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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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 claims of the '999 Patent are directed to formulations of "polysaccharide-protein conjugates," commonly-used immunogenic components of vaccines against disease-causing bacteria. The remaining ingredients of the claimed formulations – essentially buffer (to stabilize pH), salt (to match the salt concentration of the body), aluminum adjuvant (to boost immunogenicity), and surfactant (to inhibit protein aggregation) – were likewise staple vaccine components as of the earliest possible priority date of April 26, 2006. Indeed, the primary reference of this Petition, Chiron 2003 (Ex. 1011), teaches polysaccharide-protein conjugate vaccines with all of the above ingredients.

The disclosure of the '999 Patent makes clear that the only allegedly inventive aspect of the claimed formulations is that they inhibit undesirable protein aggregation induced by "siliconized" containers (*i.e.*, containers treated with a silicone oil lubricant). During prosecution, the Examiner recognized that the

claimed formulations were old, but ultimately allowed the claims in view of Patent Owner's argument that the recited formulations are distinguishable over the prior art because they are housed in siliconized containers and inhibit silicone-induced aggregation.

But there is nothing inventive about the claims of the '999 Patent. Instead, the claims reflect nothing more than a widely-known problem (protein aggregation caused by silicone oil lubricant in containers) for which there was a widely-applied solution (surfactant). As evidenced by Smith 1988 (a technical report on siliconization by "The Task Force on Lubrication of Packaging Components") (Ex. 1012), lubrication of pharmaceutical containers was a necessity, with "essentially all" such treatments involving silicone oil. And Elan 2004 (Ex. 1013) expressly teaches the addition of a surfactant to prevent protein aggregation induced by the silicone oil in standard syringes.

A person of ordinary skill in the art ("POSITA") would have been motivated to apply the teachings of Smith 1988 and Elan 2004 to the polysaccharide-protein conjugate formulations of Chiron 2003, to arrive at the claimed formulations of the '999 Patent; this is especially so since the Chiron 2003 formulations incorporate the very same solution for protein aggregation - a polysorbate surfactant - that is used in Elan 2004. Moreover, there would have been a reasonable expectation of success since surfactants were known to inhibit protein aggregation and had

already been incorporated in many licensed protein-based pharmaceuticals, including at least one Chiron polysaccharide-protein conjugate vaccine (Vaxem Hib (Exs. 1050-1055)).

The '999 Patent also suggests that aluminum salt inhibits silicone-induced aggregation. But the single independent claim 1 broadly includes **any** formulation that inhibits silicone-induced aggregation; it does not exclude surfactants, nor does it require that aluminum inhibit aggregation. There is nothing inventive about including aluminum salts in a polysaccharide-protein conjugate vaccine formulation.[1] Aluminum salts were the most commonly-used "adjuvants" (*i.e.*, to

[1] It bears noting that the mere recognition of a purportedly unappreciated property of a prior art formulation (*e.g.*, stability against silicone-induced aggregation) 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.").

boost immune responses) for any human vaccine, including licensed polysaccharide-protein conjugate vaccines. Indeed, the polysaccharide-protein conjugate formulations of Chiron 2003 (and Vaxem Hib) included both surfactant and aluminum salt.

The remaining limitations in the challenged 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 that recitation of specific bacterial polysaccharides and polysaccharide-protein conjugates in dependent claims 3-5 and 17-18 somehow renders those formulation claims nonobvious. Not so. Silicone oil induces aggregation of the **protein** in the polysaccharide-protein conjugates of the claims, and surfactant is a widespread solution to such **protein** aggregation. The fact that the 7 serotypes of claim 17 and the 13 serotypes of claim 18 are incorporated in Patent Owner's Prevnar 13®/Prevenar 13 product is of no significance. There is nothing inventive about applying the old formulation of claim 1 – that captures a widespread solution to a known *protein* problem – to

these specific serotypes. Chiron 2003 teaches that its polysaccharide-protein conjugate formulations can be used for meningococcal, pneumococcal, and other streptococcal polysaccharides, as recited in dependent claims 3-5 and 17-18. Pena 2004 (Ex. 1015) likewise discloses the 7 conjugates recited in claim 17, as well as expansion to the 13 conjugates recited in dependent 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. 1008) 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 York, NY 10022, Phone: 212-918-3000, Fax: 212-918-3100, and Email: ernest.yakob@hoganlovells.com.

