wherein the aluminum salt is aluminum phosphate.

14. The formulation claim 1, wherein the formulation further comprises a surfactant selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 85, nonylphenoxypolyethoxethanol, octylphenoxypolyethoxethanol, oxtoxynol 40, nonoxynol-9, triethanolamine, triethanolamine polypeptide oleate, polyoxyethylene-660 hydroxystearate, polyoxyethylene-35ricinoleate, soy lecithin and a poloxamer.

17. The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises an S. pneumoniae serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide, and an S. pneumoniae serotype 23F polysaccharide conjugated to a CRM_{197}.

18. The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises an S. pneumoniae serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 23F polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae

serotype 1 polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 3 polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 5 polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 6A polysaccharide conjugated to a CRM_{197} polypeptide, an S. pneumoniae serotype 7F polysaccharide conjugated to a CRM_{197} polypeptide and an S. pneumoniae serotype 19A polysaccharide conjugated to a CRM_{197} polypeptide.

19. The formulation of claim 1, wherein the siliconized container means is selected from the group consisting of a vial, a syringe, a flask, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen.

20. The formulation of claim 19, wherein siliconized container means is a syringe.

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §42.24(d), the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,562,999 contains, as measured by the word processing system used to prepare this paper, 12,675 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,562,999, along with all exhibits and other supporting documents, was served on December 1, 2016, by FedEx overnight delivery at the following address:

Pfizer Inc.
Attn: Legal Patent Department, Chief IP Counsel
235 East 42nd Street
New York, NY 10017

which is the correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,562,999.

Dated: December 1, 2016

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