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 Chiron 2003 (Ex. 1011) in view of Smith 1988 (Ex. 1012), Elan 2004 (Ex. 1013) and the general knowledge of a POSITA.

Ground 2. Claims 17-18 are unpatentable as obvious under pre-AIA 35 U.S.C. § 103(a) over Chiron 2003 (Ex. 1011) in view of Smith 1988 (Ex. 1012), Elan 2004 (Ex. 1013), 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-G *infra*; claim construction is addressed in Section VIII *infra*; and a detailed explanation of the grounds for unpatentability is provided in Section IX *infra*.

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

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.

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 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.

[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 Ex. 1050, 1052, and 1054, respectively.

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. 1008, ¶ 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), ¶ 41 (citing Ex. 1051, 1053, 1055, 1056 (at 16, 28, 39, 40, 52, 62, 73, 83, 98, 100), 1058 (at 33)). 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]).

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. 1008, ¶ 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)). Lubrication of vial stoppers is necessary for machinability and the efficient sealing of vials. *Id*., ¶ 36 (citing Exs. 1065 (at 6), 1012 (at 4)).

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

[5] Ex. 1017 is an excerpt of Ex. 1016 at 11-25.

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.

Id., ¶ 40 (quoting Ex. 1047 (at 3)) (emphasis added).

6. Aggregation of Proteins

Proteins include hydrophilic and hydrophobic regions. Ex. 1008, ¶ 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. 1008, ¶ 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. 1008, ¶ 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. 1008, ¶ 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. 1008, ¶ 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. 1008, ¶ 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. The '999 Patent

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. Dependent claims 2 and 14 are specifically directed to the use of surfactant in the formulation of claim 1 that inhibits silicone-induced aggregation.

In Example 1 of the '999 Patent, the inventors assessed the effect of surfactant on aggregation of a 13-valent polysaccharide-protein conjugate composition ("13vPnC") in siliconized BD Hypak syringes,[6] and without aluminum adjuvant. *Id*. at 19:65 - 20:16. In the absence of surfactant, the 13vPnC in the syringe "would begin precipitating out of solution within ten minutes at 2-8° C. upon gentle agitation via a horizontal orbital shaker." *Id*. at 20:17-21. In

[6] The '999 Patent explains that the BD Hypak syringes were siliconized. *See, e.g.*, Ex. 1001 at 23:36-40 (referencing "ready to use (single-dose) Becton Dickinson® (BD) Hypak Type 1 borosilicate glass syringes treated with Dow Corning® medical grade DC 360 silicone"), 28:59-67 ("syringes with higher silicone levels" include "BD Hypak syringe (control 1)").

comparison, "the 13vPnC, formulated in 0.001%, 0.005%, 0.01% or 0.05% Tween™80 and gently agitated at 2-8° C., was stable for up to twenty-five days with no visible signs of precipitation (data not shown)." *Id*. at 20:21-24. Thus, the inventors concluded "that the addition of a surfactant (e.g., Tween™80) to an immunogenic composition formulation enhances the stability of the immunogenic composition." *Id*. at 20:24-27.

Similarly, in Example 2, the inventors investigated the effect of surfactant on aggregation of a different protein-based composition (streptococcal C5a peptidase, or "SCP") in siliconized syringes without aluminum adjuvant. *Id*. at 22:45 - 23:6. The inventors again reported that surfactant inhibited silicone-induced aggregation:

> As shown in FIG. 1, the stability of SCP was greatly enhanced when formulated with Tween™80. For example, after two days on the orbital shaker, the SCP formulated without Tween™80 (FIG. 1A) demonstrated a significant decrease (e.g., greater than 90%) in the SCP concentration [with] each of the buffers tested. However, as shown in FIG. 1B, the addition of 0.025% Tween™80 to the SCP buffer formulations, prior to being placed on the orbital shaker for two days, completely inhibited the SCP loss which was observed in FIG. 1A.

Id. at 23:7-16.

The '999 Patent even investigated the effect of surfactant on aggregation of 13vPnC (without aluminum adjuvant) due to hydrophobic interfaces (the air-liquid

interfaces of air bubbles), akin to silicone oil. Ex. 1008, ¶ 66 (citing Ex. 1001 (at 20:29-49)). Again, the inventors reported that surfactant inhibited aggregation:

> As is shown in Table 1, there was a significant decrease in antigenicity of the thirteen serotype polysaccharides (formulated without Tween™80) within the two hour assay. Quite significantly however, the 13vPnC formulation comprising 0.05% Tween™80 (Table 1), demonstrated robust stability with no reduction in the antigenicity throughout the two hour antigenicity assay.

Ex. 1001 at 61-67.

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.

Notably, the purported effect of aluminum was conspicuously less than the effect of surfactant. Ex. 1008, ¶ 70. When surfactant was added to the 13vPnC formulation, the '999 Patent reported "no visible signs of precipitation." Ex. 1001 at 20:21-24. In contrast, when aluminum phosphate was included in the 13vPnC formulation without surfactant, "the 13vPnC supernatant began to show low levels of particulate in the fourth hour of observation (data not shown)." *Id*. at 26:12-14. In Example 3 (and Table 5), even with aluminum phosphate, two monovalent polysaccharide-protein conjugates still exhibited "[f]iber-like white particulates" under certain conditions. *Id*. at 26:18-57.

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. 1008, ¶ 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.[7] Ex. 1008, ¶ 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.

[7] 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. 1008, ¶ 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*.

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.

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. 1008, ¶ 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.

In response, 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 and subsequently allowed the Patent. *Id*. at 303, 334.

D. Chiron 2003

The primary prior art reference in this Petition is 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.

E. Smith 1988

In addition to Chiron 2003, this Petition relies on the prior art teachings of Smith *et al.*, "Technical Report No. 12 Siliconization of Parenteral Drug Packaging Components," *J. Parent. Sci. Techn*. 42 (Supplement 1988) written by the "Task Force on Lubrication of Packaging Components" ("Smith 1988"). Ex. 1012. Because Smith 1988 was published in 1988,[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). As explained in Smith 1988, "[m]ost parenteral packaging components **require** the use of some form of lubrication in order to improve their processability and functionality." *Id*. at 4 (emphasis added). In turn, "[e]ssentially all treatment utilized for the lubrication of parenteral components are based on the use of PDMS fluid (Silicone Oil)." *Id*. at 8.

As Smith 1988 notes, siliconization of syringe plungers and barrel interiors reduces friction between the plunger and the barrel, thereby (1) minimizing the force required to insert the plunger and to initiate plunger movement and (2) ensuring smooth drug delivery. *Id*. at 4. With respect to rubber closures (such as vial stoppers), siliconization significantly improves machinability and minimizes

[8] Petitioner notes that Smith 1988 was cataloged by the library of the NY Academy of Medicine on September 12, 1990, more than one year before April 26, 2006. Ex. 1012 at 14.

production time by reducing clumping of the components as they are fed through machine paths. *Id.* Siliconization also reduces the force required to seal vials with stoppers, and improves the integrity of the seal. *Id*.

"[S]tability, hydrophobicity, lubricity, and low toxicity" account for why silicone oil is a preferred lubricant in pharmaceutical containers. *Id*. at 5. Silicone oils are "stable at high and low temperatures and are highly resistant to changes due to 'heat or oxidation." *Id*. Silicone oils also "have been shown to be rema[r]kably devoid of toxicologic problems. No effects have been demonstrated, even at exposure levels massively exaggerated, over any conceivable use except for transient eye irritation." *Id*. at 5-6 (internal citations omitted).

Smith 1988 briefly acknowledges alternatives to silicone oil, but identifies disadvantages with such alternatives (*e.g.*, leeching into the formulation, limited applicability, inconsistency, discoloration, expense, incomplete coating, limited characterization); none are disclosed as common or preferred lubrication methods. *Id*. at 11-12. Moreover, the disclosed alternatives were only considered for "elastomeric components" (*e.g.*, rubber), distinct from the glass pre-filled syringe barrels. *Id*. at 11. As of April 26, 2006, no suitable alternative to silicone oil existed for the lubrication of the barrel interiors of pre-filled glass syringes for pharmaceuticals. Ex. 1008, ¶ 121.

F. Elan 2004

This Petition further relies on the prior art teachings of Elan Pharmaceutical's International Patent Publication No. WO 2004/071439 ("Elan 2004"). Ex. 1013. Because Elan 2004 was published on August 26, 2004, 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). Like the '999 Patent, Elan 2004 is directed to protein-based pharmaceutical formulations which inhibit silicone-oil induced protein aggregation. *Id*. at Abstract, 2:1-3, 7:26-28, 8:5-8, 9:25-26. Elan 2004 reports that silicone oil caused discernible aggregation of an antibody formulation "upon gentle agitation and room temperature storage." *Id*. at 16:6-11. However, "the addition of polysorbate 80 [a surfactant] at a concentration of 0.02% (w/v)" prevented aggregation. *Id*. at 16:13-15, 17:6-14. Inclusion of surfactant did not adversely affect the antibody protein, but did provide "increased stability during product shipping and handling in the clinical setting." *Id*. at 16:16-18. The surfactant also provided additional stability against aggregation promoted by high protein concentrations. *Id*. at 16:19-25. Although primarily directed to antibody formulations, Elan 2004 unequivocally covers any protein. *Id*. at 3:21-24, 10:2-3. Elan 2004 also discloses that polysorbate 80 surfactant is preferably included within the concentration range of "about 0.001 % to about 2.0% (w/v)." *Id*. at 2:3-4.

G. 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,[9] 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 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.

[9] 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.

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. 1008, ¶ 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."[10] 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

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

(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:

> 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. 1008, ¶ 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. 1008, ¶ 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. 1008, ¶ 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.

Patent Owner may argue that, during prosecution of the '999 Patent, it emphasized that aluminum salt could inhibit silicone-induced aggregation. But Patent Owner never argued that the claims **require** that aluminum salt inhibit silicone-induced aggregation. *Id.*, ¶ 97. To the contrary, after the Examiner rejected all of the claims because the claimed formulation and its recited ingredients were well-known in the art, Patent Owner argued: "Since Kasper does not specify a <u>siliconized</u> container means, Kasper cannot teach that the **formulation** described therein inhibits the aggregation that is caused by using a

siliconized container means." Ex. 1002 at 292 (underlining in original, bold added).

There is no clear, unmistakable and unambiguous disavowal of scope here, which would be necessary to overcome the heavy presumption in favor of the plain claim language. Ex. 1008, ¶ 100; *see, e.g.*, *Avid Tech., Inc. v. Harmonic, Inc.*, 812 F.3d 1040, 1045 (Fed. Cir. 2016) ("[F]or prosecution disclaimer to attach, our precedent requires that the alleged disavowing actions or statements made during prosecution be both clear and unmistakable.") (internal citations and quotation marks omitted); *Inverness Med. Switzerland GmbH v. Princeton Biomeditech Corp.*, 309 F.3d 1365, 1372 (Fed. Cir. 2002) (disavowal of claim scope must be "clear and unambiguous"). Indeed, every time Patent Owner referred to the claimed invention, it described the "formulation" as inhibiting silicone-induced aggregation. *See, e.g.*, Ex. 1002 at 290 ("Applicants' claimed invention is a formulation . . . The formulation is contained in a siliconized container means and inhibits aggregation induced by the siliconized container means."). At no point did the Patent Owner argue that the claims of the '999 Patent require that aluminum salt inhibit silicone-induced aggregation. Ex. 1008, ¶ 99. Nor did the Examiner suggest that patentability was based on a specific component of the formulation that inhibits silicone-induced aggregation. *Id.*

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Claims 1-6, 10-11, 14 and 17-20 Would Have Been Obvious over Chiron 2003 in View of Smith 1988, Elan 2004 and the General Knowledge of a POSITA

The claims of the '999 Patent recite polysaccharide-protein conjugate formulations in siliconized containers that inhibit silicone-induced aggregation. As detailed below, Chiron 2003 teaches or suggests every formulation ingredient recited in the challenged claims, including various bacterial antigens, buffer, aluminum phosphate adjuvant, and Tween® 80 surfactant. Ex. 1008, ¶ 23. Consistent with Smith 1988's teaching that it was standard industry practice to lubricate pharmaceutical containers with silicone oil, it would have been obvious to provide the vaccine formulations of Chiron 2003 in siliconized containers (such as vials with siliconized stoppers and pre-filled syringes with siliconized plungers and siliconized barrel interiors). *Id*. Given Elan 2004's teaching that surfactant inhibits silicone-induced protein aggregation in siliconized containers, it would have been obvious that the protein-based formulations of Chiron 2003 – which contain the very same surfactant as Elan 2004 – would have the same inhibitory property. *Id*.

1. Claim 1

a. "A formulation comprising"

Chiron 2003's teachings are "in the field of vaccine formulation." Ex. 1011 at 1:4. 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. *See, e.g., id*. at 1:27 - 2:3, 5:17-20, 11:30 - 12:15 (Example 2), 14:3 - 17:4 (Examples 7-9).

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

A "saline solution" includes a salt, usually sodium chloride. Ex. 1008, ¶ 126. 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).

Acknowledging that buffers (used to resist change in pH) are a standard component of vaccines, 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).

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. 1008, ¶ 128. 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"

Chiron 2003 "provides a composition comprising an antigen, an aluminium[11] 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,"

For any of the disclosed bacterial saccharide antigens, Chiron 2003 teaches that conjugation 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]."). The formulations of Examples 2 and 7-9 each include one or more meningococcal oligosaccharide-protein conjugates. *Id*. at 11:30 - 12:15, 14:3 - 17:4.

[11] "Aluminium" is an alternate name for "aluminum," used primarily in Europe. There is no difference between "aluminium" and "aluminum." Ex. 1008, ¶ 129.

"Oligosaccharides" are shortened versions of bacterial polysaccharides, and as discussed above, oligosaccharides and saccharides fall within the '999 Patent's express definition of "polysaccharide." Ex. 1007, ¶¶ 50-52; Ex. 1008, ¶ 131.

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

It would have been obvious to provide the formulations of Chiron 2003 in the claimed "siliconized container means," as broadly defined by the patent (to include vials, vial stoppers, syringes and syringe plungers). Ex. 1008, ¶ 133. Chiron 2003 discloses storing the polysaccharide-protein conjugated formulations of Example 8 in vials, which would have been sealed with rubber stoppers. *Id.* As evidenced by a commercialized Chiron polysaccharide-protein conjugated vaccine, Vaxem Hib, it also would have been obvious to place the Chiron 2003 formulations in syringes or pre-filled syringes. *Id.* (citing Ex. 1051, 1053). Consistent with Smith 1988, it was standard industry practice to lubricate the components of such containers (rubber vial stoppers, syringe plungers and the interiors of syringe barrels) with silicone oil. *Id.*

i. It would have been obvious to provide the polysaccharide-protein conjugate formulations of Chiron 2003 in vials with rubber stoppers, as well as in pre-filled syringes

It would have been obvious to provide the polysaccharide-protein conjugate formulations of Chiron 2003 in vials with rubber stoppers, as well as in pre-filled

syringes. Ex. 1008, ¶¶ 133-136. Example 8 of Chiron 2003 discloses that the formulations were "packag[ed] into vials" and stored at least 1 month. Ex. 1011 at 15:1-6. Given such long-term storage, a POSITA would have sealed such vials with rubber stoppers. Ex. 1008, ¶ 134. It also would have been obvious to use syringes since the Chiron 2003 formulations were designed to be injected into humans and animals, and were injected into mice. *Id*., ¶ 135 (citing Ex. 1011 (at 8:37 ("Typically, the immunogenic compositions are prepared as injectables . . ."), 15:9-10 (administration to mice))).

It also would have been obvious to store the polysaccharide-protein conjugate vaccines of Chiron 2003 in pre-filled syringes, based on the well-established benefits of pre-filled syringes, and the fact that numerous vaccines (including polysaccharide-protein conjugate vaccines) were supplied in pre-filled syringes. *Id*., ¶ 136. Indeed, Chiron had already marketed the Vaxem Hib polysaccharide-protein conjugate vaccine, with the basic ingredients claimed in the '999 Patent (pH buffered saline solution, aluminum adjuvant and surfactant) in pre-filled glass syringes. *Id*., ¶ 137 (citing Exs. 1051, 1053).

ii. Consistent with Smith 1988, standard rubber vial stoppers, syringe barrels and syringe plungers were lubricated with silicone oil

A POSITA would have understood that standard pharmaceutical vial stoppers, syringe plungers and syringe barrel interiors were siliconized. Ex. 1008,

¶ 138. As of April 26, 2006, it was well understood that pharmaceutical containers required lubrication, and that the standard lubricant was silicone oil. *See supra* at Section VI.A.5. Prior art literature taught both the ubiquity of siliconized containers, as well as the specific benefits of siliconization. *See supra* at Section VI.E.

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

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 would have been obvious to a POSITA that the Tween® 80 of Chiron 2003 inhibits silicone-induced aggregation. Ex. 1008, ¶ 139. Elan 2004 expressly teaches the use of the very same surfactant in protein-based formulations to inhibit silicone-induced aggregation. Ex. 1013 at 16:13-15, 17:6-14.

A formulator would have had every incentive to use surfactants to stabilize a polysaccharide-protein conjugate formulation from aggregation. Ex. 1008, ¶ 141. As of April 26, 2006, it was well-established that low amounts of surfactants were safe and standard components of pharmaceutical products. *Id.* 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)).

h. A POSITA would have been motivated to combine the teachings of Chiron 2003, Smith 1988 and Elan 2004 with a reasonable expectation of success

A POSITA would have had a reasonable expectation of success in providing the formulations of Chiron 2003 in "siliconized container means." Ex. 1008, ¶ 143. Based on the prevalence of siliconized containers, as evidenced by Smith 1988, a POSITA would have been motivated to formulate polysaccharide-protein conjugate compositions (including those disclosed in Chiron 2003) in siliconized containers. *Id*. Apart from the known advantages of silicone oil as a lubricant for pharmaceutical containers, silicone oil was the best-characterized lubricant for pharmaceutical containers and widely-recognized to be safe. *Id*.

A POSITA would have a reasonable expectation that applying the teachings of Elan 2004 to the polysaccharide-protein conjugated formulations of Chiron 2003 would succeed in addressing silicone-induced protein aggregation in siliconized containers. *Id*., ¶ 144. Surfactants were a widely-applied solution to the known problem of silicone-induced protein aggregation. *Id*. Significantly, both Elan 2004 and Chiron 2003 teach the use of the very same surfactant, with Chiron 2003's surfactant falling in the useful range of surfactant concentration

taught by Elan 2004. *Id*. Each of the polysaccharide-protein conjugate compositions of Chiron 2003's Examples 7-9 specifically includes 0.005% Tween® 80 surfactant. Ex. 1011 at 14:3 - 17:4. And Elan 2004 discloses the use of that same exact surfactant, in a concentration range of "about 0.001 % to about 2.0% (w/v)." Ex. 1013 at 2:3-4. In view of Elan's express teaching that Tween® 80 surfactant successfully provides a stable protein-based pharmaceutical formulation without silicone-induced aggregation, a POSITA would have had a reasonable expectation that Chiron 2003 would likewise succeed in having the same inhibitory effect. Ex. 1008, ¶ 144.

2. Claim 2

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

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).

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. 1008, ¶ 146. 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*. 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*. This is corroborated by Elan 2004, which discloses that the polysorbate 80 surfactant is preferably included at any concentration within the range of "about 0.001 % to about 2.0% (w/v)," which is entirely within the claimed range. Ex. 1013 at 2:3-4.

3. Claim 3

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

It would have been obvious to use pneumococcal polysaccharide-protein conjugates in the formulations of Chiron 2003, and that such formulations would still inhibit silicone-induced aggregation. Ex. 1008, ¶ 147. There is nothing inventive about incorporating pneumococcal polysaccharides in polysaccharide-protein conjugates; such antigens were well-known in the art long before April 26,

2006, and are expressly disclosed in Chiron 2003. Ex. 1007, ¶¶ 32, 34, 42-46; Ex. 1008, ¶ 147. 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.

The limitation to pneumococcal polysaccharide-protein conjugates also does not impact the obviousness of the "old" formulation of claim 1. A POSITA would have understood that the **protein** component of polysaccharide-protein conjugates (not the polysaccharide) is responsible for the claimed "aggregation induced by the siliconized container means." Ex. 1008, ¶ 147. And there was a known solution (surfactants) for solving that known **protein** aggregation problem.

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 formulations of Chiron 2003, and that such formulations would still inhibit silicone-induced aggregation. Ex. 1008, ¶ 148. 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. 1008, ¶ 148-149. 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).

The limitation to meningococcal polysaccharides and/or proteins also does not impact the obviousness of the "old" formulation of claim 1. A POSITA would have understood that the **protein** component of the formulation (not any polysaccharide) is responsible for the claimed "aggregation induced by the siliconized container means." Ex. 1008, ¶ 149. And there was a known solution (surfactants) for solving that known aggregation problem for all types of proteins.

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."

It would have been obvious to use streptococcal polysaccharide and/or protein antigens in the formulations of Chiron 2003, and that such formulations would still inhibit silicone-induced aggregation. Ex. 1008, ¶ 150. 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. 1008, ¶ 150-151. 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.

The limitation to streptococcal polysaccharides and/or proteins also does not impact the obviousness of the "old" formulation of claim 1. A POSITA would have understood that the **protein** component of the formulation (not any polysaccharide) is responsible for the claimed "aggregation induced by the

siliconized container means." Ex. 1008, ¶ 151. And there was a known solution (surfactants) for solving that known aggregation problem for all types of proteins.

6. Claim 6

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

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."

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").[12]

8. Claim 11

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

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."

[12] It was also known that the actual structures of the adjuvants used in the art and labeled as "aluminum hydroxide" and "aluminum phosphate" were "aluminum oxyhydroxide" and "aluminum hydroxyphosphate," respectively. Ex. 1008, ¶ 55 (citing Exs. 1069 (at 2), 1070 (at 2)).

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).

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]"[13]

It would have been obvious to use the claimed pneumococcal polysaccharide-protein conjugates in the formulations of Chiron 2003, and that such formulations would still inhibit silicone-induced aggregation. Ex. 1008, ¶ 156. There is nothing inventive about incorporating pneumococcal polysaccharides in polysaccharide-protein conjugates; such antigens were well-known in the art long before April 26, 2006, and are expressly disclosed in Chiron 2003. Ex. 1007, ¶¶ 32, 34, 42-46; Ex. 1008, ¶ 157. 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. Chiron 2003 expressly discloses "a saccharide antigen from *Streptococcus*

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

pneumoniae ," and "[t]he composition may comprise one or more of these bacterial . . . antigens." *Id*. at 2:15, 3:14.

The limitation to specific polysaccharide serotypes and a specific carrier protein (CRM_{197}) does not impact the obviousness of the "old" formulation of claim 1. A POSITA would have understood that it is the **protein** component of the formulation (not any polysaccharide) that is responsible for the claimed "aggregation induced by the siliconized container means." Ex. 1008, ¶ 157. And there was a known solution (surfactants) for solving that known aggregation problem for all types of proteins.

Patent owner may argue that the recitation of 7 specific polysaccharide-protein conjugates in this claim somehow renders this claim inventive, even if the "old" formulation of Claim 1 is not. But the commercially available, prior art Prevnar® vaccine already contained the 7 recited polysaccharide-protein conjugates.[14] Ex. 1058 at 42. (And reference 23 of Chiron 2003 explicitly

[14] Chiron 2003 provides motivation to reformulate Prevnar® (that does not contain buffer) to the Chiron 2003 formulations (which include histidine buffer): "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**

discloses a vaccine with those same 7 polysaccharide-protein conjugates. Ex. 1073 at 14.)

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]"

It would have been obvious to use the claimed pneumococcal polysaccharide-protein antigens in the formulations of Chiron 2003, and that such formulations would still inhibit silicone-induced aggregation. Ex. 1008, ¶ 159. The application of the formulation of claim 1 to the conjugates of claim 18 would have been obvious for the same reasons given with respect to claim 17. *Id.* The only difference between claims 17 and 18 is that claim 18 adds six more required pneumococcal polysaccharide-protein conjugates (*i.e.*, claim 18 requires at least 13 conjugates). Those additional recited conjugates do 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)).

The limitation to specific polysaccharide serotypes and a specific carrier protein (CRM_{197}) does not impact the obviousness of the "old" formulation of

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buffer system is included." Ex. 1008, ¶ 158 (citing Ex. 1011 at 5:17-19 (emphasis added)).

claim 1. A POSITA would have understood that it is the **protein** component of the formulation (not any polysaccharide) that is responsible for the claimed "aggregation induced by the siliconized container means." Ex. 1008, ¶ 160. And there was a known solution (surfactants) for solving that known aggregation problem for all types of proteins.

Additionally, the 13 conjugates in claim 18 are a natural progression from Patent Owner's prior art 7-valent vaccine. Ex. 1007, ¶ 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.* (citing Exs. 1034 (at 2), 1035 (at 4), 1036 (at 5), 1037 (at 4)). 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.

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.[15] *Id.*, ¶ 48, Ex. 1008, ¶ 161. 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.

[15] *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 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.").

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."

It would have been obvious to administer the disclosed formulations of Chiron 2003 in syringes. Ex. 1008, ¶ 163. And it would have been an obvious choice to store a polysaccharide-protein conjugate vaccine in pre-filled syringes, based on the known benefits of pre-filled syringes and the fact that numerous vaccines (including polysaccharide-protein conjugate vaccines) had already been supplied in pre-filled glass syringes. *Id.*; *supra* at Section VI.A.4.

13. Claim 20

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

It would have been obvious to administer the disclosed formulations of Chiron 2003 in syringes. Ex. 1008, ¶ 164. And it would have been an obvious choice to store a polysaccharide-protein conjugate vaccine in pre-filled syringes, based on the known benefits of pre-filled glass syringes and the fact that numerous vaccines (including polysaccharide-protein conjugate vaccines) had already been supplied in pre-filled glass syringes. *Id.*; *supra* at Section VI.A.4.

B. Claims 17-18 Would Have Been Obvious over Chiron 2003 in View of Smith 1988, Elan 2004, Pena 2004 and the General Knowledge of a POSITA

As discussed above with respect to Ground 1 of this Petition, it would have been obvious to provide the formulations of Chiron 2003 in siliconized containers (consistent with Smith 1988) with surfactant inhibiting silicone-induced aggregation (as evidenced by Elan 2004). It also would have been obvious to use the Chiron 2003 formulations for the specific polysaccharide-protein conjugates recited in claims 17 and 18. The recited conjugates do not impact the obviousness analysis, since it is the **protein** component of polysaccharide-protein conjugates (not the polysaccharide) that is responsible for silicone-induced aggregation, and it was known that surfactant inhibits silicone-induced aggregation for all types of protein.

Ground 2 provides an additional basis for finding claims 17 and 18 unpatentable. To the extent Patent Owner argues that the conjugates recited in claims 17 and 18 were not part of the general knowledge of one of ordinary skill in the art, Petitioner adds the Pena 2004 reference to the obviousness analysis of Ground 1.

1. Claim 17

Pena 2004 expressly discloses the 7 conjugates recited in claim 17. Ex. 1015 at 3. A POSITA would have been motivated (with a reasonable expectation

of success) to apply the formulations of Chiron 2003 to the 7 conjugates of Pena 2004.[16] Ex. 1008, ¶ 165. Chiron 2003 specifically discloses that (1) its teachings are preferably directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus, (*i.e.*, *Streptococcus pneumonia*), (2) the vaccine antigen can include "a saccharide antigen from *Streptococcus pneumoniae* ," and (3) "[t]he composition may comprise one or more of these bacterial . . . antigens." Ex. 1011 at 6:32-35; 2:15, 3:14. Indeed, reference 23 of Chiron 2003 discloses the 7 pneumococcal CRM_{197}-conjugates of claim 17. Ex. 1073 at 14.

The additional limitation to specific polysaccharide serotypes and a specific carrier protein (CRM_{197}) does not impact the obviousness of the "old" formulation of claim 1. A POSITA would have understood that it is the *protein* component of the formulation (not any polysaccharide) that is responsible for the claimed "aggregation induced by the siliconized container means." Ex. 1008, ¶ 166. And there was a known solution (surfactants) for solving that known aggregation problem for all types of proteins.

[16] As explained in Ground 1, Chiron 2003 also specifically provides motivation to reformulate Prevnar® (that does not contain buffer) to the Chiron 2003 formulations (which include histidine buffer). Ex. 1011 at 5:17-19.

2. Claim 18

The only difference between claims 17 and 18 is that claim 18 adds six more required pneumococcal polysaccharide-protein conjugates (*i.e.*, claim 18 requires at least 13 conjugates). The additional recited conjugates do not make the claim inventive. Pena 2004 discloses a 13-valent pneumococcal conjugate vaccine with the same serotypes recited in claim 18. Ex. 1015 at 7. 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.

The limitation to specific polysaccharide serotypes and a specific carrier protein (CRM_{197}) does not impact the obviousness of the "old" formulation of claim 1. A POSITA would have understood that it is the **protein** component of the formulation (not any polysaccharide) that is responsible for the claimed "aggregation induced by the siliconized container means." Ex. 1008, ¶ 168. And there was a known solution (surfactants) for solving that known aggregation problem for all types of proteins.

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. 1008, ¶ 169; *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, 13,814 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: December 1, 2016

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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.
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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.

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